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Editorial

Dear Readers

Season's Greetings

Hope all is well. The Subharti Journal of Interdisciplinary Research was started with the chief objective of publishing the quality, original and has a high visibility and readership. It has achieved the objective to some extent but still a lot needs to be done in terms of the publishing novel work We at the editorial office are continuously striving to make this journal interesting, conversant and reverent with a high degree of success thus upholding the name interdisciplinary. With this issue we present to you the first issue of 2021. A big thank you and shout out to all the contributors for this issue of Subharti Journal of Interdisciplinary Research.

Taking the liberty of divulging from the journal for a few moments, it is for everyone to note that the COVID is back and the virus is more infectious, uglier, mightier and wreaking the havoc on the human race especially across India. It is effecting the younger generation way more heavily and the numbers succumbing to the disease are much more than before. Let's observe a moment of silence for all those who succumbed to COVID 19. The mantra is to stay away from each other (observe social distancing), maintaining hand hygiene and wearing masks whenever in crowded places. Prevention seems to be the best form of cure for the disease. Stay Safe, Stay Happy and Stay Healthy. These times too shall pass.

I hope that this journal is living up to everyone's expectations. I once again seek your support and look forward to welcoming your submissions for next issue and your valuable suggestions are eagerly awaited.

Happy Reading

Dr Vijay Wadhwan

Editor-in-Chief

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Review Article

In-silico drug designing tool: Molecular docking

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Abstract

Molecular docking is an established *in-silico* structure-based method widely used in drug discovery. Docking enables the identification of novel compounds of therapeutic interest, predicting ligand-target interactions at a molecular level, or delineating structure-activity relationships (SAR),without knowing a priori the chemical structure of other target modulators. Although it was originally developed to help understanding the mechanisms of molecular recognition between small and large molecules, uses and applications of docking in drug discovery have heavily changed over the last years. In this review, we describe how molecular docking was firstly applied to assist in drug discovery tasks. Then, we illustrate newer and emergent uses and applications of docking, including prediction of adverse effects, poly-pharmacology, drug repurposing, and target fishing and profiling, discussing also future applications and further potential of this technique when combined with emergent techniques, such as artificial intelligence.

Keywords: Molecular docking, Drug discovery, Drug repurposing, Reverse screening.

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Introduction

The experimental screening of large libraries of compounds against panels of molecular targets like as High-Throughput Screening (HTS), has represented the gold standard for discovering biologically active hits. However, the high costs required to establish and maintain these screening plat form soften hamper their use for drug discovery [1]. Moreover, considering the recent developments in computer technology and the rapid increase of structural, chemical, and biological data available on an ever-growing number of therapeutic targets, it is easily understandable how the use of in silico approaches as chemoinformatics, molecular modeling, and artificial intelligence (AI) has significantly increased in the last decades [2,3,4]. Indeed, *in-silico* approaches now enable the virtual screening of millions of compounds in an affordable time, thus reducing the initial costs of hit identification and improving chances of finding the desired drug candidates. At present, several molecular modeling techniques are available to facilitate drug discovery tasks, most of them being classified into structure-based and ligand-based approaches.

Structure-based methods rely on the information derived from the knowledge of the 3D structure of a target of interest, and they allow ranking databases of molecules according to the structural and electronic complementarity of ligands to a given target [5,6]. In this context, molecular docking is among one of the most popular and successful structure-based in silico methods, which help predict the interactions occurring between molecules and biological targets[7]. This process is generally accomplished by first predicting the molecular orientation of a ligand within a receptor, and then estimating their complementarity through the use of a scoring function. Since its first appearance in the mid-1970s, docking has proved to be an important tool to help understanding how chemical compounds interact with their molecular targets, and for drug discovery and development. As a matter of fact, the number of studies reporting: (i) the use of molecular docking to identify structural determinants necessary for efficient ligand-receptor binding, and (ii) the development of more accurate docking methods, have heavily increased since its first appearance [8–21].Among the first and more interesting studies on the use of docking in drug discovery and biology is the one from Kuntz et al. in the early 1980s [13]. In this study, the authors described a computational method enabling the exploration of geometrically feasible ligand-receptor alignments for the known heme-myoglobin/metmyoglobin and thyroxine/prealbumin structures [13]. This study was not the first to employ docking for predicting potential conformations of molecular complexes [9]. However, itreported for the first time the use of a simplified function containing solely the terms “hard sphererepulsions” and “hydrogen bonding” to describe protein-ligand interactions, which strongly differed from previous studies [21, 22]. Moreover, the authors were also the first to consider the receptor as a solid rigid body, whose

binding site is constituted by “pockets”. Interestingly, the method adoptedin this study was able to predict structures close to those of already reported X-ray complexes, and also to find protein conformations that could be used for energy refinement and eventually design novel ligands [13]. Since then, molecular docking underwent dramatic improvements, for example, by employing flexible algorithms in the calculations [21,23–26]. Moreover, it also started to be used for the design and optimization of compounds with therapeutic interest. An example of this comes from a study of Ring et al., in which several structure-based drug design methods, including docking, were performed to identify novel non-peptidic inhibitors of enzymes of the serine and cysteine protease families [27]. The results achieved in this work further consolidated the use of computer-aided structure-based drug-design methods for assisting the development of lead compounds [27].

Given the potential offered by this method, increasing efforts have been directed towards the improvement of docking algorithms and for overcoming its intrinsic limitations [28–30]. Indeed major limitations characterizing docking include a restricted sampling of both ligand and receptor conformations in pose prediction, and the use of approximated scoring functions, which very often provide results that do not correlate with the experimental binding affinities [31,32]. Nevertheless, the application of docking in drug design is limited to biological targets for which crystal structures are known. Several approaches have been adopted to overcome this latter limitation. For example, the unavailability of 3D structures is often bypassed by building homology models derived from structural templates with highly-homologous sequences. Moreover, these methods could also be used in tandem with molecular dynamics (MD) to further validate and refine the *in-silico* modeled complexes [33–35].Nevertheless, the recent progress in structural biology and crystal structure determination, which are progressively increasing the accessibility to experimentally derived ligand-target complexes [36–39], will certainly mitigate this issue. In silico strategies, including molecular dynamics, have also been widely used to explore the conformational space of the investigated targets, ligands, and ligand-target complexes, and thus better describing the dynamic behavior of ligand-target complexes and refining the docking results [34,40]. More rigorous virtual screening methodologies have also been developed to improve the docking-based ligand-target complex predictions [32]. Indeed, these post-docking refinement and rescoring methods are of great interest in drug discovery because they usually provide higher hit rates in virtual screening campaigns and allow better correlation with experimental data [23,32]. A number of reviews discussing the role and applications of docking, and the possibilities it could offer in drug design and development, have been reported [34]. However, it should be noted that the uses and applications of docking have been changing since its first appearance. In fact, although it was first developed to investigate molecular recognition between large and small molecules, it is now also widely used to assist different tasks of drug discovery programs, such as hit identification and optimization, drug repositioning, a posteriori target identification (reverse screening), design, and repositioning (Figure 1) [35]. Moreover, docking allows understanding the relationships between different molecular targets involved in a given disease, which is also of high relevance for poly pharmacology [36] and modern drug discovery in general.

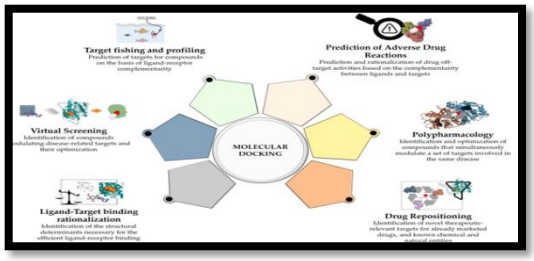

Fig.1. Applications of molecular docking

Molecular docking is currently employed to help rationalizing ligands activity towards a target of interest and to perform structure-based virtual screening campaigns, similarly to as when it was first developed. Beside these applications, it can also be used to identify series of targets for which the ligands present good complementarity (target fishing and profiling), some of them being potentially responsible forum expected drug adverse reactions (off-targets prediction). Moreover, docking is also currently employed for the identification of ligands that simultaneously bind to a pool of selected targets or interest (polypharmacology) and for identifying novel uses for chemical compounds with already optimized safety profiles (drug repositioning).In particular, the use of this technique has broadened towards novel drug discovery horizons, fueled by the improvement of docking algorithms and by the increase of the publicly accessible information on ligands and targets. For example, thanks to the improved speed and prediction power, docking has also been embedded into large-scale screening protocols to identify. [37]

Rational Design Approaches

The possibilities offered by molecular docking in drug discovery are well established [3]. However, docking presents intrinsic limitations that limit its prediction performances, the most relevant being reported in the previous section. Although docking has been mainly used as a standalone method for drug design, it is now often integrated into workflows that include other computational methods, such as ligand-based, structure-based, and AI approaches (Fig.2) [38]. This helps to account for some of the most relevant limitations.

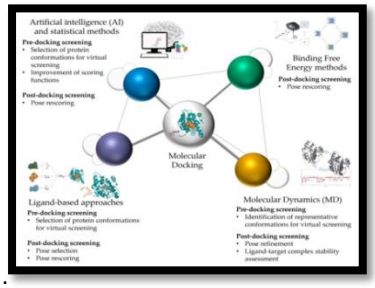

Fig. 2. Rationales of molecular docking

Integration of docking with ligand-based, molecular dynamics, binding free energy approaches, artificial intelligence (AI), and statistical methods. According to

the available information, different *in-silico* approaches can be combined with docking to generate integrated workflows with improved prediction performances. Different approaches can also be combined to integrate docking (e.g., molecular dynamics and binding free energy estimations can be combined with docking to improve virtual screening results). Likewise, different approaches can also be applied at different phases of the screening workflow to improve docking predictions. For example, molecular dynamics could be combined with AI-based methods to identify suitable receptor conformations for docking. Then, ligand-based approaches could be applied for rescoring the predicted docking poses [25].

In particular, ligand-based approaches have been used to select suitable protein conformations for docking screenings [28]. The ability of docking to discriminate active compounds from decoys can strongly depend on the used protein structures and the similarity degree of the screened ligands with those co-crystallized in the employed target conformations [26,27]. In this regard, Broccatelli et al. recently reported a study in which different ligand-based methods have been applied for the selection of protein conformations for docking, comparing the performance of different protocols in retrieving known CDK2 inhibitors within two distinct datasets [29].

Ligand-based approaches have also been used to improve the prediction performance of docking screenings, e.g., by measuring the 3D similarity between the binding conformation predicted by docking and the experimental conformation of the ligand co-crystallized in the employed protein conformation [31].

Standing on current literature data, the combination of ligand-based and structure-based approaches allows to heavily improve the prediction power, and thus hit-rates, in virtual screening campaigns. However, it should also be noted that the possibility to apply ligand-centered methods in tandem with docking could be explored solely for those targets that have at least one reported co-crystallized ligand. Structure-based approaches, such as molecular dynamics and binding free energy estimations, have also widely been used in combination with docking to improve virtual screening results. In particular, MD allows to evaluate residues flexibility in the target binding site, as well as to explore larger conformational changes potentially accessible to a given protein. Therefore, it represents an efficient tool to identify receptor conformations for docking and to evaluate the stability of the predicted complexes. The possibilities offered by MD in prospective in silico screening are particularly appealing for flexible targets with a limited number of reported crystallographic conformations. An example of this comes from a study of Wang et al. , who have performed classical MD simulations in explicit solvent to evaluate the stability of the α-helical structure of amyloid β42 (Aβ42), thus identifying a representative protein conformation to perform virtual screening of commercially available compounds. This approach allowed the selection of a set of compounds to be experimentally validated, five of them showing inhibition of Aβ42 aggregation in the micromolar range. Moreover, one of the identified hits also displayed inhibition of BACE1, which plays a key role in the pathogenesis of Alzheimer's disease. In this study, in particular, the authors firstly performed MD simulations on three flexible targets (the purine nucleoside phosphorylase PNP, the A2A receptor, and the ABL1 tyrosine-protein kinase) in search of novel protein conformations. Then, they performed clustering via the K-medoids method on the calculated molecular dynamics trajectories to identify MD-derived representative conformations of the investigated targets. Finally, the performance of the FLAP docking program in discriminating active from inactive compounds extracted from DUD-e, which is a database useful to benchmark and validate docking protocols, was assessed. LDA was used to automatically select the best combination of protein templates among MD-derived representative and experimentally observed structures yielding the best screening results. Altogether, the discussed examples demonstrated how the inclusion of classical MD in docking-based protocols could improve virtual screening performances, especially when dealing with highly flexible targets. More advanced enhanced sampling techniques, such as umbrella sampling, meta dynamics [16,23.35], and replica exchange MD , can also be applied to identify protein conformations for docking screening. Indeed, these techniques, which allow exploring a protein conformational landscape far larger with respect to that of standard MD simulations, have already been applied to study protein flexibility and function and to identify additional binding pockets that could be exploited for the design of novel inhibitors. However, it should be noted that the application of these advanced methods is computationally more demanding with respect to standard MD.

Combinations of docking with standard molecular dynamics and binding free energy estimations have also been recently explored to account for protein flexibility and to improve virtual screening predictions, respectively. In fact, results of currently available docking algorithms might be affected by poor conformational sampling. Moreover, they might provide inaccurate binding energy estimations derived by approximate scoring functions [21,28,34]. Indeed, several scoring functions based on different algorithms and concepts, which can be classified into empirical, knowledge-based, and force field-based, have been developed for docking so far. However, all of them employ a series of mathematical functions with approximations that do not accurately take into account some thermodynamic elements of the binding energy to allow the fast prediction of ligand-target complex affinity. Several approaches have been adopted to account for these issues so far.

The more advanced and computationally expensive free energy prediction methods Free Energy Perturbation (FEP), Thermodynamic Integration (TI), and funnel metadynamics can also be used for the post-processing of docking results. More recently, a method that combines MD and TI and was able to provide accurate binding affinities. The performance of their protocol was validated on five well-characterized proteins involved in several physiological processes. However, although the latter approaches are more accurate than docking scoring functions, or even other free energy methods as MM-PBSA and MM-GBSA, in predicting ligand-protein affinity, they are computationally expensive, therefore potentially less

suitable for the screening of large libraries of compounds. Very recently, statistical and Artificial Intelligence approaches have also gained a foothold in drug discovery. In fact, these methods allow to easily exploiting the ever-growing source of information contained in publicly available structural, chemical, and bioactivity databases, leading to more accurate binding affinity predictions. In particular, machine learning (ML) approaches, including Random Forest (RF) and Support Vector Machines (SVM), have been applied for improving the docking-based binding affinity predictions.[36,37]

Reverse Screening for Target

Docking has also been recently used for a variety of other purposes in drug discovery. In particular, Reverse Docking (RD), which allows predicting the biological targets of a molecule of interest, represents a valuable approach for computational target fishing and profiling.[35]

Several docking approaches and algorithms are available to enable the reverse screening of a ligand towards a library of protein structures and to assess their binding affinity. However, the application of these approaches requires suitable libraries of targets. Indeed, several databases are currently available to help performing RD screenings. Among one of the most known databases to facilitate computational target identification is PDTD [34], which provides information about protein structures, diseases, biological functions, and drugs. Moreover, tailored libraries of targets can also be manually built upon publicly available databases of crystal structures and binding pockets, such as the Protein Data Bank (PDB), sc-PDB, Pocketome, and Therapeutic Target Database (TTD). In particular, the PDB and TTD databases represent well-known reservoirs of information developed to help facilitating computational, molecular and structural biology, and to provide data about targets and diseases, respectively. The sc-PDB and Pocketome databases were instead developed for comparing protein cavities, better describing the ligand-protein pharmacophoric properties and for target identification via pocket-based virtual screening, and to benchmark docking screenings, respectively. Although these libraries of targets were not specifically developed for target fishing and profiling, they allow covering large structural spaces of the known proteome. However, it should be noted that the preparation of such libraries is a time-consuming task because each structure in the databases requires to be properly prepared for the docking calculations [20].

Prediction of Adverse Drug Reactions

The early identification of drug side effects is of high interest in drug discovery. In fact, it is well known that most of the drug candidates fail clinical trials because of side effects deriving from unexpected interactions with off-targets. Moreover, post-marketing side effect analyses on approved drugs (i.e., pharmacovigilance) are also important because they allow revealing potential safety risks that often could not be detected within clinical trials. Several computational approaches are currently available to assist this task. However, most of them require a satisfactory amount of bioactivity data or of already reported adverse effects as an input for the model training. Interestingly, molecular docking needs solely the structural information of the targets to perform its predictions. Therefore, it represents a valuable approach to predict potential side effects of compounds at early phases of clinical and pre-clinical developments, or on marketed drugs with not yet reported exhaustive drug labels and bioactivity records. Indeed, applications of RD screening for identifying drug adverse effects have already been reported in the literature. [26,27]

Polypharmacology

To avoid potentially harmful side effects, the pharmaceutical industry focused on the development of highly selective drugs. However, the high attrition rates in the late stages of clinical trials due to a lack of therapeutic efficacy have moved modern drug design towards polypharmacology, which refers to the identification of ligands that hit a set of selected, therapeutic-relevant targets. In this context, molecular docking can provide valuable opportunities because it allows the identification of chemical scaffolds that efficiently and simultaneously bind to a pool of selected targets of interest. Indeed, several studies related to the use of docking for the design of novel multi-target ligands have already been reported. Moreover, its utility for de novo poly pharmacology design has also been reviewed. The design of multi-target ligands on rational grounds is challenging .Moreover, the selection of protein conformations to be used for docking can heavily affect the success of the design .This is especially true when dealing with targets with structurally distant binding sites. Considering how difficult it can be to design multi-target ligands, docking is now generally applied in combination with other *in-silico* approaches. In particular, several studies reporting the identification of multi-target ligands are based on the combination of docking screening with pharmacophore modeling .For example, we recently reported the identification of the first Hsp90/B-Raf dual inhibitors, demonstrating that sub-structure pre-filtering and pharmacophore-guided docking can be efficiently combined to search for polypharmacology ligands that bind to structurally unrelated targets. However, workflows integrating docking with other in silico techniques have also been pursued for de novo multi-target drug design and polypharmacology in general.[15,16,17]

Drug Repositioning

Drug repositioning, or repurposing, represents an established drug discovery approach that allows identifying novel therapeutic uses for already approved drugs, candidate compounds under clinical evaluation, natural products, or already synthesized ligands in general. Given the wealth of information reported on ligands, targets and diseases into publicly available databases, increasing efforts have been made on the application of in silico repositioning-based discovery strategies over the last decades. Indeed, in silico repositioning approaches have already demonstrated to provide novel valuable opportunities for drug discovery and development.[18,20,21]

Conclusion:

Modalities by which docking is used to assist the different tasks of drug discovery have also changed along the years. In particular, although it was initially developed and used as a standalone method, docking is now mostly employed in combination with other computational approaches within integrated workflows. This allows to overcome some of the most relevant intrinsic limitations characterizing molecular docking, such as the non-exhaustive conformational sampling and the use of approximate scoring functions. The application of combined approaches usually results in improved prediction performances and allows to better exploit the information coming from different sources. Indeed, applications of combined workflows, including docking, have been explored to assist different tasks of drug discovery. For example, docking has been used in tandem with ligand-based, molecular dynamics, binding free energy calculations, and AI approaches to improve the prediction performances in de novo virtual screening, as well as to assist target fishing, ADRs prediction, polypharmacology, and drug repurposing, as discussed.

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References

1. Sliwoski G., Kothiwale S., Meiler J., Lowe E.W. Computational methods in drug discovery. Pharmacol. Rev. 2014;66:334–395. doi: 10.1124/pr.112.007336. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Song C.M., Lim S.J., Tong J.C. Recent advances in computer-aided drug design. Brief. Bioinform. 2009;10:579–591. doi: 10.1093/bib/bbp023. [PubMed] [CrossRef] [Google Scholar]
3. Macalino S.J.Y., Gosu V., Hong S., Choi S. Role of computer-aided drug design in modern drug discovery. Arch. Pharm. Res. 2015;38:1686–1701. doi: 10.1007/s12272-015-0640-5. [PubMed] [CrossRef] [Google Scholar]
4. D'Agostino D., Clematis A., Quarati A., Cesini D., Chiappori F., Milanesi L., Merelli I. Cloud Infrastructures for In Silico Drug Discovery: Economic and Practical Aspects. Biomed Res. Int. 2013;2013:138012. [PMC free article] [PubMed] [Google Scholar]
5. Jorgensen W.L. The Many Roles of Computation in Drug Discovery. Science. 2004;303:1813–1818. doi: 10.1126/science.1096361. [PubMed] [CrossRef] [Google Scholar]
6. Kapetanovic I.M. Computer-aided drug discovery and development (CADDD): In silico-chemico-biological approach. Chem. Biol. Interact. 2008;171:165–176. doi: 10.1016/j.cbi.2006.12.006. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
7. Kitchen D.B., Decornez H., Furr J.R., Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nat. Rev. Drug Discov. 2004;3:935–949. doi: 10.1038/nrd1549. [PubMed] [CrossRef] [Google Scholar]
8. DesJarlais R.L., Sheridan R.P., Dixon J.S., Kuntz I.D., Venkataraghavan R. Docking flexible ligands to macromolecular receptors by molecular shape. J. Med. Chem. 1986;29:2149–2153. doi: 10.1021/jm00161a004. [PubMed] [CrossRef] [Google Scholar]
9. Levinthal C., Wodak S.J., Kahn P., Dadivanian A.K. Hemoglobin interaction in sickle cell fibers. I: Theoretical approaches to the molecular contacts. Proc. Natl. Acad. Sci. USA. 1975;72:1330–1334. doi: 10.1073/pnas.72.4.1330. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
10. Goodsell D.S., Olson A.J. Automated docking of substrates to proteins by simulated annealing. Proteins. 1990;8:195–202. doi: 10.1002/prot.340080302. [PubMed] [CrossRef] [Google Scholar]
11. Salemme F.R. An hypothetical structure for an intermolecular electron transfer complex of cytochromes c and b5. J. Mol. Biol. 1976;102:563–568. doi: 10.1016/0022-2836(76)90334-X. [PubMed] [CrossRef] [Google Scholar]
12. Wodak S.J., Janin J. Computer analysis of protein-protein interaction. J. Mol. Biol. 1978;124:323–342. doi: 10.1016/0022-2836(78)90302-9. [PubMed] [CrossRef] [Google Scholar]
13. Kuntz I.D., Blaney J.M., Oatley S.J., Langridge R., Ferrin T.E. A geometric approach to macromolecule-ligand interactions. J. Mol. Biol. 1982;161:269–288. doi: 10.1016/0022-2836(82)90153-X. [PubMed] [CrossRef] [Google Scholar]
14. Kuhl F.S., Crippen G.M., Friesen D.K. A combinatorial algorithm for calculating ligand binding. J. Comput. Chem. 1984;5:24–34. doi: 10.1002/jcc.540050105. [CrossRef] [Google Scholar]
15. DesJarlais R.L., Sheridan R.P., Seibel G.L., Dixon J.S., Kuntz I.D., Venkataraghavan R. Using shape complementarity as an initial screen in designing ligands for a receptor binding site of known three-dimensional structure. J. Med. Chem. 1988;31:722–729. doi: 10.1021/jm00399a006. [PubMed] [CrossRef] [Google Scholar]
16. Warwicker J. Investigating protein-protein interaction surfaces using a reduced stereochemical and electrostatic model. J. Mol. Biol. 1989;206:381–395. doi: 10.1016/0022-2836(89)90487-7. [PubMed] [CrossRef] [Google Scholar]
17. Jiang F., Kim S.H. "Soft docking": Matching of molecular surface cubes. J. Mol. Biol. 1991;219:79–102. doi: 10.1016/0022-2836(91)90859-5. [PubMed] [CrossRef] [Google Scholar]
18. Meng X.Y., Zhang H.X., Mezei M., Cui M. Molecular docking: A powerful approach for structure-based drug discovery. Curr. Comput. Aided. Drug Des. 2011;7:146–157. doi: 10.2174/157340911795677602. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
19. Amaro R.E., Baudry J., Chodera J., Demir Ö., McCammon J.A., Miao Y., Smith J.C. Ensemble Docking in Drug Discovery. Biophys. J. 2018;114:2271–2278. doi: 10.1016/j.bpj.2018.02.038. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
20. Abagyan R., Totrov M. High-throughput docking for lead generation. Curr. Opin. Chem. Biol. 2001;5:375–382. doi: 10.1016/S1367-5931(00)00217-9. [PubMed] [CrossRef] [Google Scholar]
21. Carlson H.A. Protein flexibility and drug design: how to hit a moving target. Curr. Opin. Chem. Biol.

2002;6:447–452. doi: 10.1016/S1367-5931(02)00341-1. [PubMed] [CrossRef] [Google Scholar]
22. Greer J., Bush B.L. Macromolecular shape and surface maps by solvent exclusion. Proc. Natl. Acad. Sci. USA. 1978;75:303–307. doi: 10.1073/pnas.75.1.303. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
23. Rarey M., Kramer B., Lengauer T., Klebe G. A fast flexible docking method using an incremental construction algorithm. J. Mol. Biol. 1996;261:470–489. doi: 10.1006/jmbi.1996.0477. [PubMed] [CrossRef] [Google Scholar]
24. Rosenfeld R., Vajda S., DeLisi C. Flexible docking and design. Annu. Rev. Biophys. Biomol. Struct. 1995;24:677–700. doi: 10.1146/annurev.bb.24.060195.003333. [PubMed] [CrossRef] [Google Scholar]
25. Sherman W., Beard H.S., Farid R. Use of an induced fit receptor structure in virtual screening. Chem. Biol. Drug Des. 2006;67:83–84. doi: 10.1111/j.1747-0285.2005.00327.x. [PubMed] [CrossRef] [Google Scholar]
26. Leach A.R. Ligand docking to proteins with discrete side-chain flexibility. J. Mol. Biol. 1994;235:345–356. doi: 10.1016/S0022-2836(05)80038-5. [PubMed] [CrossRef] [Google Scholar]
27. Ring C.S., Sun E., McKerrow J.H., Lee G.K., Rosenthal P.J., Kuntz I.D., Cohen F.E. Structure-based inhibitor design by using protein models for the development of antiparasitic agents. Proc. Natl. Acad. Sci. USA. 1993;90:3583–3587. doi: 10.1073/pnas.90.8.3583. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
28. Coupez B., Lewis R.A. Docking and scoring--theoretically easy, practically impossible? Curr. Med. Chem. 2006;13:2995–3003. [PubMed] [Google Scholar]
29. Ain Q.U., Aleksandrova A., Roessler F.D., Ballester P.J. Machine-learning scoring functions to improve structure-based binding affinity prediction and virtual screening. Wiley Interdiscip. Rev. Comput. Mol. Sci. 2015;5:405–424. doi: 10.1002/wcms.1225. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
30. Guedes I.A., Pereira F.S.S., Dardenne L.E. Empirical scoring functions for structure-based virtual screening: Applications, critical aspects, and challenges. Front. Pharmacol. 2018;9:1089. doi: 10.3389/fphar.2018.01089. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
31. Elokely K.M., Doerksen R.J. Docking challenge: Protein sampling and molecular docking performance. J. Chem. Inf. Model. 2013;53:1934–1945. doi: 10.1021/ci400040d. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
32. Pantsar T., Poso A. Binding affinity via docking: fact and fiction. Molecules. 2018;23:1899. doi: 10.3390/molecules23081899. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
33. Salmaso V., Moro S. Bridging molecular docking to molecular dynamics in exploring ligand-protein recognition process: An overview. Front. Pharmacol. 2018;9:923. doi: 10.3389/fphar.2018.00923. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
34. De Vivo M., Masetti M., Bottegoni G., Cavalli A. Role of molecular dynamics and related methods in drug discovery. J. Med. Chem. 2016;59:4035–4061. doi: 10.1021/acs.jmedchem.5b01684. [PubMed] [CrossRef] [Google Scholar]
35. Alonso H., Bliznyuk A.A., Gready J.E. Combining docking and molecular dynamic simulations in drug design. Med. Res. Rev. 2006;26:531–568. doi: 10.1002/med.20067. [PubMed] [CrossRef] [Google Scholar]
36. Bard J., Ercolani K., Svenson K., Olland A., Somers W. Automated systems for protein crystallization. Methods. 2004;34:329–347. doi: 10.1016/j.ymeth.2004.03.029. [PubMed] [CrossRef] [Google Scholar]
37. Gavira J.A. Current trends in protein crystallization. Arch. Biochem. Biophys. 2016;602:3–11. doi: 10.1016/j.abb.2015.12.010. [PubMed] [CrossRef] [Google Scholar]
38. Dauter Z., Wlodawer A. Progress in protein crystallography. Protein Pept. Lett. 2016;23:201–210. doi: 10.2174/0929866523666160106153524. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
39. Grimes J.M., Hall D.R., Ashton A.W., Evans G., Owen R.L., Wagner A., McAuley K.E., von Delft F., Orville A.M., Sorensen T., et al. Where is crystallography going? Acta Crystallogr. Sect. D. 2018;74:152–166. doi: 10.1107/S2059798317016709. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
40. Durrant J.D., McCammon J.A. Molecular dynamics simulations and drug discovery. BMC Biol. 2011;9:71. doi: 10.1186/1741-7007-9-71. [PMC free article] [PubMed] [CrossRef] [Google Scholar].

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Review Article

Microwave assisted synthesis of organic compounds in drug design & process chemistry

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ABSTRACT

Green Chemistry with its twelve principles would like to see changes in the conventional chemical synthesis and the use of less toxic starting materials. Green Chemistry would like to increases the efficiency of synthetic methods, to use less toxic solvents, reduce the stages of the synthetic routes and minimize waste as far as practically possible. In this way, chemical synthesis will be part of the effort for sustainable development. Microwave assisted synthesis has revolutionized chemical synthesis. Small molecules can be built in a fraction of the time required by conventional methods. In conventional heating methods oil bath or hot plate are used as a source of heat to a chemical reaction Microwave irradiation is widely used as a source of heating in chemical synthesis. The basic mechanisms observed in microwave assisted synthesis are dipolar polarization and conduction. Microwave-assisted synthesis provides clean synthesis with the advantage of enhanced reaction rates, higher yields, greater selectivity, and economic for the synthesis of a large number of organic molecules, have provided the momentum for many chemists to switch from conventional heating method to microwave assisted chemistry. Microwave-assisted synthesis is rapidly becoming the method of choice in modern chemical synthesis and drug discovery. The present article will highlight the applications of microwave-assisted synthesis in organic synthesis, inorganic synthesis, polymer synthesis, nanotechnology, peptide synthesis and discuss the basic mechanism involved in microwave heating.

Key words: Green Chemistry, Microwave-assisted synthesis

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Introduction

The term Green Chemistry is becoming the worldwide term used to describe the design of chemical products and processes that reduce or eliminate the use or generation of substances hazardous to human health.[1] The term was coined by the US Environmental Protection Agency and has been defined as: the utilization of a set of principles that reduce or eliminate the use or generation of hazardous substances in the design, manufacture and application of chemical products[2,3] This goal can be achieved by use of twelve principles of Green Chemistry which are as follows.

(1) It is better to prevent waste than to treat or clean up waste after it has been created.

(2) Synthetic methods should be designed to maximize the incorporation of all materials used in the process, into the final product.

(3) Synthetic methods should be designed to use and generate less hazardous/toxic chemicals.

(4) Chemical products should be designed to affect their desired function while minimizing their toxicity.

(5) The use of solvents and auxiliary substances should be made unnecessary wherever possible and innocuous when used.

(6) Energy requirements of chemical processes should be minimized, and synthetic methods should be conducted at ambient temperature and pressure if possible.

(7) A raw material should be renewable rather than depleting whenever practicable.

(8) Unnecessary derivatization should be minimized or avoided if possible.

(9) Catalytic reagents are superior to stoichiometric reagents.

(10) Chemical products should be designed so that at the end of their function they break down into innocuous degradation products that do not persist in the environment.

(11) Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

(12) Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents.[4-6] Organic synthesis on a large scale involves the use of basic chemical ingredients from the petrochemical sector and catalysts; and after the end of the reaction, separation, purification, storage, packaging, distribution etc. Conventional methods of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents or reagents. During these processes there are many problems of health and

safety for workers in addition to the environmental problems caused by their use and disposition as waste.[80] Green Chemistry would like to increases the efficiency of synthetic methods, to use less toxic solvents, reduce the stages of the synthetic routes and minimize waste as far as practically possible. Microwave synthesis is considered as an important approach toward green chemistry, because this technique is more eco-friendly.[9,10] Due to its ability to couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.[11,12]

Microwave chemistry is the science of applying microwave radiation to chemical reactions. Microwave synthesis represents a major breakthrough in synthetic chemistry methodology; a dramatic change in the way chemical synthesis is performed. Conventional heating, long known to be inefficient and time consuming, has been recognized to be creatively limiting too.[13] Microwave synthesis gives the chemists more time to expand their creativity, test new theories and develop new processes. Instead of spending hours or even days synthesizing a single compound, chemists can now perform the same reaction in minutes. The problem associated with waste disposal of solvents has been overcome by performing reactions without a solvent under microwave irradiation.[14] Coupling of microwave irradiation with the use of mineral-supported catalysed reactions, under solvent-free conditions, provides clean chemical processes with the advantage of enhanced reaction rates, higher yields, greater selectivity, and greater ease of manipulation.[15,16] Thus microwave synthesis acts as a potential tool for green chemistry. Microwave irradiation provides an alternative to the conventional methods, for heating or introducing energy into the system. It utilizes the ability of mobile electric charges present in liquid or conducting ions in solid to transform electromagnetic energy into heat. Microwave radiations are electromagnetic waves.[17] In the electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radio waves. Microwaves have wavelength of 1 mm to 1 mcorrespond-ing to frequencies between 0.3 and 300 GHz. Telecommunication and microwave radar equipment occupy many of the band frequencies in this region.[18] Microwave dielectric heating; uses the ability of some liquids and solids to transform electromagnetic radiation into heat to drive chemical reactions. This technology opens up new opportunities to the synthetic chemist in the form of new reactions that are not possible using conventional heating.[19,20]

1.1 Mechanism of Microwave Heating

All the materials are not susceptible to microwave heating as response of various materials to microwave radiation is diverse.[21] Based on their response to microwaves, materials can be broadly classified as-
(1) Materials that are transparent to microwaves, e.g. sulphur
(2) Materials that reflect microwaves, e.g. copper
(3) Materials that absorb microwaves, e.g. water
Microwave absorbing materials are of utmost important for microwave chemistry and three main different mechanisms are involved for their heating namely

1. Dipolar
2. polarization,

Conduction mechanism and Interfacial polarization.

1.2 Dipolar Polarization

For a substance to generate heat when irradiated with microwaves it must possess a dipole-moment. It is the electric field component of the microwave radiation, rather than magnetic field component that is responsible for heating, when a dipole tries to reorient itself with respect to an alternating electric field; it loses energy in the form of heat, by molecular friction.[22] Dipolar polarization can generate heat by either interaction between polar solvent molecules such as water, methanol and ethanol; or interaction between polar solute molecules such as ammonia and formic acid. The key requirement for dipolar polarization is that the frequency range of the oscillating field should be appropriate to enable adequate inter-particle interaction. If the frequency range is very high, intermolecular forces will stop the motion of a polar molecule before it tries to follow the field, resulting in inadequate inter-particle interaction. On the other hand, if the frequency range is low, the polar molecule gets sufficient time to align itself in phase with the field. Microwave radiation has the appropriate frequency (0.3-30 GHz) to oscillate polar particles and enable enough inter-particle interaction. This makes it an ideal choice for heating polar solutions.[23]

1.3 Conduction Mechanism:

The conduction mechanism generates heat through resistance to an electric current. The oscillating electromagnetic field generates an oscillation of electrons or ions in a conductor, resulting in an electric current. This current faces internal resistance, which heats the conductor. A solution containing ions, or even a single isolated ion with a hydrogen bonded cluster, in the sample the ions will move through the solution under the influence of an electric field, resulting in expenditure of energy due to able to believe that the more polar the solvent, the more readily the microwave irradiation is absorbed and the higher the temperature obtained. Where the irradiated sample is an electrical conductor, the charge carriers (electrons, ions, etc.) are moved through the material under the influence of the electric field, resulting in a polarization. These induced currents will cause heating in the sample due to any electrical resistance. Major limitation of the method is that it is not applicable for materials with high conductivity, since such materials reflect most of the energy that falls on them.[24]

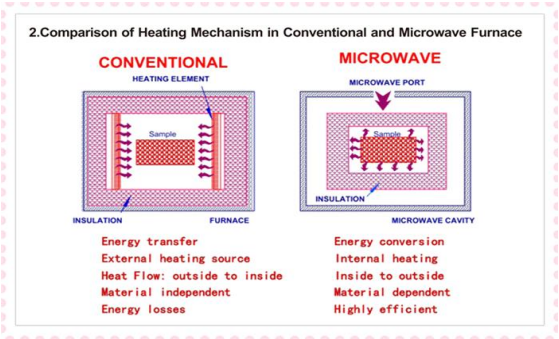
1.4 Interfacial Polarization:

The interfacial polarization method can be considered as a combination of both the conduction and dipolar polarization mechanisms. It is important for heating systems that comprise a conducting material dispersed in a nonconducting material. For example, consider the dispersion of metal particles in sulphur. Sulphur does not respond to microwaves and metals reflect most of the microwave energy they are exposed to, but combining the two makes them a good microwave-absorbing material. However, for this to take place, metals have to be used in powder form.

This is because, unlike a metal surface, metal powder is a good absorber of microwave radiation. It absorbs radiation and is heated by a mechanism that is similar to dipolar polarization. The environment of the metal powder acts as a solvent for polar molecules and restricts the motion of ions by forces that are equivalent to inter-particle interactions in polar solvents. These restricting forces under the effect of an oscillating field induce a phase lag in the motion of ions, resulting in random motion of ions, and ultimately heating of the system.[25]

1.5 Microwave versus Conventional Synthesis

Conventional synthesis usually involves the use of a furnace or oil bath which heats the walls of the reactors by convection or conduction . The core of the sample takes much longer to achieve the target temperature. This is a slow and inefficient method for transferring energy into the reacting system. On the other hand in microwave assisted synthesis microwave penetrates inside the material and heat is generated through direct microwave-material Interaction. Microwave-assisted synthesis has several advantages over conventional reactions in that the microwave allows for an increase in reaction rate, rapid reaction optimization, and rapid analogue synthesis. It also uses both less energy and solvent, and it enables difficult compound synthesis. Specifically, microwave synthesis has the potential to impact upon medicinal chemistry efforts in at least three major phases of the drug discovery process: lead generation, hit-to-lead efforts, and lead optimization. Microwave chemistry can be carried out very efficiently in a parallel format using dedicated rotors or microliter plate systems. Several hundred reactions can be performed in a single microwave experiment using multimode microwave devices. Researchers have shown the benefits gained by employing microwave heating in tandem with combinatorial chemistry. A few reactions which were carried out using microwave heating and compared with conventional heating indicating time and energy efficiency of the technique are compiled.[26,27]



.Fig.1. Comparison between conventional and microwave

2. Microwave Synthesis Apparatus

The apparatus for microwave assisted synthesis include; single-mode microwave ovens, and multi-mode microwave ovens.

Table.1. Comparison of reaction times using microwave versus conventional heating

Compound synthesized Reaction time	Microwave Reaction time	Conventional time
Methyl benzoate	5 minutes	8 hrs.
4-nitrobenzyl ester	2 minutes	15 hrs
Zeolite synthesis	30 second	60 hrs
Cubanite	03 minutes	03 days
NaAlH4	08 hrs	02 hrs

2.1 Single-Mode Microwave Apparatus

The differentiating feature of a single-mode apparatus is its ability to create a standing wave pattern. This interface generates an array of nodes where microwave energy intensity is zero, and an array of antinodes where the magnitude of microwave energy is at its highest. One of the limitations of single-mode apparatus is that only one vessel can be irradiated at a time. However, the apparatus is user friendly.[28] An advantage of single-mode apparatus is their high rate of heating. This is because the sample is always placed at the antinodes of the field, where the intensity of microwave radiation is the highest. These apparatus can process volumes ranging from 0.2 to about 50 ml under sealed-vessel conditions, and volumes around 150 ml under open-vessel conditions. Single-mode microwave ovens are currently used for small-scale drug discovery, automation and combinatorial chemical applications.

2.2 Multi-Mode Microwave Apparatus:

An essential feature of a multi-mode apparatus is the deliberate avoidance of generating a standing wave pattern inside it. The goal is to generate as much chaos as possible inside the apparatus.[29] The greater the chaos, the higher is the dispersion of radiation, which increases the area that can cause effective heating inside the apparatus. As a result, a multi-mode microwave heating apparatus can accommodate a number of samples simultaneously for heating, unlike single-mode apparatus where only one sample can be irradiated at a time. Owing to this characteristic, a multimode heating apparatus is used for bulk heating and carrying out chemical analysis processes such as ashing, extraction, etc.In large multi-mode apparatus, several litres of reaction mixture can be processed in both open and closed-vessel conditions. A major limitation of multi-mode apparatus is that, heating samples cannot be controlled efficiently because of lack of temperature uniformity.[30]

2.3 Benefits of Microwave Assisted Synthesis

Microwaves can accelerate the rate of reaction, provide better yields and higher purity, uniform and selective heating with lower energy usage, achieve greater reproducibility of reactions and help in developing convenient and cleaner synthetic routes.[31] The main advantages of microwave assisted organic synthesis are:

2.4 Faster Reaction

Based on experimental data it has been found that microwave-enhanced chemical reaction rates can be faster than those of conventional heating methods by as much as 1,000-fold.[32] The microwave can use higher temperatures than conventional heating system, and consequently the reactions are completed in few minutes instead of hours, for instance, synthesis of fluorescein, which usually takes about 10 hours by conventional heating methods, can be conducted in only 35- minutes by means of microwave heating.

2.5 Better Yield and Higher Purity

Less formation of side products are observed using microwave irradiation, and the product is recovered in higher yield. Consequently, also the purification step is faster and easier. [32]

For example- microwave synthesis of aspirin results in an increase in the yield of the reaction, from 85 % to 97%.

2.6 Energy Saving

Heating by means of microwave radiation is a highly efficient process and results in significant energy saving. This is primarily because microwaves heat up just the sample and not the apparatus, and therefore energy consumption is less.[33]

2.7 Uniform and Selective Heating

In conventional heating, the walls of the oil bath get heated first, and then the solvent. As a result of this distributed heating in an oil bath, there is always a temperature difference between the walls and the solvent. In the case of microwave heating, only the solvent and the solute particles are excited, which results in uniform heating of the solvent. Selective heating is based on the principle that different materials respond differently to microwaves. Some materials are transparent whereas others absorb microwaves.[34]

2.8 Green Synthesis

Reactions conducted using microwaves are cleaner and more eco-friendly than conventional heating methods. Microwaves heat the compounds directly; therefore, usage of solvents in the chemical reaction can be reduced or eliminated. Synthesis without solvent, in which reagents are absorbed on mineral support, has a great potential as it offers an eco-friendly green protocol in

synthesis. The use of microwaves has also reduced the amount of purification required for the end products of chemical reactions involving toxic-reagents.[30,42]

2.9 Reproducibility

Reactions with microwave heating are more reproducible compared to the conventional heating because of uniform heating and better control of process parameters. The temperature of chemical reactions can also be easily monitored.[35]

3. Limitations of Microwave Assisted Synthesis

The yield obtained by using microwave apparatus available in the market is limited to a few grams. Although there have been developments in the recent past, relating to the scalability15 of microwave equipment, there is still a gap that needs to be spanned to make the technology scalable. The use of microwaves as a source of heating has limited applicability for materials that absorb them. Microwaves cannot heat materials such as sulphur, which are transparent to their radiation. Improper use of microwave heating for rate enhancement of chemical reactions involving radioisotopes may result in uncontrolled radioactive decay. Certain problems, with dangerous end results, have also been observed while conducting polar acid-based reactions, for example, microwave irradiation of are action involving concentrated sulphuric acid may damage the polymer vessel used for heating. Conducting microwave reactions at highpressure conditions may also result in uncontrolled reactions and cause explosions. Health hazards related to microwaves are caused by the penetration of microwaves. While microwaves operating at a low frequency range are only able to penetrate the human skin, higher frequency-range microwaves can reach body organs. Research has proven that on prolonged exposure microwaves may result in the complete degeneration of body tissues and cells. It has also been established that constant exposure of DNA to high frequency microwaves during a biochemical reaction may result in complete degeneration of the DNA strand.[36]

4. Enhanced Microwave Synthesis

Recently, an alternative method for performing microwave assisted organic reactions, termed Enhanced Microwave Synthesis, has been examined. By externally cooling the reaction vessel with compressed air, while simultaneously administering microwave irradiation, more energy can be directly applied to the reaction mixture.[37] EMS ensures that a high, constant level of microwave energy is applied. Simultaneous cooling enables a greater amount of microwave energy to be introduced into a reaction, while keeping the reaction temperature low. This results in significantly greater yields and cleaner chemistries. EMS was employed in the synthesis of a variety of α-keto amides (Scheme 1) to support a protease inhibitor discovery project. This may eventually lead to improved treatments for stroke, Alzheimer's disease, and muscular dystrophy. Under conventional heating conditions, this took between 2 to 6 hours for completion; whereas under optimized EMS conditions, the two steps were completed in 2 min and in 21-74% yields.

5. Applications Of Microwave Assisted Synthesis

Application of microwave irradiation in chemical synthesis involves its use in the acceleration of chemical synthesis.[38] Microwave-enhanced synthesis results in faster reactions, higher yields, and increased product purity. In addition, due to the availability of high-capacity microwave apparatus, the yields of the experiments have now easily scaled up from milligrams to kilograms, without the need to alter

reaction parameters. Microwave-assisted synthesis can be suitably applied to the drug discovery process.

5.1 Organic Synthesis

Microwave-assisted organic synthesis has been the foremost and one of the most researched applications of microwaves in chemical reactions. Literature survey reveals that scientists have successfully conducted a large range of organic reactions. These include Diels-Alder reaction, Ene reaction, Heck reaction, Suzuki reaction, Mannich reaction, Hydrogenation of [beta]-lactams, Hydrolysis, Dehydration, Esterification, Cycloaddition reaction, Epoxidation, Reductions, Condensations, Cyclisation reactions, Protection and deprotection, Microwave-assisted organic synthesis is being widely applied in the pharmaceuticals industry, particularly for developing compounds in the lead optimization phase of drug discovery and development. In this phase, chemists use diverse synthetic techniques to develop candidate drugs from lead compounds. Based on reaction conditions, organic synthesis reactions can be conducted in the following techniques.[39]

5.2 Microwave-Assisted Organic Synthesis at Atmospheric Pressure:

Microwave-assisted organic synthesis can be most conveniently conducted at atmospheric pressure in reflux conditions, for example, oxidation of toluene to benzoic acid with KMnO4 under normal conditions of refluxing takes 10-12 hours compared to reaction in microwave conditions, which takes only 5 minutes shows an increased yield of 200 % for the oxidation of hexanenitrile and 150 % for the hydrolysis of cyclohexene when the reaction is conducted in the microwave batch reactor.

Table.2. Heterogeneous reactions under microwave and classical heating

Chemical reaction	Time (minutes)	MW Yield (%)	Classical Yield (%)
Hydrolysis of hexanenitrile	60	40	26
Oxidation of cyclohexene	60	26	12

5.3 Microwave-Assisted Organic Synthesis At Elevated Pressure

Microwaves can be used to directly heat the solvents in sealed microwave-transparent containers. The sealed container helps in increasing the pressure in the reactor, which facilitates the reaction that will take place at much higher temperatures.[38,39] This results in a substantial increase in the reaction rate of microwave assisted organic synthesis.

5.4 Microwave-Assisted Organic Synthesis under Solvent Free Conditions

Microwave-assisted solvent-free organic synthesis has been developed as an environmentally friendly process as it combines the selectivity associated with most reactions carried out under microwaves with solvent and waste-free procedures in which organic solvents are avoided throughout all stages.[37,38] The solvent-free organic syntheses are of three types:

(i) Reactions using neat reactants

(ii) Reactions using solid-liquid phase transfer catalysis (PTC)

(iii) Reactions using solid mineral supports.

The microwave-assisted reaction could be completed within two to three minutes, compared to conventional oil-bath heating at 75 °C for 40 hours.

5.5 Inorganic Synthesis

A variety of materials such as carbides, nitrides, complex oxides, silicides, zeolites, apatite, etc. have been synthesized using microwaves. A series of A3B and A4 type mesoporphyrinic complexes were synthesized with superior yields using microwave irradiation under solvent-free conditions. Solvent-free synthesis by microwave irradiation has been successfully applied to obtaining mesoporphyrinic compounds because the absence of solvent from the reaction environment has the effect of decreased interaction time between reactant molecules and improves the reaction yield.[40] Two new iso-structural coordination polymers with novel anionic metal-organic frameworks were synthesized using microwave-assisted technique. Microwave-assisted synthesis of pinacol boronates from aryl chlorides catalysed by a palladium/imidazolium salt system was reported.

5.6 Synthesis of Nanotechnology Products

Amongst the several methods that exist for synthesizing of nanoparticles, the use of microwave assisted synthesis has shown promise. Synthesis of silver nanoparticles from silver nitrate employing starch as the reductant as well as stabilizing agent has been carried out under direct heating, controlled heating and microwave irradiation.[39,40] The microwave irradiation was considered as better for reduction of silver ions to silver nanoparticles. It also afforded smaller particle sizes and particle size distribution. Compared to conventional methods, microwave assisted synthesis was faster and provided particles with an average particle size of 12 nm. Nanostructures with smaller sizes, narrower size distributions, and a higher degree of crystallization were obtained under microwave heating than those in conventional oil-bath heating. The gold nanoparticles have been prepared by microwave high-pressure procedure with alcohol as the reducing agent. A method has been reported for microwave-assisted non-aqueous synthesis of zinc oxide nanoparticles. Particularly the fast reaction rates, better product yields and the possibility to automatically combine different experimental parameters makes microwave assisted synthesis suitable for the studies of the influences of the reaction conditions on the morphology and sizes of zinc oxide nanoparticles particles, which determine its properties and applications. Pt/C and PtCo3O4/C nano catalysts were prepared using microwave assisted methods. The results of XRD and TEM revealed that the prepared catalysts have small and uniform shapes with high dispersion ability. The developed approach is a useful method for preparing platinum and platinum supported electro catalysts, which can be used in the field of fuel cells and other related fields. Strontium stannate

(SrSnO3) nanostructures were obtained by microwave-assisted calcination of a SrSn(OH)6 precursor powder. Compared to other conventional calcination methods mentioned in the literature, this procedure led to a remarkable decrease of the reaction time and the synthesis temperature owing to direct interaction of radiation with the material.

5.7 Polymer Synthesis

Polymer chemistry, including ceramic processing, forms the single-largest application area of microwave chemistry. The use of polar reactants in polymerization reaction results in controlled synthesis and a combination of this with direct heating of reactants makes microwave heating an
Economically viable option.[37,38] Using microwave radiation in curing has greatly increased the rate of the reactions. It has been found that the rate of a curing reaction, using microwaves, is not dependent on the power applied but on the way the pulse is applied. Controlled solvent-free synthesis and modification in polymer materials can be rapidly and effectively done with the help of microwave heating using large scale reactors The first microwave assisted organic synthesis of Poly Lactic Acid was carried out with SnOct as catalyst by using toluene as a solvent.

A microwave-assisted, rapid solid phase peptide synthesis procedure has been reported. The synthesis protocol is based on the use of cycles of pulsed microwave irradiation with intermittent cooling of the reaction during the removal of the Fmoc protecting group and during the coupling. The desired nonapeptide was obtained in highest yield and purity by employing MicroKan technology. The protocols for the synthesis of cystine-rich peptides in the presence of microwave radiation with solid phase peptide synthesis have been reported. The method is broadly applicable for a wide range of peptides using Boc-SPPS, especially for SPPS of large peptides via native chemical ligation. Microwave radiation produces peptides in high yield and with high purity, and the time for the assembly of approximately 30 amino acids peptide chains was reduced to an overnight reaction in the automated microwave-assisted synthesis. The applications of microwaves in the field of peptides and glycopeptides have been reported.

5.8 Synthesis of Radiopharmaceuticals

Microwave-assisted organic synthesis at an elevated pressure has been used in pharmaceutical industry for the synthesis of radiopharmaceuticals. During pre-clinical trials, these radiopharmaceuticals are used as tracers to generate a nuclear medical image. A multi-mode microwave oven was used in the first trial of this kind and it was observed that the rate of reaction increased substantially. This has resulted in the enhanced use of microwaves to produce radiopharmaceuticals. Advantages of microwaves include the fast reaction rates and high yield of the reaction. This can be attributed to the short half-life of reactants, for example, saving five minutes in a synthesis with carbon-11 resulted in an enhanced production rate of 15%. It has also been observed that several reactions could only be achieved by using microwaves.[40]

Conclusion

Microwave-assisted synthesis is a convenient way toward the goal of green chemistry. Microwaves irradiation can be used to in chemical synthesis as a heat source; it is very efficient and can be used to significantly reduce reaction times of numerous synthetically useful chemical transformations. Thus, microwave-assisted synthesis has advantages over conventional technology: it is more energy efficient and it can lead to improved isolated yields of products with green synthesis. The advantages of this enabling technology have, more recently, been exploited in the context of multistep total synthesis and medicinal drug discovery, and have additionally penetrated related fields such as polymer synthesis, material sciences, nanotechnology and biochemical processes. In order to achieve further development in this field, novel instruments, which give rise to reproducible performances and that constitute a minimal hazard should be used instead of the domestic microwave ovens.

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References

1. Sheldon RA,Arends I, Hanefeld U. Green Chemistry and Catalysis, Wiley, Wienheim,2007; 1-2
2. Anastas, PT, Warner JC. Green Chemistry: Theory and Practice, Oxford University Press, Oxford,2000; 2-5
3. Lancaster M. Green Chemistry: An Introductory Text,Royal Society of Chemistry, Cambridge, 2010; 1-16
4. Joshi UJ, Gokhale KM, Kanitkar AP. Green Chemistry: Need of the Hour, Indian J PharmEduc Res, 2011 45(2): 168-174
5. Clark JH, Macquarrie DJ. Handbook of Green Chemistry and Technology, first Edition, Wiley, 2002; 10-25
6. Ravichandran S,Karthikeyan E. Microwave Synthesis-A Potential Tool for Green Chemistry. Int J ChemTech Res, 2011; 3(1): 466-470
7. Krstenansky JL, I. Cotterill I. Recent advances in microwave-assisted organic syntheses, CurrOpin Drug DiscovDevel, 2000; 3(4): p. 454-461.
8. Hayes BL. Microwave Synthesis: Chemistry at the Speed of Light, CEM Pub, 2002; 11-23
9. Sekhon BS. Microwave-Assisted Pharmaceutical Synthesis: An Overview,Int J PharmTech Res, 2010; 2(1): 827-833
10. Rajak H, Mishra P. Microwave assisted combinatorial chemistry: The potential approach for acceleration of drug discovery,J SciInd Res, 2004; 63(8): 641-654
11. Wathey B, Tierney J, Lidström P, Westman J. The impact of microwave-assisted organic chemistry on drug discovery,Drug Discov Today, 2002; 7(6): 373-80.
12. Lidström P, Tierney J, Wathey B, Westman J. Microwave assisted organic synthesis—a review,Tetrahedron, 2001; 57(45): 9225-9283
13. Gabriel C, Gabriel S, Grant EH, Grant EH, Halstea BSJ, Mingos DMP. Dielectric

parameters relevant t microwave dielectric heating, ChemSoc Rev, 1998; 27(3): 213-224
14. 14. Strauss CR, Trainor RW. Developments in Microwave-Assisted Organic Chemistry, Aust J Chem, 1995; 48(10): 1665-1692
15. Langa F, Cruz P de la, Hoz A de la, Díaz-Ortiz A, Díez-Barra E. Microwave irradiation: more than just a method for accelerating reactions,ContempOrg Synth 1997; 4(5): 373-386
16. Lidström P, Westman J, Lewis A. Enhancement of combinatorial chemistry by microwave-assisted organic synthesis,Comb Chem High Throughput Screen**,** 2002;5(6): 441-458
17. Algul O, Kaessler A, Apcin Y, Yilmaz A, Jose J. Comparative studies on conventional and microwave synthesis of some benzimidazole, benzothiazole and indole derivatives and testing on inhibition of hyaluronidase. Molecules, 2008; 13(4): 736-748
18. Collins MJ Jr. Future trends in microwave synthesis,Future Med Chem, 2010; 2(2): 151-155
19. Saxena, VK, Chandra U. Microwave Synthesis: A Physical Concept,Microwave Heating, D.U. Chandra(Editor), 2011: 3-22
20. Larhed M,Hallberg A. Microwave-assisted high-speed chemistry: a new technique in drug discovery,Drug Discov Today, 2001; 6(8): 406-416
21. Lew A, Krutzik PO, Hart ME, Chamberlin AR. Increasing rates of reaction: microwave-assisted organic synthesis for combinatorial chemistry, J Comb Chem, 2002; 4(2): 95-105
22. Stadler A, Yousefi BH, Dallinger D, Walla P, Eycken EV, Kaval N, Kappe CO. Scalability of Microwave-Assisted Organic Synthesis. From Single-Mode toMultimode Parallel Batch Reactors,Org Proc Res Dev, 2003; 7(5): 707-716
23. Wilson NS, Sarko CR, Roth GP. Development and Applications of a Practical Continuous Flow Microwave Cell,Org Proc Res *Dev*, 2004; 8(3): 535-538
24. Ley SV, Baxendale IR. New tools and concepts for modern organic synthesis,Nat Rev Drug Discov, 2002, 1(8): 573-586
25. Gaba M, Dhingra N. Microwave Chemistry: General Features and Applications, Indian J PharmEduc Res, 2011; 45(2): 175-183
26. Montes I, Sanabria D, García M, Castro J, Fajardo J. Greener Approach to Aspirin Synthesis Using Microwave Irradiation, JChemEduc, 2006; 83(4): 628- 631
27. Panda J, Patro VJ, Sahoo BM, Mishra J. Green Chemistry Approach for Efficient Synthesis of Schiff Bases of Isatin Derivatives and Evaluation of Their Antibacterial Activities,J Nanopart, 2013; Article ID 549502, 5 pages
28. Mordini A, Faigl F. New Methodologies and Techniques for a Sustainable Organic Chemistry, Springer, Netherlands, 2008; 193-223
29. Loupy A, Petit A, Hamelin J, Texier-Boullet F, Jacquault P, Mathé D.New solvent free organic synthesis using focused *microwaves,Synthesis*, 1998; 9: 1213-1234
30. Krstenansky JL, Cotterill I. Recent advances in microwave-assisted organic syntheses,CurrOpin Drug DiscovDevel, 2000; 3(4): 454-461
31. Baghurst DR,Mingos DMP. Superheating effects associated with microwave dielectric heating, Journal of the Chemical Society, J ChemSoc, ChemCommun, 1992(9): 674-677
32. Surati MA, Jauhari S, Desai KR. A brief review: Microwave assisted organic reaction,Indian J PharmEducRes, 2012; 4(1): 645-661
33. Charde MS, Shukla A, Bukhariya V, Chakole RD. Areview on: a significance of microwave assist technique in green chemistry,Int J Phytopharm, 2012; 2(2): 39-50.
34. Hayes BL. Recent Advances in Microwave-Assisted Synthesis,AldrichimicaActa, 2004; 37(2): 66-76
35. Chen JJ, Deshpande SV. Rapid synthesis of α-ketoamides using microwave irradiation–simultaneou cooling method,TetrahedronLett, 2003; 44(49): 8873-8876
36. Chemat-Djenni Z, Hamada B, Chemat F. Atmospheric pressure microwave assisted heterogeneous catalytic reactions, Molecules, 2007; 12(7): 1399-1409
37. Liu Y, Lu Y, Liu P, Gao R, Yin Y. Effects of microwaves on selective oxidation of toluene to benzoi,acid over a V2O5/TiO2 system,ApplCatal *A*-Gen, 1998 170(2): 207-214
38. Gupta M, Paul S, Gupta R. General Characteristics and Applications of Microwaves in Organic Synthesis,ActaChimicaSlovenica, 2009; 56: 749-764
39. Fürstner A, Seidel G.microwave-assisted synthesis of pinacol boronates from aryl chlorides catalyzed by a palladium/imidazolium salt system, Org Lett, 2002; 4(4): 541-543
40. Lin Z, Wragg DS, Morris RE. Microwave-assisted synthesis of anionic metal-organic frameworks under ionothermal conditions, Chem Commun, 2006(19): 2021-2023

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Review Article

Photochemical reaction and applications in organic synthesis

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Abstract

Chemical as well as physical property that may occur under the influence of light is called Photochemistry. Photochemical transformations have been governed by two fundamental principles. These principals are First law: This law is also called as Grotthuss-Draper law; it states that for a photochemical reaction to take place it should be essential that light must be absorbed by a compound. Second law: The second law or Stark-Einstein law gives a photo equivalence law which is states that for each photon of light absorbed by a compound only one molecule of compound is activated for corresponding reaction. The efficiency of each photochemical process is calculated by Quantum Yield (Φ). Many photochemical reactions are complex, thus the quantum yield is specified for a particular event. It is defined as "ratios of the number of moles of a reactant disappearing, or the number of moles of a product obtained, per one mole of light absorbed by compound." After that many of secondary reactions proceeded (shown in the gray box). Absorption of light (uv/vis) induces energy sufficient in molecule to break covalent bonds. Since, E = hc / λ, hence, longer wavelength have less energy and vice-versa. Consequently, ultraviolet light is most effect photochemical reactions. In this review we discuss about amongst all some of photochemical reactions collectively which are initiated by ultraviolet light specifically.

Keywords: Electromagnetic Radiations, Singlet State, Triplet State, Excited State, Photochemical transformations

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INTRODUCTION

In the early 1900's Giacomo Ciamician from University of Bologna used sunlight for his research hence he is the father of photochemistry. Before that era, many sources used for a photochemical reaction these are bright incandescent lamps (chiefly infrared and visible light), low, medium and high pressure mercury lamps (185 - 255 nm, 255 -1000 nm & 220 -1400 nm respectively), high intensity flash sources and lasers. In careful studies of specific chromophore, sources of monochromatic light may be desired. In this review we focus on electronic excited states which are formed when a photon is absorbed by a chromophoric functional group present in molecule. Ultraviolet radiation having wavelengths less than 200 nm is sufficient to excite a electron to a higher energy orbital. A pictorial diagram showing the various kinds of possible electronic excitation in organic molecules is shown below (fig 1).

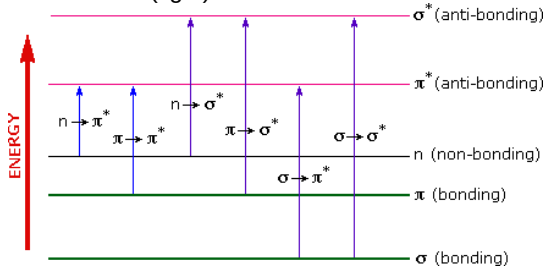


Fig. 1: Pictorial diagram showing the various kinds of possible electronic excitation

All the six transitions outlined are achieved by the energies available in the 200 to 800 nm spectrum. Energetically favored electron excitation will be from the **highest occupied molecular orbital (HOMO)** to the **lowest unoccupied molecular orbital (LUMO)**, and the resulting state is called an **excited state**. Electronic transition in the molecule is occurring only after; sufficient light energy will be absorbed. On excitation electron promoted to a higher energy orbital. The spectrum is drawn as a graph of absorbance (A) versus wavelength. Absorbance usually ranges from 0 (no absorption) to 2 (99% absorption), and is precisely defined in context with spectrometer operation. Franck-Condon Principle state that this electronic transition so faster than nuclei can respond. Bonding in an excited state is usually lower than in the ground state. Thus, bond length is increased in the excited state. Finely, electron in excited state may return to the ground state by emitting a photon (light blue line). This radiative decay is called **fluorescence** if it takes place rapidly from the initial excited state. It is termed **phosphorescence** if it occurs slowly by way of other excited states

Excited states are of two types, **singlet** and **triplet.** This difference is just because of electron spin angular momentum. Most ground states are singlet, hence excited states initially formed by absorption of light is singlet. With loss of heat energy (relaxation), **Internal conversion** of excited states to lower energy states takes place. Also, an excited state may return back to the ground state via emitting a photon. The conversion of a singlet state to triplet state, or vice versa, is

termed **intersystem crossing.** This process is slower than internal conversion. Radiative decay from a triplet state is called phosphorescence and is generally quite slow.

Types of electromagnetic radiation

Electromagnetic wave is only wave which is able to travel in empty space. Energy which is related with electromagnetic wave is called as electromagnetic energy and this is energy in the form of waves. Einstein and Max Plank said in his theory that Electromagnetic radiation exists in form of small packet of energy which is called photons. This energy behaves as waves and energy packets. Thus we can say that Electromagnetic energy is type of energy which originated from electromagnetic waves. This can also be defined as energy that transmits information (in the form of waves) from one place (material) to another or wave which is produced when charged particles that are placed in magnetic and electric field which are right angle to each other undergoes acceleration. The oscillation of the particles in the wave emits energy called electromagnetic wave energy. This information can be in the form of light, heat, or in any other form. Let us understand step by step what electromagnetic energy is. This energy radiation have same speed as speed of light and it contains radio waves, TV waves, radar waves, heat, light, X-rays, visible waves, etc. The Sun, the earth and the ionosphere are main sources of electromagnetic energy in nature {table 1}.

Table 1: Approximate Boundaries of Electromagnetic Radiations

Region Name	Energy, J	Wavelength	Frequency, Hz
X-ray	5×10^{-19}	10 nm	3×10^{19}
Vacuum ultraviolet	2.5×10^{-19}	10-200nm	3×10^{16}
Near ultraviolet	6.6×10^{-20}	200-400nm	1.5×10^{15}
Visible	5×10^{-19}	400-800nm	7.5×10^{14}
Near Infrared	2.5×10^{-19}	0.8-2.5 um	3.8×10^{14}
Fundamental infrared	6.6x10-20	2.5-50 um	1×10^{14}
Far Infrared	4x10-21	50-300 um	6×10^{12}
Microwave	6.6×10^{-22}	0.3 mm-0.5 m	1×10^{12}
Radio wave	4×10^{-25}	0.5-300 x 10^{6}	6×10^{3}

Some Facts about Electromagnetic Energy

1. According to formulae E = hc / λ the higher the energy of the particles of electromagnetic wave, shorter is their wavelength.
2. It can travel through any material as well as through vacuum.
3. Their speed in vacuum is same as that of light, i.e. approximately 1, 86,000 miles per second or 3, 00,000 kilometers per second.
4. Most important thing is when it enter into matter, they get slow down i.e. their energy decreases, hence wavelength increases.

When this hits an object, it generates heat at the surface, this heat in turn causes the particles of that object to vibrate while in reverse when object is heated, particles get accelerated which causes change in their electric and magnetic fields, which leads to generate electromagnetic wave. Heat and vibration generated via this mode depends on the wavelength and energy of the electromagnetic wave (fig. 2).

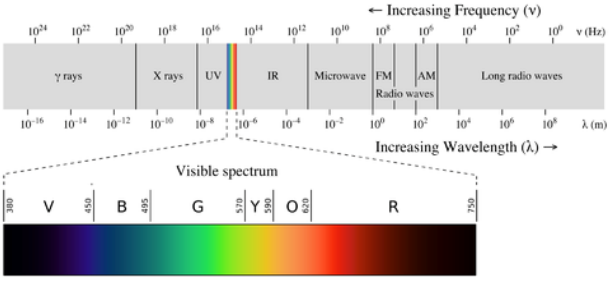


Fig. 2. Graphical representation of electromagnetic diagramme

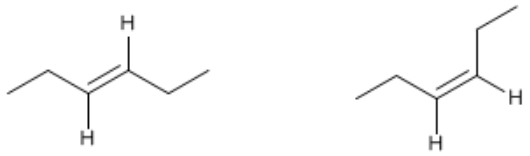
PHOTOCHEMICAL REACTION

Chemical reactions initiated by light are called as photochemical reactions. Energy in form of photon is absorbed or emitted by matter.

After absorption of light an electronic excitation from ground state to excited state takes place. This leads to promote an electron. The types of excitation are like $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$ etc. Most of photochemical reactions take place during excitation from S1 and T1 excited states.

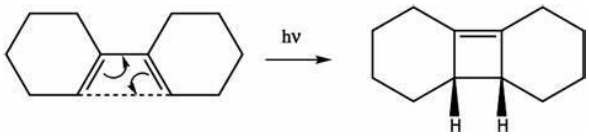
If a molecule absorbs energy, it can undergo photochemical reactions or there is possibility of they loss of energy via two methods: radiative processes which involve emission of a photon. Example of radiative phenomenon is phosphorescence which occur when electron relaxation to a lower state with different multiplicity, such as T1→S0 (spin forbidden). Other example is fluorescence in which relaxation occur to lower state of same multiplicity, such as S1→S0 (spin allowed). The non-radiative processes lead to no emission of photon. In this case the internal conversion occure which not involves spin change, such as S1→S0. The intersystem crossing-involves change in spin multiplicity. Excitation by energy transfer is Sensitization (deactivation is Quenching). There are lots of photochemical reactions. Some of these are discuss in this review.

1. Geometrical Isomerism: photochemical cis/trans (E / Z) isomerism in mostly leads to thermodynamically less stable cis-isomer -cis-isomer have less conjugation b/c of non-bonded interactions hence it typically absorbs at a lower λ [1].

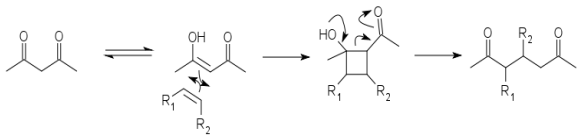


trans-3-hexeno *cis*-3-hexeno

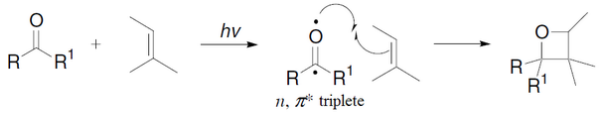
2. Electrocyclizations: Photochemical electrocyclization occur via LUMO 4n - disrotatory 4n + 2 – conrotatory. In this case a new σ-bond form between the termini of the conjugated π-system. Both bond breaking and bond formation process take place at the same time [2].



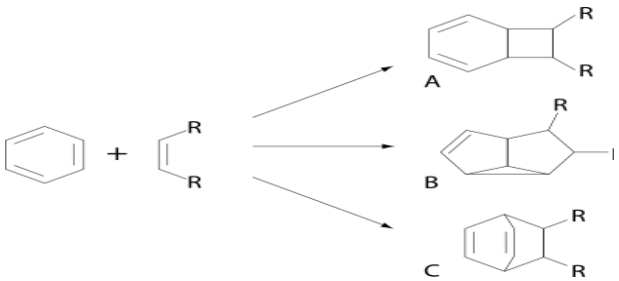
3. DeMayoReaction: In this reaction [2 + 2] cycloaddition takes place involving double bond of an enol and another olefin and the retro-aldol reaction [3].



4. **Paterno-Büchi Reaction[4]:** Paterno and Chieffi observed the first example of a [2 + 2] cycloaddition between a carbonyl and an olefin to make an oxetane [4].

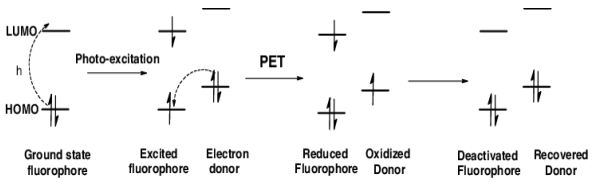


5. Arene-Olefin Cycloadditions: a photocatalyzed cycloadditions reaction between arenes and an olefin takes place all three positions available in arenes. On this basis these are summarized as ortho cycloadditions-[2 + 2], para cycloadditions-[4 + 2] and meta cycloadditions-[3 + 2] [5].

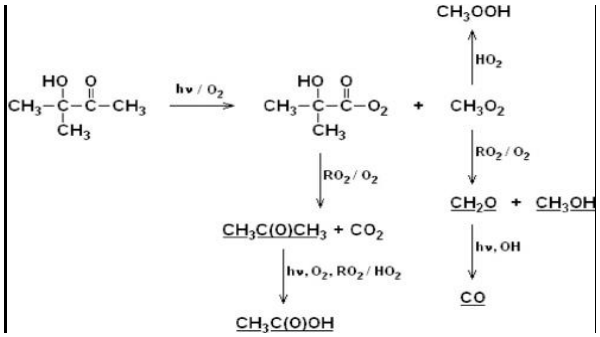


6. Photo induced Electron Transfer (WitkopCyclization): polar solvents facilitate the generation of radical ions and subsequent chemical reactions [6].

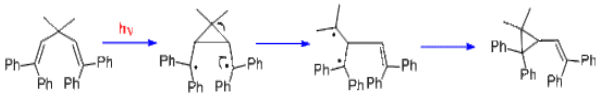
Acceptor + Donor ⟶ A•- + D•+ ⟶ chemistry



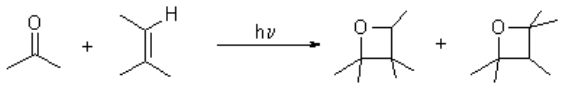
7. Photolysis of 3-hydroxy-3-methyl-2-butanone: photolysis of 3-hydroxy-3-methyl-2-butanone in presence of UV radiation leads to five major reaction products acetone, acetic acid, formaldehyde, CO and methanol [7].



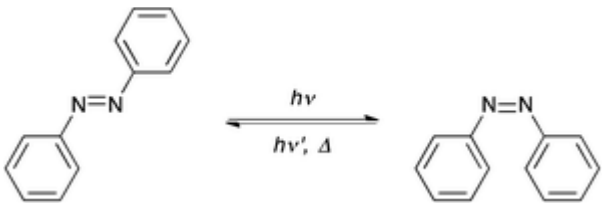
8. Di-pi methane rearrangement: reaction involves the photolysis of molecule having two pi-bonds bonded to single sp3 hybridized C atom resulted into synthesis of cyclopropane [8].



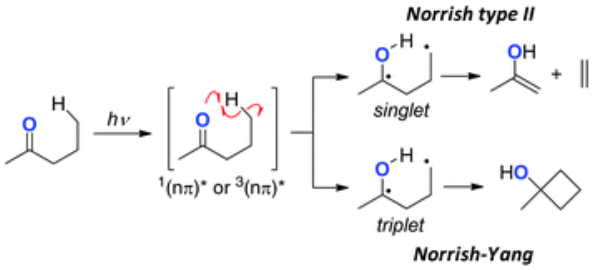
9. Paterno buchi reaction: when carbonyl compound react with alkene in presence of light resulted in trimethylene oxide [9].



10. Photoinduced isomerization of azobenzene: the simplest photoinduced isomerisation is seen in azobenzene [10].

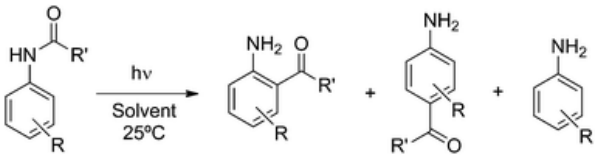


11. Norrish type II reaction: when photo-excited ketone abstract their H-radical from γ-position leads to corresponding biradicals, which is further resulted into cyclobutane is called Norrish type II reaction [11].

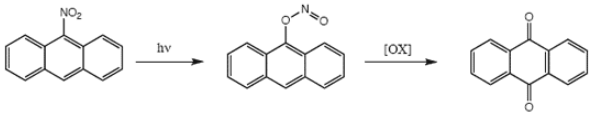


12. Novel photochemical rearrangement: 2-formyl phenylalkeno-derivatives in presence of UV light in benzene solution afforded thepolysubstituted isochromanones through Novel photochemical rearrangement [12].

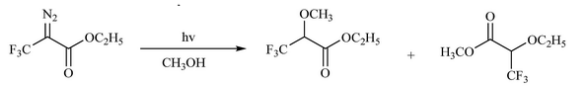
13. Photo-Fries rearrangement: this photochemical reaction involves the homolytic cleavage of C–O, C–S and C–N, of esters, amides, thioesters etc [13].



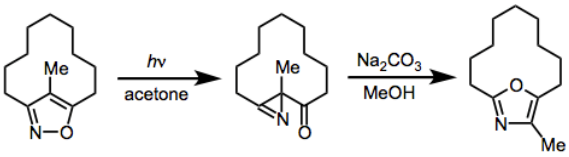
14. Nitro-nitrite rearrangement: in this type of rearrangement nitro aromatic species undergoes photochemical initiated rearrangement [14].



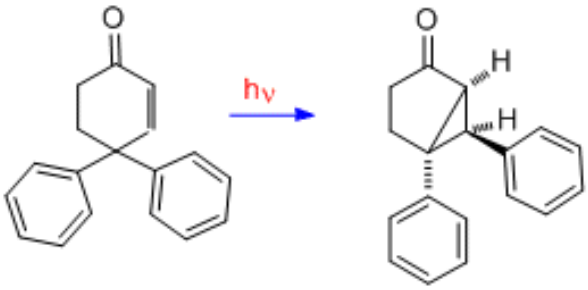
15. Photochemical reaction of ethyl diazotrifluoropropanoate: photolysis of ethyl diazotrifluoropropanoate rearranges and resulted into efficient insertion reaction with the O–H bond [15].



16. Photochemical rearrangements of isoxazoles: this photochemical reaction afford acyl azirines, which resulted into the corresponding oxazoles [16].

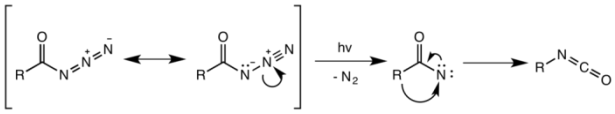


17. 4,4-Diphenylcyclohexenone rearrangement: in such type of photo catalytic rearrangement one double bond and one of the phenyl groups, C-4, migrated to C-3 [17].

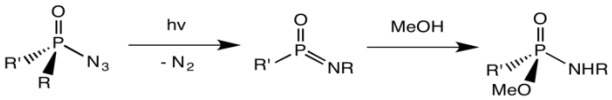


18. Photochemical rearrangements of Natural Product: the best result of such rearrangement is found in santonin which in presence of light converted into lumisantonin [18].

19. Photochemical Curtius rearrangement[19]: in curtius rearrangement migration takes place along with full retention of configuration at R-group [19].



20. Photochemical Harger rearrangement: in Harger rearrangement the phosphinic azide forms a metaphosphonimidate in presence of light followed by methanol. This is actually R-groups which migrate [20].



CONCLUSION

Photochemistry itself is a mature science in this review, we have discussed about the unique features of photochemical reactions. A variety of photochemical reactions is described above. Overview of photochemical reaction also discusses significance of such reactions and is mainly focused on implications for main product. Ubiquity of photochemical reactions implies the importance of understanding the underlying processes and mechanisms on a molecular level. Now there is more need for new and exciting theory in this explored field. This is expected to be discovered in the future. It seems a promising field for future research.

CONFLICT OF INTERESTS

There is no any possibility of conflict of interest.

Source of Support: Nil
Conflict of interest: Nil
Acknowledgement: None

REFERENCES

1. Zhan K, Li Yi, Visible-Light Photocatalytic E to Z Isomerization of Activated Olefins and Its

Application for the Syntheses of Coumarins. Catalysts 2017; 7: 337.
2. Woodward RB, Hoffmann R. Stereochemistry of Electrocyclic Reaction. J. Am. Chem. Soc 1965; 87: 395.
3. Challand BD, Hikino H, Kornis G, Lange G, de Mayo P. de Mayo P reaction. J. Org. Chem 1969**;** 34*:* 794-806.
4. Mihailovic M, Lorenc L, Pauolvic V, Kalvoda J. vitamin D3 analogs. Tetrahedron 1977; 33: 441.
5. Wilzbach KE, Kaplan LA, Photochemical 1,3 Cycloaddition of Olefins to Benzene. J. Am. Chem Soc 1966; 88: 2066–2067.
6. Yonemitsu O, Cerutti P, Witkop B, Photoreductions and photocyclizations of tryptophan. J.Am.Chem.Soc 1966; 88: 3941.
7. Bouzidi H, Laversin H, Tomas A. Reactivity of 3-hydroxy-3-methyl-2-butanone: Photolysis and OH Reaction kinetics. Atmospheric Environment 2014; 98: 540-548.
8. Hixson SS, Mariano SS, Zimmerman EH. Di-.pi.-methane and oxa-di-.pi.-methane rearrangements. Chem. Rev 1973; 73: 531-551.
9. Büchi G, harles Inman GC, Lipinsky ES, Light-catalyzed Organic Reactions. The Reaction of Carbonyl Compounds with 2-Methyl-2-butene in the Presence of Ultraviolet Light. J. Am. Chem. Soc 1954; 76: 4327-4331.
10. Chatani S, Kloxin JC, Bowman NC. The power of light in polymer science: photochemical processes to manipulate polymer formation, structure, and properties. Polym. Chem 2014; 5: 2187-2201.
11. Chiba S, Chen H, sp^3 C–H oxidation by remote H-radical shift with oxygen- and nitrogen-radicals: a recent update. Org. Biomol. Chem 2014; 12: 4051-4060.
12. Xia W, Shao Y, Gui W, Yang C. Efficient synthesis of polysubstituted isochromanones *via* a novel photochemical rearrangement. Chem. Commun 2011; 47: 11098-11100.
13. Iguchi D, Balsells RE, Bonesi SM. Photo-Fries rearrangement of aryl acetamides: regioselectivity induced by the aqueous micellar green environment. Photochem. Photobiol. Sci 2016; 15: 105-116.
14. Saito I, Takami H, Matsuura T. Nitro-nitrite rearrangement and intramolecular cycloaddition in the photochemistry of nitro-olefins. Tetrahedron Letters 1975; 16: 3155-3158.
15. i) Ge SS, Chen B, Wu YY et al, Current advances of carbene-mediated photoaffinity labeling in medicinal chemistry. RSC Adv 2018, 8**:** 29428-29454. ii) Chowdhry V, Vaughan R, and Westheimer F H, 2-diazo-3,3,3-trifluoropropionyl chloride: reagent for photoaffinity labeling. PNAS 1976, 73: 1406-1408
16. Beccalli EM, Majori L, Marchesini A. Torricelli, Science of Synthesis: Oxazoles. C. Chem. Lett. 1980; 659.
17. Zimmerman HE, Wilson JW, Mechanistic and Exploratory Organic Photochemistry, IX. Phenyl Migration in the Irradiation of 4.4-Diphenylcyclohexenone. J. Am. Chem. Soc 1964; 86: 4036-4042.
18. Barton DH, R, De Mayo P, Shafiq M, Photochemical transformations Part II. The constitution of lumisantonin. J. Chem. Soc 1958; 140-145.
19. Scriven, EFV, Turnbull K. Azides: their preparation and synthetic uses. Chemical Reviews 1988; 88: 297-368.
20. i) Smith PAS. The Curtius reaction Organic Reactions. 1946; 3: 337-449. Ii) Warren JD, Press JB. Formation and Curtius rearrangement of acyl azides from unreactive acid chlorides. Synth. Commun 1980; 10: 107-110.

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Review Article

Purification techniques for Organic solvents

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Abstract

Organic solvents are known as carbon-based solvents and their general property is primarily based on their volatility, boiling point, the molecular weight and color. Having enormous hazards associated with the organic solvents, they are used for millions of purposes which alert us to think more on its toxicity points. Almost all of the solvents are hazardous to health, if swallowed or inhaled more than the limit quantity and on contact to the skin most of them cause irritation. Some of the common solvents are acetone, ethyl acetate, hexane, heptane, dichloromethane, methanol, ethanol, tetrahydrofuran, acetonitrile, dimethylformamide, toluene, dimethylsulfoxide etc. Researchers, scientists, workers in the chemical industry and research institutes use these solvents on regular basis leading them to be affected in major aspects. But also, the nearby persons are affected by the contamination to the soil, water, air etc. If constantly exposed with solvents, it will badly affect the function of CNS and other body parts. The level of impact, sign and symptoms will depend on concentration, time, duration, frequency and nature of solvents, leading to common effects like headache, dizziness, tiredness, blurred vision, behavioral changes, unconsciousness, and even death. To overcome it, the green chemistry concept is growing rapidly, and the solvent selection guide is in practice in many big company and research institute. A researcher or chemical worker is the primary person who works with solvents and they need to consider throughout these things while performing their activities for their own good health and for the sake of the world. The purpose of this review is to provide needed basic knowledge about common organic solvents and their potential toxicities which will alert researchers to think twice and always think for their health as well as for the environment via safe and green practice.

Keywords: Globally harmonised system, Green practice, Toxicity point.

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1. Introduction

The presence of solvents in any vegetables, fruits, meats etc. makes them easily deteriorated when stored for long at room temperature which means that the solvents make many easy things to happen i.e. occurrence of chemical reaction, which results in change in its form. The dry meat, dry fish, dry vegetables, dry grains etc. remains very stable in normal condition if the dryness maintained properly.[1,2] This basic understanding teaches us how the chemical reactions are done in the liquid state. The common organic solvents are generally classified as an aliphatic hydrocarbon, aromatic hydrocarbon, cyclic hydrocarbon, halogenated hydrocarbon, amines, ketones, esters, ether, aldehyde, alcohols etc. It's hard to talk about organic synthesis without organic solvents. In common, the organic solvents are chemicals that are used to dissolve other chemicals but in detail, we need to understand the reactivity of respective solvents on specific reactions conditions. So, the selection of appropriate solvents for a reaction is to be noted always.[3] The choice of solvents is usually done by previous experience with particular solvents or the following similar pattern literature review and practice it in a laboratory setting. However, the scenario does not remain same nowadays because of some strict rules and regulation we need to consider like solvent power, volatility that leads to toxicity to the researcher and to our society and overall environment. This leads to search new and new best option and because of which, nowadays the solvent-free organic synthesis is rapidly growing.[4] Many research about the toxicity of solvents gives us the molecular mechanism and possible major body parts to be affected. The knowledge of risk associated with organic solvents is increasing rapidly among the researcher and in a lesser amount to the public which creates a louder voice for safety, strict rules and regulation; these all decreases the potential danger and associated health effects.[5] Now the well-equipped laboratory setup, proper ventilation to draw the solvent and reagent fumes to the highly diluted atmosphere, proper disposal system is rapidly increasing; but the scale of synthesis, the number of researchers are increasing

rapidly which has resulted in larger volume of organic solvent consumption that still become risk factor and many organizations are working on it. As the skeleton of organic solvents contain carbon and hydrogen as major with hetero atoms some time so, they show high lipophilicity and very volatile. In toxicity view, the lipophilicity influences the distribution of solvents to various body parts. The lipophilic compounds need to be converted to a water-soluble form via several osmotic conversions that enhances the excretion via the kidney. Sometime the resulting metabolite could be more toxic than the original one.[6,7] Due to the high lipophilicity character of organic solvents, they can easily enter the brain and affects severely sometimes. At high dose with respect to certain chemical can cause anesthetic effects, anxiolytic effects, convulsant effect, anticonvulsants, narcotic effects (Trichloroethylene), antidepressants (benzyl chloride). Due to the rapid growth of plastic and chemical industries, major population is affected by organic solvents. Since the organic solvents are highly volatile, it leads to the exposure of solvents to air rapidly.[8] It is being inhaled via respiration, so lungs are the primary organ to be affected which alerts to have enough ventilation in workplace.

2. Purification methods of organic solvents

In order to obtain satisfactory, or even any results, in many syntheses it may be necessary to purify solvents to remove reactive impurities such as water or other acidic materials, or atmospheric contaminants such as oxygen or carbon dioxide.[8,9] Removal of non-gaseous contaminants must be tailored to the specific solvent and often the specific contaminant to be removed. An excellent source for methods of purification of a wide variety of solvents is “Purification of Laboratory Chemicals”. Sometimes simply using a freshly opened bottle of solvent certified by the vendor for a certain level of purity is satisfactory, but when really sensitive reagents are used and/or analytical results are required then organic solvents usually must be purified. The time and effort expended to purify solvents can be lost if the glassware to be used for an experiment is not also clean AND dry. The extent to which glassware must be treated varies with the sensitivity of the reagents, but at a minimum all glassware should be oven dried for several hours or flame dried if time is short, and assembled while warm under an inert atmosphere. Remember that glass is composed of silica and that water forms hydrogen bonds with the bridging oxygen.[10] Removal of oxygen and other gaseous atmospheric contaminants (degassing) can be done in several ways. The simplest is to spray the solvent with a readily available, oxygen free, inert gas such as nitrogen or argon. The length of time required depends upon the amount of solvent to be degassed and may range from a few minutes up to a half h or more. Obviously this requires considerable compressed gas and will result in significant loss of a volatile solvent.[11,12] It may be inappropriate when only a small amount of solvent is available. It is also not the most effective method. A better method, and one that would be easily employed when distillation was required for removal of other impurities, is distillation under an inert atmosphere. The process of boiling expels gases from the solvent. If this process is done under an inert atmosphere then the dissolved gases will be expelled and replaced by the inert gas. Note that saturation of an unstirred liquid is quite slow.[13] If the amount of material available is very small, or if it is thermally sensitive, then degassing by multiple freeze, pump thaw cycles may be appropriate. In this process the liquid to be degassed is placed in a vessel equipped with a stopcock or valve that is suitable for evacuation. The liquid is frozen using an appropriate cold bath and the head space evacuated.[14] The stopcock is closed and the liquid allowed to melt. After a few minutes preferably with swirling of the vessel to achieve equilibration between the liquid and gas phases, it is again frozen and the headspace evacuated. The process is repeated 3-5 times. At this point the liquid should be essentially free of gaseous impurities and can be transferred to the reaction vessel. If this is to be done without exposure to the atmosphere then there must be some provision for breaking the vacuum with an inert gas and bringing the system to atmospheric pressure and provision for removing the liquid with a syringe or other “airless” transfer method.[15]

2.1 Chromatography separation

2.1.1 Gas-Liquid Chromatography

Many separation methods are based on chromatography, that is, separation of the components of a mixture by differences in the way they become distributed (or partitioned) between two different phases.[16] To illustrate with an extreme example, suppose we have a mixture of gaseous methane and ammonia and contact this mixture with water. Ammonia, being very soluble in water (- 90 g per 100~~ of water at 1 atm pressure), will mostly go into the water phase, whereas the methane, being almost insoluble (- 0.003 g per 100 g of water) will essentially remain entirely in the gas phase.[16,17] Such a separation of methane and ammonia would be a one-stage partitioning between gas and liquid phases and, clearly, could be made much more efficient by contacting the gas layer repeatedly with fresh water. Carried through many separate operations, this partitioning procedure is, at best, a tedious process, especially if the compounds to be separated are similar in their distributions between the phases. However, partitioning can be achieved nearly automatically by using chromatographic columns, which permit a stationary phase to be contacted by a moving phase. To illustrate, suppose a sample of a gaseous mixture of ammonia and methane is injected into a long tube (column) filled with glass beads moistened with water (the stationary phase), and a slow stream of an inert carrier gas, such as nitrogen or helium, is passed in to push the other gases through. A multistage partitioning would occur as the ammonia dissolves in the water and the resulting gas stream encounters fresh water as it moves along the column. Carrier gas enriched with methane would emerge first and effluent gas containing ammonia would come out later. This is a crude description of the method of gas-liquid chromatography (abbreviated often as glc, GC, or called vapor-phase chromatography, vpc). This technique has become so efficient as to revolutionize the analysis and separation of almost any organic

substance that has even a slight degree of volatility at some reasonably attainable temperature.[15,18] The most modern glc equipment runs wholly under computer control, with preprogrammed temperatures and digital integration of the detector output. A wide variety of schemes is available for measuring the concentration of materials in the effluent carrier gas, and some of these are of such extraordinary sensitivity that only very small samples are necessary. In the usual glc procedure, a few microliters of an organic liquid to be analyzed are injected into a vaporizer and carried with a stream of gas (usually helium) into a long heated column that is picked with a porous solid (such as crushed firebrick) impregnated with a nonvolatile liquid. Gas-liquid partitioning occurs, and small differences between partitioning of the components can be magnified by the large number of repetitive partitions possible in a long column. Detection often is achieved simply by measuring changes in thermal conductivity of the effluent gases, these are separated from the main peak. Glc also can be used effectively to purify materials as well as to detect impurities. To do this, the sample size and the size of the apparatus may be increased, or an automatic system may be used wherein the products from many small-scale runs are combined.[16]

2.1.2 Liquid-Solid Chromatography

Liquid-solid chromatography originally was developed for the separation of colored substances, hence the name chromatography, which stems from the Greek word chvoma meaning color. In a typical examination, a colored substance suspected of containing colored impurities is dissolved in a suitable solvent and the solution allowed to percolate down through a column packed with a solid adsorbent, such as alumina or silica, as shown in Figure 9-3. The "chromatogram" then is "developed" by passing through a suitable solvent that washes the adsorbate down through the column. What one hopes for, but may not always find, is that the components of the mixture will be adsorbed unequally by the solid phase so distinct bands or zones of color appear.[18] The bands at the top of the column contain the most strongly adsorbed components and the bands at the bottom the least strongly held components. The zones may be separated mechanically, or sufficient solvent can be added to wash, or elute, the zones of adsorbed materials sequentially from the column for further analysis. Liquid-solid chromatography in the form just described was developed first by the Russian biochemist M. S. Tswett, about 1906. In recent years, many variations have been developed that provide greater convenience, better separating power, and wider applicability. In thin-layer chromatography, which is especially useful for rapid analyses, a solid adsorbent containing a suitable binder is spread evenly on a glass plate, a drop of solution to be analyzed is placed near one edge and the plate is placed in a container with the edge of the plate below the spot, dipping into an eluting solvent.[17,19] The solvent ascends the plate and the materials in the spot move upward at different rates, as on a Tswett column. Various detecting means are used- simple visual observation for colored compounds, differential fluorescence under ultraviolet light, and spraying of the plate with substances that will give colored materials with the compounds present. In favorable cases, this form of liquid-solid chromatography can be carried out with submicrogram quantities of materials. An extremely important improvement on the Tswett procedure is highpressure solid-liquid chromatography. Increasing the input pressure on the system to 20-70 atmospheres improves the speed of separations by permitting the use of much smaller \olid particles (with more surface area) than would be practical for gravity-flow Tswett columns. Automatic monitoring of the column effluent by ultraviolet spectroscopy (Section 9-9) or by changes in the refractive index usually provides an effective means of determining how the separation is proceeding. [20]

3. Health hazards of organic solvents

3.1 Neurotoxicity

Due to the low boiling point of most of the organic solvents, it can easily enter in our body via respiration as well as distribution in the air is rapid so the large group of mass is affected including the atmosphere. So, this becomes the most emerging issue in the field of occupational health.[21] In recent decade major presentation, meetings, and discussion with controversial subjects are happening. The nervous system is a major part which handles all the body. To be a person fit and fine he/she should have a good mental state. For fruitful research, a researcher should first survive with good health and mental condition. So, this is the key factor to be considered and various safety measures are recommended to follow for their life. Since once damaged to CNS or PNS is a potentially irreversible process such repeated exposure results in severe cumulative impairments. Usually, the neurotoxic solvents on exposure show neuropathy, psychosis, dyskinesia, peripheral neuropathy, pyramidal and other types of irreversible brain dysfunction, trigeminal neuralgia, anorexia, ototoxicity, encephalopathy, transverse myelopathy, facial paralysis, and limb numbness etc. The organic solvent exposure and contrast sensitivity comparison between men and women shows, the men visual impaired is wider than that of women over wide range of spatial frequencies, the researcher conclude this is due to higher body fat mass in women that can serve as a protective factor against neurotoxic effects in comparison to men.[20,21]

3.2 Normal Hexane and Other Alkanes

n-Hexane is a known chronic human neurotoxicant [4,23]. In animal and human, nHexane is metabolized into a gamma diketone, 2,5-hexanedione which is more potent neurotoxicant than the parent alkane [4]. The comparative study of the toxicity of n-heptane, nhexane, and n-pentane in peripheral nerve of the rat also shows n-hexane is far more neurotoxic than the Pentane and Heptane to the peripheral nerves of the rat [5,24]

3.3 Aromatic Hydrocarbons

Benzene, xylenes, and toluene are aromatic hydrocarbon solvents widely used in past time and still popular but are quite limited due to their toxicity. In liver the Cytochrome P450 2E1 converts benzene to

its metabolic form benzene oxide, which can further metabolize to various other intermediate like o-benzoquinone and pbenzoquinone, which are the major metabolite for benzene toxicity. Based on the exposed dose the benzene affects the bone marrow that cause anemia, leukopenia, and thrombocytopenia, if even more exposure continued for longer time it leads to aplasia and pancytopenia. Due to this severe toxic effect of benzene, it is replaced with little safe xylene and toluene which has hematopoietic toxicity. The toluene is widely used in paints, thinner, glue, cleansing agent and the widely abused as an inhalant.[5,22]

3.4 Halogenated Hydrocarbons

Those containing at least one halogen atom like fluorine, chlorine, bromine, and iodine are referred to as a halogenated hydrocarbon. Some common halogenated hydrocarbon solvents are methyl chloride, chloroform, trichloroethylene, and tetrachloroethylene.[23]

3.4.1 Chloroform toxicity

In 1847 chloroform was introduced as an anesthetic but due to its toxic effect no longer practiced as an anesthetic in human. Various options to chloroform are tried but due to some special character in organic synthesis it is still used in laboratory and chemical industry as solvents to put reaction, for extraction, purification etc. The metabolic product of chloroform is toxic because it can bind to the macromolecules like protein and lipids of the endoplasmic reticulum. The primary affecting organ is liver and causing necrosis. After liver, the kidney is the second target of chloroform after oral or inhalation exposure causing tubular necrosis, swelling, increased weight of kidney in rats after oral administration. Other carcinogenicity and chronic toxicity are reported with inhalation of chloroform .Depends on species, strain, and sex of the animals, metabolizing enzymes, chloroform shows kidney and liver tumor in a dose-dependent manner. The metabolic product of chloroform to phosgene severely affect the kidney. Chloroform toxicity in mice is being largely studied by many researchers. Different pathway of chloroform metabolism has been studied.[24]

3.4.2 Methylene chloride toxicity

It is also known as dichloromethane (DCM), the widely used solvent in organic synthesis.[21, 22] It can dissolve a wide variety of chemical compounds. Its density is higher than water so during extraction processes in organic synthesis it makes convenient not to collect the water layer to a separate flask, just put more DCM then shake and collect again repeated the same process and finally trace aqueous undesired part. But it is more toxic than ethyl acetate and cause burning irritation on contact with skin because it can easily melt the latex gloves and enter inside but cannot evaporate easily due to covered with gloves so cause irritation for a long time. So, if contact occurs with skin immediately remove the gloves and use a new one. In past, it was used in hairspray until 1989 and to remove caffeine from coffee. It is a potential human carcinogen which is the primary concern of it. The oral exposure to DCM can increase liver cancer.[23]

3.5 Alcohols

Various kinds of alcohols are used in organic synthesis as a solvent, cleansing agents, and a reagent. Most common are methanol, ethanol, isopropanol, cyclohexanol, diethylene glycol etc. Usual pronounced term is ‘toxic alcohol’ which is a collective meaning representing methanol, ethylene glycol and isopropyl alcohol.[24]

3.5.1 Methanol toxicity

Methanol can cause serious effects like acidosis and retinal damage. In liver methanol converted to formate in the presence of enzyme alcohol dehydrogenase, which is toxic. Methanol can produce severe acidosis and retinal damage. The intoxication by methanol can cause various effects like retinal edema, ocular lesions, loss of ganglion cells, demyelination of temporal retina, necrosis of cells with or without significant hemorrhage . Methanol can cause abnormal movement of the body usually due to drinking of homemade liquor contaminated with methanol.[25]

3.6 Ether

The commonly used ether solvents are diethyl ether, tetrahydrofuran, 1,4-dioxan etc. The ether solvents are toxic, many experimental models showed the toxicity of ether to the HepG2 cells [59], toxicity to blood lymphocytes [60], testicular toxicity [61], carcinogenicity. The tetrahydrofuran (THF) shows CNS toxicity with dizziness, headache, loss of sense of smell and fatigue etc. [23,24]

3.7 Miscellaneous Solvents

3.7.1 Acetonitrile toxicity

Acetonitrile is a common organic solvent used in organic synthesis and chemical industry. It is hazardous to health and even can cause death. Usually, the effect associated with it is from the inward breath of its vapors or contact of fluid to skin and eyes. Acetonitrile interferes with oxygen requirement for cell breath and leading to cytotoxic anoxia. The potential safety hazards with acetonitrile should be considered when using strong acid or strong base because acetonitrile can be hydrolyzed by it.[25, 26] The concurrent exposure to acetonitrile and acetone increases the toxicity of acetonitrile. The metabolized form of acetonitrile is cyanide which is severely toxic to animals and human. The amount of formation of cyanide from acetonitrile is increased with co-administration to acetone. The mechanism of acetonitrile toxicity revealed the detail pharmacokinetic distribution of acetonitrile to the different body parts, leading to a CNS major toxicity. [26] The acetonitrile toxicity in human is due to the in vivo formation of cyanide as a metabolite, the associated onset signs and symptoms depend on exposure route, amount, and duration of exposure. However, it is typically delayed from 2 to 13 h due to the slow conversion rate to cyanide. Various signs and symptoms are: a) respiratory: bronchial/chest tightness, respiratory insufficiency; b) Cardiovascular: bradycardia, tachycardia, hypotension, cardiac arrhythmia, cardiac arrest, and death; c) neurologic: headache, dizziness, confusion, agitation, seizures, weakness, and coma; d) gastrointestinal: initially nausea and vomiting are common, leading to metabolic acidosis and lactic

acidosis. The 1-2 g/kg of acetonitrile ingestion is lethal. The proper understanding of acid-base chemistry with structural interactions could be helpful in finding the solvents interactions and generation of relative toxic products. [21]

3.7.2 Dimethylformamide

In short it is written and spoken as DMF. It is a polar aprotic solvent with high boiling point. It is miscible with water and majority of the organic solvents. At an elevated temperature DMF hydrolyzed by strong acid and base. It is also used as a reagents in many cases, like a reagent in the Vilsmeier-Haack reaction where it first convert to chloroiminium ion known as Vilsmeier reagent that attacks arenes. Many research has been carried out to reveal the toxicity of DMF, viz hepatotoxicity and other many more.[19,23]

3.7.3 Acetone

Acetone is a simplest and smallest ketone, colorless, volatile and a flammable liquid, widely used in cleansing purposes in chemical industry, research institute and other generalized form. It is miscible with water that increases its use in cleansing.[18]

4. Conclusion

In research laboratory and chemical industry, organic solvents belong to the most important group of chemicals due to its huge amount of use annually. Thus, the solvents revel a major part of human as well as environmental toxicants. In the research and chemical industry, the selection of solvents for reaction process as well as cleansing and other chemical processes and the waste solvent management all mostly depends on economic, logistic and safety considerations. The environmental concerns are often of minor consideration for the decision makers also due to lack of easy availability of proper tools, which accumulates such happenings from large groups of chemicals industry, institute, researcher etc. which leads to a big problem to the environment, human and all around us, leading to a chemical toxicity. In this review, we have presented a general overview of solvent's nature and their toxicity. The primary person who works with chemicals is the key person, so after studying these kinds of detail information we hope the researchers and all the concern bodies will make a proper solvent selection and practice accordingly to save their life as well as the environment where we live.

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References

1. Smallwood I. Handbook of organic solvent properties. Butterworth-Heinemann; 2012.
2. Tanaka K, Toda F. Solvent-free organic synthesis. Chemical Reviews. 2000;100(3): 1025-1074.
3. Varma RS. Solvent-free accelerated organic syntheses using microwaves. Pure and Applied Chemistry. 2001;73(1):193-198.
4. Spencer PS, Schaumburg HH. Organic solvent neurotoxicity: Facts and research needs. Scandinavian Journal of Work, Environment & Health. 1985;53-60.
5. Takeuchi Y, et al. A comparative study of the toxicity of n-pentane, n-hexane, and nheptane to the peripheral nerve of the rat. Clinical Toxicology. 1981;18(12):1395-1402.
6. Baker EL. Organic solvent neurotoxicity. Annual review of public health. 1988;9(1): 223-232.
7. Dumas O, et al. Respiratory effects of trichloroethylene. Respiratory Medicine. 2018;134:47-53.
8. Bowen SE, et al. Abstinence following toluene exposure increases anxiety-like behavior in mice. Neurotoxicology and Teratology. 2018;65:42-50.
9. Fink M. The seizure, not electricity, is essential in convulsive therapy: The flurothyl experience. The Journal of ECT. 2014;30(2):91-93.
10. Cruz SL, Gauthereau-Torres MY, RiveraGarcía MT. Structure-activity relationship for the anticonvulsant effects of organic solvents. Neurotoxicology. 2016;57:121- 127.
11. Marchetti P, et al. Molecular separation with organic solvent nanofiltration: A critical review. Chemical Reviews. 2014;114(21): 10735-10806.
12. Capello C, Fischer U, Hungerbühler K. What is a green solvent? A comprehensive framework for the environmental assessment of solvents. Green Chemistry. 2007; 9(9):927-934.
13. Tobiszewski M, et al. A solvent selection guide based on chemometrics and multicriteria decision analysis. Green Chemistry. 2015;17(10):4773-4785.
14. Alfonsi K, et al. Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. Green Chemistry. 2008;10(1):31-36.
15. Bruckner J, Warren D. Casarett and Doull's toxicology: The basic science of poisons; 2001.
16. Firestone JA, GospeJr SM. Organic solvents. in Clinical Neurotoxicology. Elsevier. 2009;401-414.
17. Jingzhi G, Approaching MSDS [J]. Sulphuric Acid Industry. 2009;4:005.
18. Keith LH, Walters DB. Compendium of safety data sheets for research and industrial chemicals. Part II Dearfield Beach: VCH Publishers; 1985.
19. Eastlake A, et al. A critical evaluation of material safety data sheets (MSDSs) for engineered nanomaterials. Journal of Chemical Health and Safety. 2012;19(5): 1-8.
20. Phillips CC, et al. The efficacy of material safety data sheets and worker acceptability. Journal of Safety Research. 1999;30(2): 113-122.
21. Tang SL, Smith RL, Poliakoff M. Principles of green chemistry: Productively. Green Chemistry. 2005;7(11):761-762.
22. Oliveira A, et al. Organic solvent exposure and contrast sensitivity: Comparing men and women. Brazilian Journal of Medical and Biological Research. 2018;51(3).
23. DeCaprio A. n-Hexane neurotoxicity: A mechanism involving pyrrole adduct formation in axonal cytoskeletal protein. Neurotoxicology. 1987;8(1):199-210.
24. Takeuchi Y, et al. A comparative study on the neurotoxicity of n-pentane, n-hexane, and n-heptane in the rat. Occupational and Environmental Medicine. 1980;37(3):241- 247.
25. King MD. Neurological sequelae of toluene abuse. Human Toxicology. 1982;1(3):281- 287.
26. Vitale CM, Gutovitz S. Aromatic (Benzene, Toluene) Toxicity; 2018.

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Original Article

Assessment and Management of common Impairments in Cerebral Palsy: A Systematic review

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Abstract

Rationale, aim and objectives: Cerebral palsy is a common cause of physical inability. This review was aimed to recognize the evaluative tools and various treatment protocols for person of cerebral palsy. **Method:** We had done a review of literature of Cochrane library, Ovid MEDLINE and GOOGLE SCHOLAR, CINAHL till February 2021. We evaluate scales available for different symptoms in CP child as well treatment for these impairments. **Result:** Cerebral palsy was the primary goal of findings in 248 studies. Out of these, 58 studies were not proved the definition of cerebral palsy. 96 studies reported treatment of cerebral palsy for different domain, 25 studies used assessment and 19 studies define alone and 50 for the physiotherapy treatment of the CP child. **Conclusion :** Many cerebral palsy scales are available, but only a very small number of scales were thoroughly validated for use in clinical practice in India. There are different management techniques available but none of them cure most of symptoms.

Keywords: Assessment Scales, Cerebral Palsy, Constraint-induced Movement therapy, Multidisciplinary, Psychometric Properties.

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Introduction

Cerebral palsy (CP) is an Broad term for many conditions.[1] It is a neurological problem which mainly affects the children.[2] Due to the damage of fetal brain the movement and posture disorder occurs and also affects intelligence, vision, hearing,[3]gait, cognition, growth and sensations. 2 to 2.5 children per 1,000 born are suffered with CP in the United States.[4] In this disorder a permanent non progressive changes were occur in fetal brain.[5] The incidence of CP worldwide is approximately 2 to 2.5/1000 live births. Developmental delay and motor deficits are usually main presentations of CP child.[6] The overall birth prevalence of CP is approx 2 per 1,000 live births.[7] The movement and posture disturbance are sometimes permanent which causes problem in daily living.[8] CP can be classified on the basis of both Pathophysiology and area of brain involve, and presentation of symptoms.[9] Presentation of CP shows both some negative sign like weakness of skeletal muscles and delayed milestones and some positive signs like a velocity dependent increased muscle tone with spasticity, Clonus, rigidity, spasms and hyper reflexia. Mixed CP are those who shows a combination of features such as epilepsy, feeding, nutrition, growth problem, mental retardation.[10] There are so many other problems which CP child suffer with like bladder dysfunctions, bowel dysfunction, drooling, sleep disturbances, hearing loss, visual abnormalities, orthopedic associated sensory impairment which are not properly understood.[11] CP classified as Hemiplegics, Paraplegics, Tetraplegics, Diplegic, or Monoplegics.[10] Inflammation and coagulation abnormalities are the main cause of CP along with hypoxic ischemic encephalopathy.[12] Some other causes of CP are placental insufficiency, uterine infection, metabolic disorder, placenta previa and neonatal asphyxia; and intra ventricular hemorrhage of the newborn, Periventricular Leukomalacia (PVL), blood infection, and perinatal stroke.[13] CP can only be Diagnose after a few months from the birth. Evaluation of CP can be done by monitoring the signs and symptoms, growth and development, medical history and by conducting a proper physical examination. A series of tests to make a diagnosis and rule out other possible causes are brain-imaging technologies as, MRI which can often identify lesions or abnormalities in child's brain by using radio waves and a magnetic field to produce detailed 3D or cross-sectional images of child's brain. A cranial ultrasound uses high-frequency sound waves to produce images of the brain. Electroencephalogram (EEG) is also helpful in diagnosis as it records the electrical activity of child's brain. Tests on the blood, urine or skin might be used to screen for genetic or metabolic problems along with some specialized tests are also to be used to assess the associated problems like Vision, Hearing, Speech, Intellect, Development and Movement disorder should assess.[14]

Physiotherapy is one of the most important parts of treatment. It involves exercises and activities that can maintain or improve muscle strength, balance, and movement, helps the child learn skills such as sitting, walking, or using a wheelchair. Other types of therapy

like Occupational therapy , Recreational therapy, Speech and language therapy and Orthotic devices, Assistive devices and technologies include special computer-based communication machines, Velcro-fastened shoes, or crutches, which can help make daily life easier. Certain medications can also be used as they help to relax stiff or overactive muscles and reduce abnormal movement. Surgery may also be required if symptoms are severe. For instance, surgery can lengthen stiff, tightly contracted muscles.[15]

Physical therapy can improve

Coordination, Balance, Strength, Flexibility, and Endurance, Pain management, Posture, Gait and Overall health. These different types of exercise have specific benefits for each type of cerebral palsy.[16] These exercise improve varying degrees of muscle control, balance, and mobility, maintain muscle tone, decrease the chances of deformities and also reduces physical discomfort and pain.[14] Physiotherapy is much helpful in treatment [17]of deformities which are related to the Cerebral Palsy.[18]

Methods

We review the literature by various online search engines like Cochrane library, Ovid MEDLINE and EBSCO CINAHL for research articles published in English, using the following search terms: cerebral palsy, assessment scales for cerebral palsy, different assessment tools for cerebral palsy, treatment protocol for cerebral palsy, Physiotherapy management of cerebral palsy, treatment techniques for cerebral palsy, treatment and management of different impairment of cerebral palsy. Research studies (review and research) that reported assessment and management of cerebral palsy for both children and adults were included in the literature. No date restrictions were used, with citations published until February 2021 included. Initially the titles and abstracts were screened for relevance. The most relevant articles were downloaded and evaluated for inclusion in the review. The reference lists of these articles were also checked for other potential relevant studies, and these studies were also retrieved.

Treatment and Assessment of Different Impairments

Approaches: So many approaches are effective for treatment of different impairments these are-

- ✓ Neurodevelopmental treatment also known as Bobath Approach[19]
- ✓ Sensory integration, Body-weight support treadmill training, Conductive education hyperbaric oxygen therapy [18]
- ✓ Constraint -induced Movement therapy[20]
- ✓ The patterning [21]
- ✓ Passive Stretching[22]
- ✓ Weight bearing [23] and
- ✓ Serial casting[24]

Spasticity

Spasticity is one of the main reason of disability in children and adults suffering from CP.[25] For the assessment of spasticity Ashworth, Modified Ashworth and Tardieu are most commonly used.[26] The Tardieu Scale shows excellent intra rater and inter rater reliability.[27] Total 24 scales are present which are use for the assessment of the spasticity.[28] There are a number of treatments available for the management of spasticity.[29] These are:

- Splinting, Casting and Orthoses and Serial Casting[29] along with Pharmacological interventions including oral administration of baclofen, diazepam, dantrolene and tizanidine, intrathecal baclofen, and local injections of botulinum toxin, phenol, and alcohol.[30]

Selective dorsal rhizotomy[31] is the surgical management of hypertonia.[32] There are a number of different approaches related to Physiotherapy which seems effective in the treatment of spasticity are the Bobath technique, Sensory integration therapy, Poprioceptive neuromuscular facilitation, Massage, Stretching, Bracing , Serial Casting, Ice (cold), heat and positioning.[29]

Dyskinesia

Dyskinesia, a non-specific term, generally refers to abnormal movements.[33] Dyskinesia is the second most common type of impairment of cerebral palsy.[25] It is a neurological movement disorder characterized by involuntary muscle contractions, slow repetitive movements, and abnormal postures of the trunk, neck, face, or arms and legs.[34] In Dyskinetic CP, sudden tight involuntary contraction and involuntary twitching and writhing are present simultaneously.[35] The Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS), Barry–Albright Dystonia Scale (BADS), Unified Dystonia Rating Scale (UDRS), Movement Disorder-Childhood Rating Scale (MD-CRS), Movement Disorder-Childhood Rating Scale 0–3 Years (MD-CRS 0–3), and the Dyskinesia Impairment Scale (DIS) are used to assess dyskinesia.[36] Oral drugs, intrathecal baclofen and deep brain stimulation, are promising options for the treatment of Diskinesia.[37] Muscle relaxants, medicines for sleep problems, and gastric reflux medicines are also effective in some cases.[33]

Dystonia

Dystonia is classified in to primary and secondary dystonia.[2] The assessment of dystonia is still not well understood due to the complexity of the symptoms and lack of researches.[38] The Amiel- Tison Neurological Assessment (ATNA) at term, Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS), Premie-Neuro for newborn infants, and the Hammersmith Infant Neurological Examination (HINE) for infants aged 2 months to 2 years. For children more than 2 years, the Neurological Sensory Motor Developmental Assessment (NSMDA) scales are used for rating of dystonia.[39] Bobath's neuro-developmental technique, inhibitory splinting and casting technique are much helpful in hypertonia.[40] Passive stretching is effective as it causes change in a joint that already has contracture.[41]

Motor abilities

Gross Motor skills are fundamental to childhood development.[42] For the assessment of the motor abilities in CP child 17 tools are used.[12] Functional limitation of CP child not only depends on the age of

the child but also according to Gross motor function classification.[43] The Gross Motor Function Classification System (GMFCS) is used to explain motor function in children with Cerebral Palsy (CP).[44] The gross motor functioning is mainly assessed by two tools: Gross Motor Function Classification System (GMFCS) and Functional Mobility Scale (FMS)[10] Sarah scale also used.[45] Gross Motor Function Measure (GMFM-88) is also used for the assessment of gross motor functioning.[46] Gross Motor Function Measure (GMFM-88) and (GMFM-66) were used as outcome measures to determine the changes in gross motor function in children with cerebral palsy undergoing treatment.[47] The Gross Motor Function Measure (GMFM) and the Pediatric Evaluation of Disability Inventory,[48] fulfill the criteria of reliability and validity with respect to responsiveness to change.[49] The autologous bone marrow-derived mesenchymal stromal cell transplantation improves motor function in patients with central nervous system disorders.[42] The Neurodevelopmental treatment improved gross motor function in children with cerebral palsy in four dimensions (laying and rolling, sitting, crawling and kneeling, and standing). However, walking, running,[50] and jumping[51] did not improve significantly.[52] The recreational horseback riding therapy (HBRT)[18], Modified Adeli suit therapy (MAST)[53], Throwing and Catching games**,** Running and Changing Direction**,** Jumping activities**,** Climbing activities**,** Balancing activities**,** Target practice**,** Ball games and Skipping activities are also improves the gross motor functioning.[51]

Gait

Motor problems in CP causes gait deviations.[54] So assessment of gait in these children is essential.[55] Spastic CP most commonly suffering from disorder of gait.[56] Observational tools are found from the available literature from which the Edinburgh Visual Gait Scale, the Visual Gait Assessment Scale and the Observational Gait Scale are commonly used for the assessment of gait in CP child.[57] Edinburgh Visual Gait Score[58]**,** Physician Rating Scale in children with hemiplegic cerebral palsy also shows good psychometric properties[59] for walking abnormalities.[60] Multichannel neuromuscular electrical stimulation, can substantially improve gait patterns and promote muscle strength in children with spastic CP.[61] Physical therapists use a range of mobility aids to make *therapy* more effective. Braces, casts, splints Exercise, balls and shoe inserts are types of orthotic equipment used to help with *walking*, posture and joint mobility.[62]

Balance

Postural control and balance is also an important component of gait disorder in CP child.[63] We found 22 tools for the assessment of the balance. These are the Berg Balance Scale (BBS), the Functional Reach Test, the Functional Walking Test, the Heel-to-Toe Stand, the Level of Sitting Ability, the Level of Sitting Scale, the Modified Posture Assessment Scale, the Pediatric Balance Scale, the Pediatric Reach Test, the Pediatric Clinical Test of Sensory Interaction for Balance, the Posture Assessment Scale, the Posture and Posture Ability Scale, the Seated Posture Control Measurement the Segmental Assessment of Trunk Control , the Sit- ting Assessment for Children with Neuromotor Dysfunction, the Sitting Assessment Scale, the Spinal Alignment for Range of Motion Measure, the Timed One-Leg Stance, the Timed Up and Down Stairs, the Timed Up and Go, the Trunk Control Measurement Scale, and Trunk Impairment Scale.[64] Physical therapy provides patients with exercises, stretching techniques, balance routines, and other regimes that promote strength, balance, coordination, increase muscle tone, and more. Aquatic therapy, Mobility Aids, Orthotic devices can help children with walking and reduce the chances of falling include Foot or ankle-foot orthotics, Spinal orthotics, Knee orthotics, Knee-ankle orthotics and walkers also come in various kinds, including: (Two-wheeled walkers, Four-wheeled walkers, Gait trainers, Walkers with chest support and Suspension Walkers).

Canes can also be used, common types of canes include (:Non-folding, Folding, Quad, Tripod and Folding canes with seats). When walking issues are severe, orthopedic surgery may be recommended for correction of spinal curvatures correction of joints and tendons and prevention of hip dislocation.[65]

Cognition

Cognition impairment is most commonly seen in CP child.[66] Nine give psychometric result for CP children. The included tests were The Columbia Mental Maturity Scale, The Leiter International Performance Scale, The Peabody Picture Vocabulary Test, The Pictorial Test of Intelligence, The Raven's Colored Progressive Matrices, The Stanford–Binet Intelligence Scales, The Wechsler Adult Intelligence Scale, the Wechsler Intelligence Scale for Children, and The Wechsler Preschool and Primary Scale of Intelligence.[67] For the treatment of cognition Aerobic activity, seems effective along with Muscle-strengthening activities should be done.[65]

Pain

In CP children pain is also a significant factor that impacts the quality of life of these children.[68] Pain in children with CP is not commonly known and left untreated so it becomes chronic.[69] Chronic pain affects health both emotionally and psychologically.[70] For more than 3 months, pain remains known as chronic pain. The literature includes a total of 54 chronic pain assessment tools which have strong psychometric properties from which 15 chronic pain assessment tools were chosen for inclusion in the best practice toolbox. The tools are Body Diagram, non-communicating Children's Pain Checklist-Revised, Pediatric Pain Questionnaire, and track pain over time (Bath Adolescent Pain Questionnaire, Child Activity Limitations Interview, Pediatric Pain Interference Scale, or both (Pediatric Pain Profile). They relied on observational, self-report (Body Diagram), or combination reporting styles. All tools had been validated with a pediatric population and a diverse variety of medical conditions.[71]

Medications can be one strategy for reducing pain in children with cerebral palsy, although they are not typically used alone. Antispasmodic medications,

Anticholinergic drugs, anti-inflammatory, Baclofen an antispasmodic and Surgery is used sometime.[72] Other strategies to help relieve pain include muscle assage, acupuncture, ice packs and heat therapy, hydrotherapy, and cognitive behavioral therapy.[73]

Discussion

In this systematic analysis of clinical studies using cerebral palsy as the primary endpoint, we found various descriptions of cerebral palsy, 167 separate assessment scales for 8context, a large variance in evaluation methods and CP rates recorded, and very little psychometric examination of the current scales. CP is manifestation of a wide range of cortical or sub cortical cerebral attacks that occur during the first year of life.[4] There are broad range of symptoms found in cerebral palsy from them spasticity, dystonia, dyskinesia, gait abnormalities, balance disorders, cognition abnormalities and chronic pain are the problem which are commonly face by person suffering from cerebral palsy.[74] There is no uniformity of composite measures as to how many symptoms can be present to apply for cerebral palsy.

Numerous incremental measures of symptoms severity gradation have been developed over the past 40 years.[75] The most appropriate technique and duration to produce the required effect.[15] Physical management, Pharmacotherapy, Neurosurgical, and Orthopedic procedures combindly gives good results.[31] There is a need of Multidisciplinary Approach in order to promote the independence of the child with impairment, both functionally and psychologically and to increase the quality of life of both the child and their family.[65]

Limitations

There are numerous shortcomings to our analysis. Like, we only collected researches that were conducted in English, analyzing various CP domains. Some domains are still not reviewed like scales for fine motor skills, hand functions and sensory assessment. We did not approach authors of the analysis to inquire for possibly undisclosed psychometric results. We are unable to find any older paper (pre-1985) that mentioned CP, so some earlier CP resources could have been missing. It is also likely that newer and undisclosed CP scales and treatment strategies are in use and yet unpublished, they not included in the study.

Conclusion

The selection of appropriate measurement tools is essential to clinical practice yet, it is unclear how best to assess CP because no existing scale has undergone for all impairments of CP. So many scales are available but most of them assess only one or two limitations of CP. For 8 impairments there are total 167 scales are available but only 53 have psychometric properties and none of the scale is available which assess all impairments of CP. A wide range of therapeutic interventions has been used in the treatment and management of children with cerebral palsy. There is a need one or several different types of treatment depending on how severe the symptoms are and what parts of the body are affected. The treatment differs from person to person, depending on each one's specific needs. There is a need of a proper treatment protocol to improve function and adjustments for the young nervous system and musculoskeletal system. If Physiotherapy treatment begin soon after diagnosis shows effective results.

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References

1. Blair E, Cans C. The definition of cerebral palsy. In: *Cerebral Palsy: A Multidisciplinary Approach, Third Edition*. Springer International Publishing; 2018:13-17.
2. Donald KA, Samia P, Kakooza-Mwesige A, Bearden D. Pediatric cerebral palsy in Africa: A systematic review. *Semin Pediatr Neurol*. 2014;21(1):30-35.
3. Garfinkle J, Li P, Boychuck Z, Bussières A, Majnemer A. Early Clinical Features of Cerebral Palsy in Children Without Perinatal Risk Factors: A Scoping Review. *Pediatr Neurol*. 2020;102:56-61.
4. Krigger KW. *Cerebral Palsy: An Overview*.; 2006.
5. Ghasia F, Brunstrom J, Gordon M, Tychsen L. Frequency and severity of visual sensory and motor Deficits in children with cerebral palsy: Gross motor function classification scale. *Investig Ophthalmol Vis Sci*. 2008;49(2):572-580.
6. Mutlu A, Livanelioglu A, Gunel MK. Reliability of Ashworth and Modified Ashworth Scales in children with spastic cerebral palsy. *BMC Musculoskelet Disord*. 2008;9(1):44.
7. Stavsky M, Mor O, Mastrolia SA, Greenbaum S, Than NG, Erez O. Cerebral Palsy-Trends in Epidemiology and Recent Development in Prenatal Mechanisms of Disease, Treatment, and Prevention. *Front Pediatr*. 2017;5:21.
8. Spastic Diplegia - an overview | ScienceDirect Topics.
9. Rethlefsen SA, Ryan DD, Kay RM. Classification Systems in Cerebral Palsy. *Orthop Clin NA*. 2010;41:457-467.
10. Bayon C, Raya R, Lara SL, Ramirez O, J IS, Rocon E. Robotic Therapies for Children with Cerebral Palsy: A Systematic Review. *Transl Biomed*. 2016;7(1).
11. Wingert JR, Burton H, Sinclair RJ, Brunstrom JE, Damiano DL. Tactile sensory abilities in cerebral palsy: deficits in roughness and object discrimination. *Dev Med Child Neurol*. 2008;50(11):832-838.
12. Beckung E, Hagberg G. Neuroimpairments, activity limitations, and participation restrictions in children with cerebral palsy. *Dev Med Child Neurol*. 2007;44(5):309-316.
13. Compagnone E, Maniglio J, Camposeo S, et al. Functional classifications for cerebral palsy: Correlations between the gross motor function classification system (GMFCS), the manual ability classification system (MACS) and the communication function classification system (CFCS). *Res Dev Disabil*. 2014;35(11):2651-2657.
14. Cerebral palsy - Diagnosis and treatment - Mayo Clinic. Accessed March 10, 2021. https://www.mayoclinic.org/diseases-conditions/cerebral-palsy/diagnosis-treatment/drc-20354005

15. What are common treatments for cerebral palsy? | NICHD - Eunice Kennedy Shriver National Institute of Child Health and Human Development. Accessed March 10, 2021. https://www.nichd.nih.gov/health/topics/cerebral-palsy/conditioninfo/treatments
16. Das SP, Ganesh GS. Evidence-based approach to physical therapy in cerebral palsy. *Indian J Orthop*. 2019;53(1):20-34.
17. Chrysagis N, Skordilis EK, Stavrou N, Grammatopoulou E, Koutsouki D. The effect of treadmill training on gross motor function and walking speed in ambulatory adolescents with cerebral palsy: A randomized controlled trial. *Am J Phys Med Rehabil*. 2012;91(9):747-760.
18. Molnar GE. Rehabilitation in cerebral palsy. *West J Med*. 1991;154(5):569-572. Accessed March 10, 2021. /pmc/articles/PMC1002833/?report=abstract
19. Zanon MA, Porfírio GJM, Riera R, Martimbianco ALC. Neurodevelopmental treatment approaches for children with cerebral palsy. *Cochrane Database Syst Rev*. 2015;2017(9).
20. DeLuca SC, Echols K, Ramey SL, Taub E. Pediatric Constraint-Induced Movement Therapy for a Young Child With Cerebral Palsy: Two Episodes of Care. *Phys Ther*. 2003;83(11):1003-1013.
21. Domagalska-Szopa M, Szopa A. Postural pattern recognition in children with unilateral cerebral palsy. *Ther Clin Risk Manag*. 2014;10(1):113-119.
22. Kalkman BM, Bar-On L, O'Brien TD, Maganaris CN. Stretching Interventions in Children With Cerebral Palsy: Why Are They Ineffective in Improving Muscle Function and How Can We Better Their Outcome? *Front Physiol*. 2020;11.
23. Pin TWM. Effectiveness of static weight-bearing exercises in children with cerebral palsy. *Pediatr Phys Ther*. 2007;19(1):62-73.
24. McNee AE, Will E, Lin JP, et al. The effect of serial casting on gait in children with cerebral palsy: preliminary results from a crossover trial. *Gait Posture*. 2007;25(3):463-468.
25. Verrotti A, Greco R, Spalice A, Chiarelli F, Iannetti P. Pharmacotherapy of spasticity in children with cerebral palsy. *Pediatr Neurol*. 2006;34(1):1-6.
26. Platz T, Eickhof C, Nuyens G, Vuadens P. Clinical scales for the assessment of spasticity, associated phenomena, and function: A systematic review of the literature. *Disabil Rehabil*. 2005;27(1-2):7-18.
27. Gracies JM, Burke K, Clegg NJ, et al. Reliability of the Tardieu Scale for Assessing Spasticity in Children With Cerebral Palsy. *Arch Phys Med Rehabil*. 2010;91(3):421-428.
28. Mutlu A, Livanelioglu A, Gunel MK. Reliability of Ashworth and Modified Ashworth Scales in children with spastic cerebral palsy. *BMC Musculoskelet Disord*. 2008;9(1):1-8.
29. Shamsoddini A, Amirsalari S, Hollisaz M-T, Rahimnia A, Khatibi-Aghda A. Management of spasticity in children with cerebral palsy. *Iran J Pediatr*. 2014;24(4):345-351. Accessed March 10, 2021. http://www.ncbi.nlm.nih.gov/pubmed/25755853
30. Patel DR, Soyode O. Pharmacologic interventions for reducing spasticity in cerebral palsy. In: *Indian Journal of Pediatrics*. Vol 72. The Indian Journal of Pediatrics; 2005:869-872.
31. Carvalho AL de, Ventura P, Taguchi T, Brandi I, Brites C, Lucena R. Cerebral Palsy in Children With Congenital Zika Syndrome: A 2-Year Neurodevelopmental Follow-up. *J Child Neurol*. 2020;35(3):202-207.
32. Nahm NJ, Graham HK, Gormley ME, Georgiadis AG. Management of hypertonia in cerebral palsy. *Curr Opin Pediatr*. 2018;30(1):57-64.
33. Termsarasab P. Medical treatment of dyskinetic cerebral palsy: translation into practice. *Dev Med Child Neurol*. 2017;59(12):1210-1210.
34. Jankovic J. Treatment of dystonia. *Lancet Neurol*. 2006;5(10):864-872.
35. Stewart K, Harvey A, Johnston LM. A systematic review of scales to measure dystonia and choreoathetosis in children with dyskinetic cerebral palsy. *Dev Med Child Neurol*. 2017;59(8):786-795.
36. Dystonia - an overview | ScienceDirect Topics.
37. Monbaliu E, Himmelmann K, Lin JP, et al. Clinical presentation and management of dyskinetic cerebral palsy. *Lancet Neurol*. 2017; 16(9):741-749.
38. JETHWA A, MINK J, MACARTHUR C, KNIGHTS S, FEHLINGS T, FEHLINGS D. Development of the Hypertonia Assessment Tool (HAT): a discriminative tool for hypertonia in children. *Dev Med Child Neurol*. 2009; 52(5):e83-e87.
39. Goo M, Tucker K, Johnston LM. Muscle tone assessments for children aged 0 to 12 years: a systematic review. *Dev Med Child Neurol*. 2018; 60(7):660-671.
40. Bovend'Eerdt TJ, Newman M, Barker K, Dawes H, Minelli C, Wade DT. The Effects of Stretching in Spasticity: A Systematic Review. *Arch Phys Med Rehabil*. 2008; 89(7):1395-1406.
41. Jo HM, Song JC, Jang SH. Improvements in spasticity and motor function using a static stretching device for people with chronic hemiparesis following stroke. *NeuroRehabilitation*. 2013; 32(2):369-375.
42. Wang X, Cheng H, Hua R, et al. Effects of bone marrow mesenchymal stromal cells on gross motor function measure scores of children with cerebral palsy: A preliminary clinical study. *Cytotherapy*. 2013; 15(12):1549-1562.
43. Curtis DJ, Butler P, Saavedra S, et al. The central role of trunk control in the gross motor function of children with cerebral palsy: A retrospective cross-sectional study. *Dev Med Child Neurol*. 2015; 57(4):351-357.
44. Carnahan KD, Arner M, Hägglund G. Association between gross motor function (GMFCS) and manual ability (MACS) in children with cerebral palsy. A population-based study of 359 children. *BMC Musculoskelet Disord*. 2007; 8(1):1-7.
45. Pinto KS, Carvalho CGC, Nakamoto L, Nunes LGN. The Sarah evaluation scale for children and adolescents with cerebral palsy: description and results. *Brazilian J Phys Ther*. 2016; 20(3):267-274.
46. Wiedemann LG, Ward S, Lim E, et al. High-density electromyographic data during isometric contractions of the ankle joint in children with cerebral palsy pre and post BoNT-A treatment. *Data Br*. 2019; 24.
47. Alotaibi M, Long T, Kennedy E, Bavishi S. The efficacy of GMFM-88 and GMFM-66 to detect changes in gross motor function in children with cerebral palsy (CP): A literature review. *Disabil Rehabil*. 2014; 36(8):617-627.
48. Bodkin AW, Robinson C, Perales FP. Reliability and Validity of the Gross Motor Function Classification System for Cerebral Palsy. *Pediatr Phys Ther*. 2003; 15(4):247-252.
49. Ketelaar M, Vermeer A, Helders PJ. Functional motor abilities of children with cerebral palsy: a

systematic literature review of assessment measures. *Clin Rehabil*. 1998; 12(5):369-380.
50. Labaf S, Shamsoddini A, Taghi Hollisaz M, Sobhani V, Shakibaee A. Effects of neurodevelopmental therapy on gross motor function in children with cerebral palsy. *Iran J Child Neurol*. 2015; 9(2):36-41.
51. Lucas BR, Elliott EJ, Coggan S, et al. Interventions to improve gross motor performance in children with neurodevelopmental disorders: a meta-analysis. *BMC Pediatr*. 2016; 16(1):193.
52. Mahani MK, Karimloo M, Amirsalari S. Effects of Modified Adeli Suit Therapy on Improvement of Gross Motor Function in Children with Cerebral Palsy. *Hong Kong J Occup Ther*. 2011; 21(1):9-14.
53. Clutterbuck G, Auld M, Johnston L. Active exercise interventions improve gross motor function of ambulant/semi-ambulant children with cerebral palsy: a systematic review. *Disabil Rehabil*. 2019; 41(10):1131-1151.
54. Armand S, Decoulon G, Bonnefoy-Mazure A. Gait analysis in children with cerebral palsy. *EFORT Open Rev*. 2016; 1(12):448-460.
55. Maathuis KGB, van der Schans CP, van Iperen A, Rietman HS, Geertzen JHB. Gait in Children With Cerebral Palsy. *J Pediatr Orthop*. 2005;25(3):268-272.
56. Mcintyre S, Morgan C, Walker K, Novak I. CEREBRAL PALSY-DON'T DELAY. *Dev Disabil Res Rev*. 2013; 17:114-129.
57. Brown CR, Hillman SJ, Richardson AM, Herman JL, Robb JE. Reliability and validity of the Visual Gait Assessment Scale for children with hemiplegic cerebral palsy when used by experienced and inexperienced observers. *Gait Posture*. 2008; 27(4):648-652.
58. Rathinam C, Bateman A, Peirson J, Skinner J. Observational gait assessment tools in paediatrics - A systematic review. *Gait Posture*. 2014; 40(2):279-285.
59. Dickens WE, Smith MF. Validation of a visual gait assessment scale for children with hemiplegic cerebral palsy. *Gait Posture*. 2006; 23(1):78-82.
60. Overview of Four Functional Classification Systems Commonly Used in Cerebral Palsy. *Children*. 2017; 4(12):30.
61. Tosi LL, Maher N, Moore DW, Goldstein M, Aisen ML. Adults with cerebral palsy: A workshop to define the challenges of treating and preventing secondary musculoskeletal and neuromuscular complications in this rapidly growing population. In: *Developmental Medicine and Child Neurology*. Vol 51. ; 2009:2-11.
62. novak I, Mcintyre S, Morgan C, et al. A systematic review of interventions for children with cerebral palsy: State of the evidence. *Dev Med Child Neurol*. 2013; 55(10):885-910.
63. Woollacott M, Shumway-Cook A, Hutchinson S, Ciol M, Price R, Kartin D. Effect of balance training on muscle activity used in recovery of stability in children with cerebral palsy: a pilot study. *Dev Med Child Neurol*. 2007; 47(7):455-461.
64. Saether R, Helbostad JL, Riphagen II, Vik T. Clinical tools to assess balance in children and adults with cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2013; 55(11):988-999.
65. Rose J, Wolff DR, Jones VK, Bloch DA, Oehlert JW, Gamble JG. Postural balance in children with cerebral palsy. *Dev Med Child Neurol*. 2002; 44(01):58.
66. Fisher L, Blair RJR. Cognitive impairment and its relationship to psychopathic tendencies in children with emotional and behavioral difficulties. *J Abnorm Child Psychol*. 1998; 26(6):511-519.
67. Yin Foo R, Guppy M, Johnston LM. Intelligence assessments for children with cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2013; 55(10):911-918.
68. Houlihan CM, O'Donnell M, Conaway M, Stevenson RD. Bodily pain and health-related quality of life in children with cerebral palsy. *Dev Med Child Neurol*. 2007; 46(5):305-310.
69. Penner M, Xie WY, Binepal N, Switzer L, Fehlings D. Characteristics of pain in children and youth with cerebral palsy. *Pediatrics*. 2013; 132(2):e407-e413.
70. Pelrine E, Novacheck T, Boyer E. Association of Knee Pain and Crouch Gait in Individuals with Cerebral Palsy. *J Pediatr Orthop*. 2020; 40(6):E504-E509.
71. Kingsnorth S, Orava T, Provvidenza C, et al. Chronic Pain Assessment Tools for Cerebral Palsy: A Systematic Review. *Pediatrics*. 2015; 136(4):e947-60.
72. Johnson E, Nilsson S, Adolfsson M. How pain management for children with cerebral palsy in South African schools complies with up-to-date knowledge. *African J Disabil*. 2019; 8(0).
73. Hirsh AT, Kratz AL, Engel JM, Jensen MP. Survey results of pain treatments in adults with cerebral palsy. *Am J Phys Med Rehabil*. 2011; 90(3):207-216.
74. Gupta R, Appleton RE. Cerebral palsy: not always what it seems. *Arch Dis Child*. 2001; 85(5):356-360.
75. Knox V, Evans AL. Evaluation of the functional effects of a course of Bobath therapy in children with cerebral palsy: A preliminary study. Dev Med Child Neurol.2002; 44(7):4447-460.

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Review Article

Internet of things (IOT)- at forensic on road highways parameters (introductory)

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Abstract

Today's world is the internet world; all the work should be systematic with the help of internet. Internet is available globally in all over the parts of the world. The basic parameter should be use in the today's world is Internet of Things which should be known as IOT. IOT is used globally in all over the world like forensic Science, medical, engineering Architecture etc. In this Paper we represent IOT in forensic for road safety which is used in National Highways to decrease the crime rate occurred most probably in National Highways. There are different types of sensors are also used for each and nearby traffic light which can detect and analysis and transmit the signal within time.

Keywords Traffic Lights, Sensors (Humidity, Accelerometers, Sound&Image), Networking Devices (LORA, WAN).

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Introduction

Internet of things (IOT) it is a basically an advance network comparable to internet. It is used for both living and non-living things. It is also called as network and sensing devices, worked and based on real base data. It is not basically a computer, it may be phone, watch thermostater, electric meters, cloth, sensors etc. it is depend on 5'A i.e. Anything, Anywhere, Anytime, Anyway & Anyhow.Internet of things (IOT) means Instruments, Interconnect, intelligently processed. With the help of IoT We can find the things quickly and can also Delegate the things which is connected to the internet based on IoT. IoT is depend on the 4 Levels of Smartness which are as follows:

a.) Passive:-It is used for communication to read the Radio Frequency Identification, as IoT is based on the Radio Frequency Parameters.
b.) Active: - It is used in communication with the help of Sensors like home auto mobilization.
c.) Aware: - Purpose of work based on simple calculation and computation.
d.) Autonomous: - Basically used to find the decision which is programmed in the devices. Decision should be based on the input and output strategies.

Internet of Brains: It is used to communicate the living things. It is used to send the signal from one person to another person. This application is used for preferably handicapped person who are not able to move from one place to another place and facing difficulties to send or receive signal.

This paper basically focuses on road (highway) crime activities such as Drug Smuggling, Human trafficking, Child Exploitation, Organized , kidnapping, Knife activities so on…We can keep an eye on these type of activitiesby the help of 4 types of sensors which are embedded in IoT device .We use IoT forensic techniques to investigate the crime on road . IoT is a

booming technology in it sector that give new direction to human being life. It is accessing via internet.

IoT is a type of network connecting device such as sensor, electronic device, CCTV camera etc. This is programmed in such way that it provide automation for the electronic devices that are connected in IoTinfrastructure .Some of the common devices that are used in day by day life are such as fan, refrigerators, AC, and TV etc.

This technology promises smartly integrated technology &equipped together in form of IoT product.

IoT is further advancement of machine learning and Artificial Intelligence (AI).

The demand of IoT is increases day by day.

There is no limitation of this technology and also an it is available in every field such as medical, healthcare, agriculture, home appliances and smart industries and many more.

INTERNET is a global computer network that consists group of networks and these network provide variety of information and communication facilities of consisting it also uses standard protocol.

Things are object that are present in our surroundings.

Internet of Things is a dynamic technology in this technology objects recognize themselves and it has good decision taking capabilities which is based on real life facts and information.

Basically this technology aims to make the effective object and then human can control and coordinate these objects according to their needs and access these objects anytime, anywhere.

Today's a is very busy life so IoT play very important roles in this situation suppose that have you ever been in situation where you want to the office and forget to switch off your home appliances like TV,

refrigerator, and light & right now you are helpless that you cannot return home to switch off? This situation IoT comes in your mind. And then IoT will remind you to essential tasks that often forget to do.
Also using the mobile application you can access your home appliances which is integrated with IoT that's why you can access it anytime anywhere from the world.

IOT FORENSIC: In IoT device there are many opportunity to bad actor access your personal data for miscellaneous use so that we use digital forensic.
IoT forensic also called digital forensic basically this is a technique and we also can say it is a process identifying, preserving, analyzing and presenting digital evidence to the court of law.

SENSORS: It is a device that receives a signal & response to inventive form of the electrical signal. The output signals crosses ponds some of the electrical signal such as voltage & current. The sensor received different type of signal such as Chemical, Physical,and Biological signal and convert them electrical signal. In IoT the main purpose of sensor is to collect all the data from surrounding environment and it is most important part of IoT infrastructure because IoT work based on the data which is collected by sensor. In this research we use 4 different sensors Such as

Humidity Sensor: IOT Humidity Sensor used to sense the amount of surrounding temperature and humidity and send the data to the actuators. Then actuator transfer the weather related information to the cloud then cloud send data to meteorological department and this information help to the weather forecasting.
This sensor helps to decreases the accidents due to causes of weather. There are many type of temperature and humidity sensor but in this scenario we use DHT11 sensor is a basic ultra-low-cost digital temperature and humidity sensor. This is used to measure temperature and this is a good range for measure both humidity and temperature.
Relative Humidity range of DHT11 is 20-95%
Temperature range of 0-50 ^{o}c with accuracy of +/- 2 ^{o}c

TABLE OF HUMIDITY SENSOR 1.1

SENSOR NAME	OPERATING HUMIDITY RANGE	OPERATING TEMPERATURE RANGE	On-Board Antenna	SUPERIER LOS RANGE
HUMIDITY SENSOR	0 to 100%	-40 TO + 85 ^{0}C	2 Miles Range with 900 MHz	28 Miles With 900 MHZ High Gain Antennas

Accelerometers:
One of sensing device is the name of Accelerometers and it detect an object acceleration that is rate change of the object speed with respect to the time .It is also detect changes to gravity. Accelerometers include smart pedometers and monitoring driving fleets. They can also be used anti-theft protection altering the system if an object should be stationary is moved.

TABLE OF ACCELEROMETERS 1.3

LOCATION	USAGE	FREQUENCY	ACCELERATION
HEAD	Tilt	0-8HZ	xx
HAND, WRIST,FINGER	Cont.	8-12HZ	0.04-1.0 g
HAND, ARMS, UPPER, BODY	Cont.	0-12HZ	0.5-9.0 g
FOOT, LEG	Cont.	0-12HZ	0.2-6.6 g

Sound sensor:
Sound sensor is a defined as a module that detect the sound wave through it sound intensity that convert the sound wave to electrical signal. When sound sensor device detects the change in intensity. It captures sound and then sends the cloud. The Simple sound sensors like the ones present from Seed Studio are mainly in expensive and there are many use can For example, detecting the presence of sound in an otherwise quiet room. There are also sound recorders available in sensor which is not only detect sound but also record it as soon as the intensity changes. That's particularly useful in security.

TABLE OF SOUND SENSOR 1.4

SENSOR NAME	SOUND SENSOR
OPERATING CURRENT	4~5MA
OPERATING VOLTAGE	3.3/5V
VOLTAGE GAIN	26(V=6V, F=1KHZ)
SIGNAL TO NOISE RATIO	54DB

Image Sensor:
Image sensor is a sensing device which is gather the information related to the images. We can also say that it is smart camera which has a capability to capture the images and also change its mode according to our convenience.

TABLE OF IMAGE SENSOR 1.2

SENSOR NAME	STRUCTURE TYPE	CHROMA TYPE	SHUTTER TYPE	CLASSIFICATION
IMAGE SENSOR	CCD OR CMOD	Color OR Monochromatic	Global or Rolling Shutter	Resolution, Frame Rate, Pixel Size and Sense format

LoRa WAN:
LoRa WAN is stand for Low power wide area network. Which is developed for IoT and M2M devices.It is low power wireless standard for providing a cellular style low data rate connectivity over the significant distance.
LoRa is a modulation and radio interference. This is to be designed and optimized to offer the exactly type of communication network needed to IoT and M2M.
LoRa is a physical layer and wireless network it is used to create long distance communication link.
LoRa is a network topology is based on Chirp spread spectrum modulation. This is similar to the FSK (Frequency Shift Key) modulation & it increased the

range of network significant.

Chirp Spread Spectrum Modulation:

The term Chirp spread spectrum modulation uses its entire allocation bandwidth to broadband signal. It is broad band spectrum and also resistant to multi path fading even when it has operating at very low power.

Introduction Diagram:

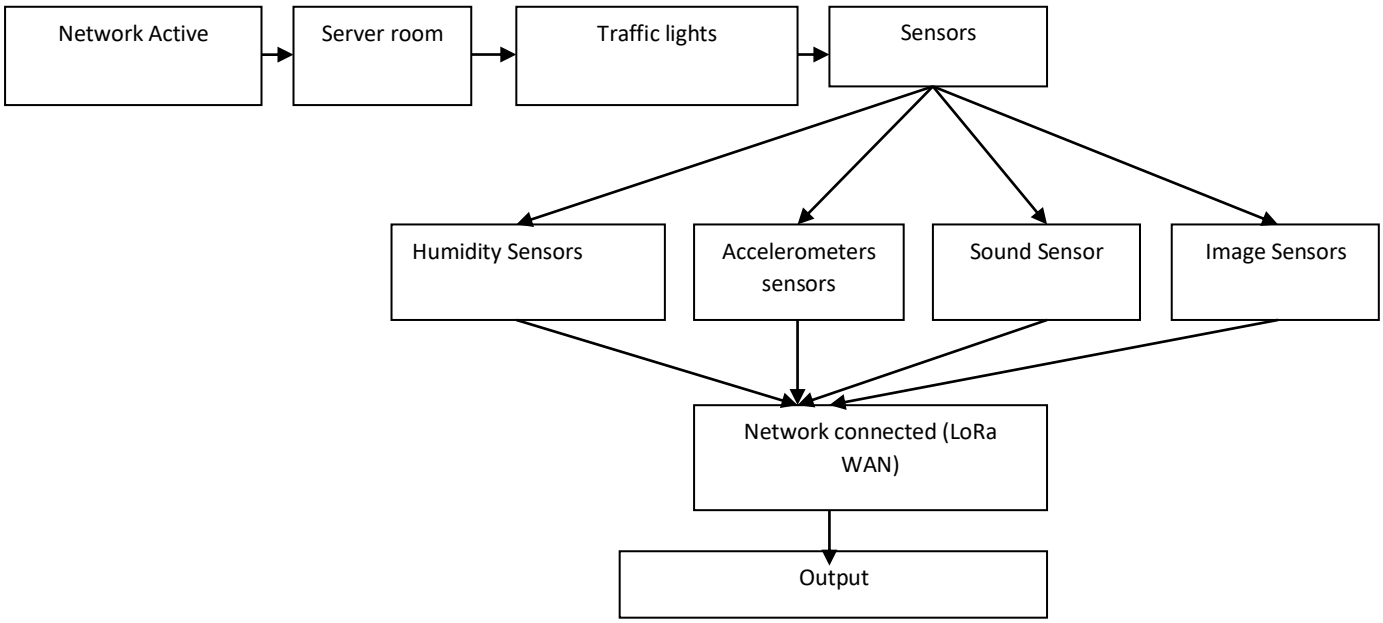

Fig indicates the General description of the IoT network Routing, in this block diagram an Active Network which is installed in the server room. Server room was connected to main centre of the branch of the configuration room. Then the server room is connected via network room and traffic lights are connected to the both server room and IoT network. At traffic lights four types of sensors are connected in such a way that the output is occurred when any illegal activity occur

The four types of sensors are Humidity sensors which works as a weather monitoring, AccelerometersSensors which is used to measure the Movement of object on theearth. Sound sensors is used to capture the sound on the highway and Image Sensors is used to check and analysis the image for criminal activity. Then all the sensors are connected in the Network which is a Long Range wide area network (LoRaWAN), finally output is received in the server room.

Block Diagram of IOT at Forensic on Road

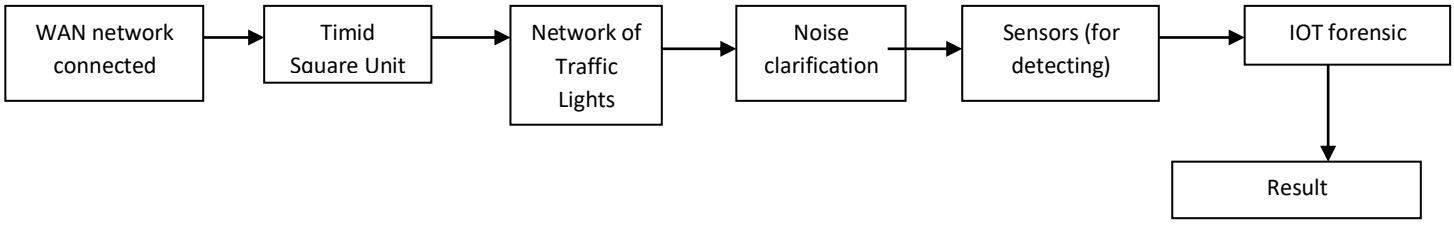

Fig Shows the block Diagram of the IoT at forensic on Road, in this Block Diagram wide area network is connected to the server room and at a traffic lights timid square unit is connected which work as a timing square to analysis the time for traffic lights. Then at the same time server room of active network is connected to the traffic lights which analysis the all activity at a proper time. For Clarification Noise filter is also used to clarify the noise at the same time. Then after the sensors are active when any illegal activity occurred. All the sensors is active and send the signal to the server room which IoT forensic technology is active and with the help of sensors all output is received by server room instantly so that within time the process should be done.

Block Diagram of Proposed Resolution Output of IOT at Forensic

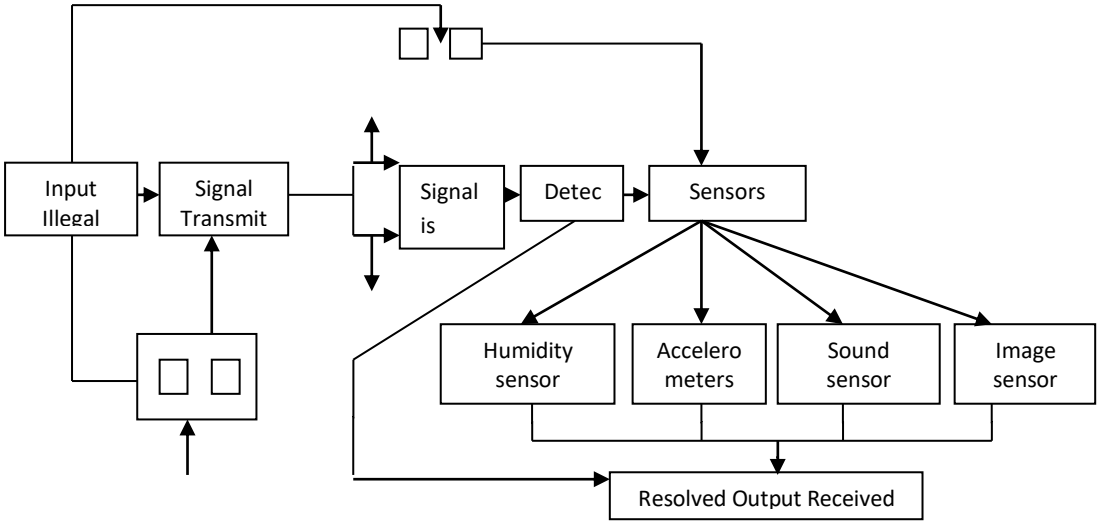

Fig shows the proposed methodology of the IoT forensic on road, In this methodology the process should be started when any illegal activity is occurred through the sensors, when sensors detect the any illegal activity after that signal is transmitted through wireless and at the same time signal is also transmitted to the server room and the controlled room precisely the signal is transmitted to both through wireless and controlled room. When signal is received to the server room at the detected centre the sensors are active at a time so that all the illegal work occurred at the same time.The four types of sensors are Humidity sensors which works as a weather monitoring, Accelerometers Sensors which is used to measure the movement of object on the earth. Sound sensors is used to capture the sound on the highway and Image Sensors is used to check and analysis the image for criminal activity.

At the output the resolved output is received in the server.

All the processes should be done through the sensors all sensors should be inactive when no illegal activity occurred, as any illegal activity occurred all the sensors and server room is active to analysis the activity. As crime rate is increases day by day and mostly crime and illegal activity happened on roads specially highways and national highways so for precautionary measure we installed this system to try to low the crime rate and appropriate process can be taken without delay. Mostly crime rate is increases in night so and all traffic light is activated 24 hours by using this our IoT software work in all day and night to try find out the illegal activity.

Proposed Methodology:-

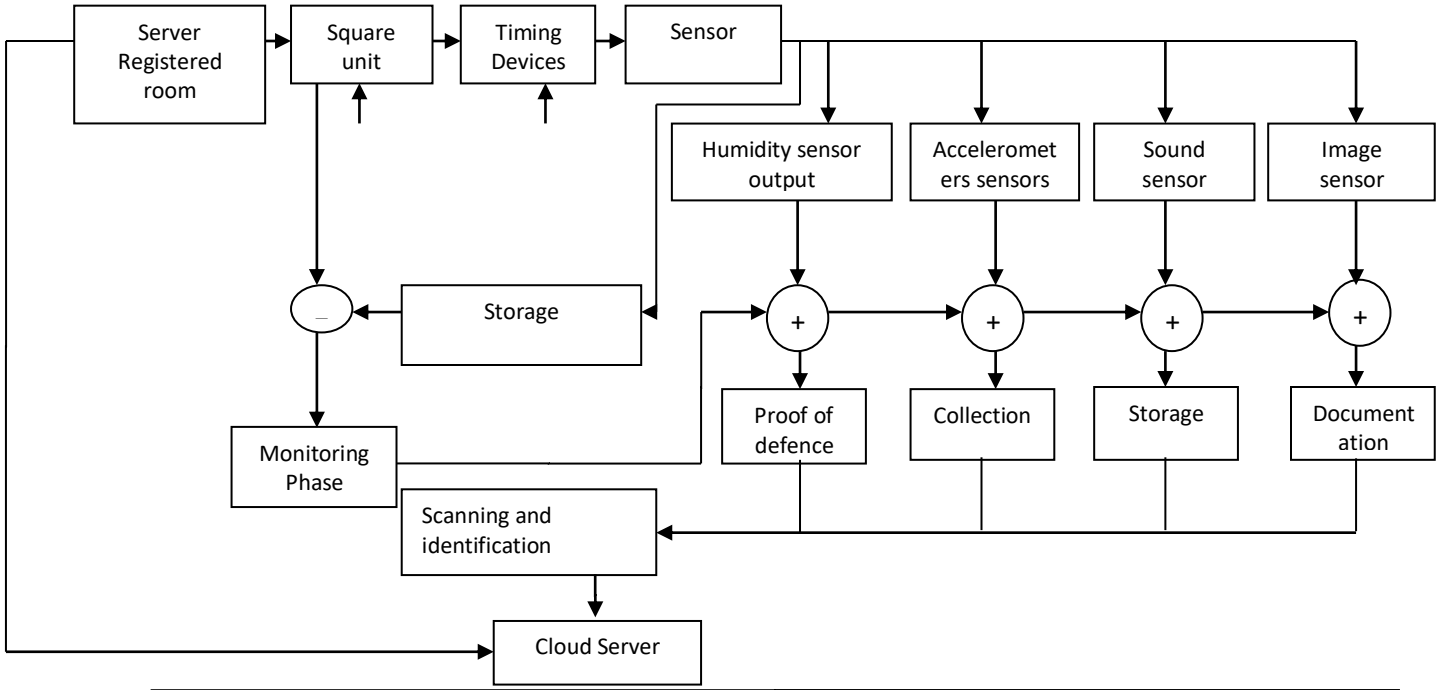

Fig shows the proposed methodology of the IoT based forensic on road with in methodology all the signal and should be transmitted to the cloud server which is worked as a output of the server room

Proposed Technique:-In this proposed technique all the sensors are connected which gives the following function to each sensors which are as follows:

a) Storage: it is used to store the data at the particular time; Data depend upon the storage of the devices. All the storage data should be store in the controlled or server room.
b) Monitoring Phase: it is used to monitoring the road and active when any illegal activity occurred.
c) Scanning and identification: In this scanning of each every moment is active on the road and the sensors works only when any activity occurred in the Highways. Identification message also sends to the controlled room via server.
d) Cloud Server: It is work as an Output in which all the data is stored.

Within this proposed techniques any illegal activity or any mish peening thing happened on the road then all the sensors are active and sends the message signal

Result and Discussion: In the Result we get all the data followed by sensors to the controlled room or server room for find out the facts related to the activity. As crime rates is increases day by day so with the help of this Project we can overcome or limitation the illegal activity happened on highways and National Highways.

Future Scope: In Future scope we add the following this which are as follows:

a. A sensors is used to detect the history of vehicles like owner Registration.
b. GPS arealso enabled.

Key characteristic of LoRa:

Batter battery life
Low Cost.
Limitation of data throughput of capacity.
Large deployment

Advantage:

This network topology used communication technology long range capability such as signal gateway based station & it can give services to entire city or hundreds of square kilometer.

LoRa is a better link budget greater than any other any other standard communication technique.

Conclusion:

The proposed techniques which is based on the IoT gives the promising result in terms of network based on wireless area network sensor which can detect the illegal activity. This various connected devices in nature allows us to conceive new data analysis that are very expensive in terms of acquiring latest computer resources and tools. The knowledge management and could not be carried by a single tools or network device or secure firewall to protect from intruders from time to time. The forensic investigation process on these devices can be taken as challenge for modern forensic investigators but should get the results within idle time of the computer available in the forensic laboratory.

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Conflict of interest: Nil
Acknowledgement: None

References:

1. World Internet Users and 2017 Population Stats, 10th July, 2017 [http://http://www.internetworldstats.com/stats.htm]
2. IoT' connected smart devices.‖ Juniper Research, 28 July 2015. Web. Retrieved 8 Mar. 2016.
3. FBI, IC3. ICCC (IC3) 2015. Web. Retrieved 10 March 2016. http://www.ic3.gov/media/2015/150623.aspx
4. SCADA vulnerability on the rise - EETimes. Rich Quinnell, 24 Sept. 2015. Web. 26 Apr. 2016. Id=1327785
5. Kushner, David. The real story of stuxnet.‖ IEEE Spectrum. 2016.
6. Morgan, Steven C. —Cyber Security Market Report.‖ 2016.
7. Zawoad, S. & Hasan, R., 2015. FAIoT: Towards Building a Forensics Aware Eco System for the Internet of Things. - 2015 IEEE International Conference on Services Computing, SCC 2015. pp. 279–284.
8. Charlie Osborne, 2016. Insulin pump vulnerabilities could lead to overdose (2016).
9. Borgohain, T., Kumar, U. & Sanyal, S., 2015. Survey of Security and Privacy Issues of Internet of Things.
10. Huuck, R., 2015. IoT: The Internet of Threats and Static Program Analysis Defense
11. Al-Masri, E., Bai, Y. and Li, J. (2018) 'A Fog-Based Digital Forensics Investigation Framework for IoT Systems', in 2018 IEEE International Conference on Smart Cloud (SmartCloud), pp. 196–201.
12. Alabdulsalam, S. et al. (2018) 'Internet of Things Forensics – Challenges and a Case Study', in IFIP International Conference on Digital Forensics, pp. 35–48.
13. Atlam, H. F., Alenezi, A., Hussein, R. K., et al. (2018) 'Validation of an Adaptive Risk-based Access Control Model for the Internet of Things', International Journal of Computer Network and Information Security (IJCNIS), pp. 26–35.
14. Atlam, H. F., Alassafi, M. O., Alenezi1, A., et al. (2018) 'XACML for Building Access Control Policies in Internet of Things', in f the 3rd International Conference on Internet of Things, Big Data and Security (IoTBDS 2018), pp. 253–260.
15. Zulkipli, N. H. N., Alenezi, A. and Wills, G. B. (2017) 'IoT Forensic: Bridging the Challenges in Digital Forensic and the Internet of Things', in The 2nd International Conference on Internet of Things, Big Data and Security, IoTBDS, pp. 315–324.
16. J. Gantz and D. Reinsel. THE DIGITAL UNIVERSE IN 2020: Big data, bigger digital shadows, and biggest growth in the Far East. http://www.emc.com/collateral/analystreports/idc-the-digital-universe-i n-2020.pdf

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Original Article

To compare the reliability of Modified Ashworth Scale and Modified Tardieu Scale in treatment of spastic cerebral palsy using tactile stimulation.

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Abstract

Background: CP is a group of clinical syndromes that describe permanent disorders of movement and posture. **Spastic cerebral palsy** is the most common form of the disorder. Children affected with spastic cerebral palsy have stiff muscles which cause jerky on repeated movements. To assess spasticity various scales are present. The purpose of this study is to analyse the interrater reliability of Modified Ashworth scale and Modified Tardieu Scale in children with Spastic Cerebral Palsy using Tactile Stimulation. **Material and Method:** This was an experimental study in which 14 children affected with spastic cerebral palsy were selected and then for seven days therapeutic intervention was given to them to reduce spasticity. Pre and Post readings of Modified Ashworth Scale & Modified Tardieu Scale were then recorded by two raters to compare the reliability of the scales. **Statistical Analysis:** The data was compiled and analysed by using EZR statistical software. Pearson's Correlation Coefficient was used to obtain the reliability of MAS & MTS and Paired t-test was applied to determine the effectiveness of the intervention given. **Result & Conclusion:** Study concluded thatinterclass correlation coefficient for MAS obtained was excellent (between 0.75-1.00). However for MTS the results obtained were between moderate to good (fair being- 0.40-0.59 while good being 0.60-0.74). Hence, the results for correlation between the two raters obtained were reliable. However, the effectiveness of the therapy was non-optimistic (p value >0.05, which was considered standard).

Key words: Cerebral Palsy, Spasticity, Reliability, Raters, MAS (Modified Ashworth Scale), MTS (Modified Tardieu Scale).

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Introduction

Cerebral palsy (CP) is a childhood condition in which there is a motor disability (palsy) caused by a static, non-progressive lesion in the brain. CP is a group of clinical syndromes that describe permanent disorders of movement and posture. It is characterized by abnormal muscle tone, posture, and movement, thereby limiting the activity of the affected person. The motor disorders of Cerebral Palsy are often accompanied with disturbances of sensation, perception, cognition, communication and behavior, epilepsy, and secondary musculoskeletal problems[1].

There are several types of cerebral palsy, classified according to the type of movement disorderinvolved, the body parts affected, and how severe the symptoms are. Some types involve intellectual and developmental disabilities (IDDs) as well as movement problems.

Spastic cerebral palsy is the most common form of the disorder. Children affected with spastic cerebral palsy have stiff muscles which cause jerky on repeated movements. There are different topographical distributions of spastic cerebral palsy, depending on the body parts affected. Diseases such as stroke, traumatic brain injury, spinal cord injury, cerebral palsy and multiple sclerosis are associated with significant spasticity[2].

Spasticity as classically defined by Lance as a motor disorder characterised by a velocity dependent increase in tonic stretch reflexes[3] or a velocity dependent increased resistance to passive muscle stretch[4-6], or alternatively as inappropriate involuntary muscle activity associated with upper motor neuron paralysis. Spasticity can result in functional problems with daily living activities (ADL) such as gait, feeding, washing, toileting and dressing[7].

The Modified Ashworth Scale and the Modified Tardieu Scale are two clinical rating scales that are widely used for assessing the spasticity[8-10].

To assess spasticity accurately in clinical practise and for research purposes, reliable and valid tools must be used. The Modified Ashworth Scale is a globally trusted clinical tool used to measure hypertonicity. In 1964, Bryan Ashworth released the Ashworth Scale as a method of grading hypertonicity. The original scale was a five point numerical scale that graded hypertonicity from zero to four where zero denotes no resistance and four denotes the limb in question as either being rigid in flexion or extension. However, in 1987, while conducting a study Bohannon and Smith amended the Ashworth Scale by adding 1+ to the scale to increase its sensitivity.

Since its alteration the scale was renamed as Modified Ashworth Scale and it has been applied in practice as a measure of hypertonicity.

The Tardieu Scale was developed by Tardieu et al in 1954. Held and Pierrot-Deseilligny modified it in 1969, and it was further modified in 1999 by Boyd and Graham. This latest version of the Tardieu Scale is called the Modified Tardieu Scale (MTS). The Tardieu Scale has been thought as a better alternative to the Modified Ashworth Scale for assessing Spasticity, as it measure and compare the muscle reaction to passive stretch at both slow and fast velocities[11]. The MTS considers R2, R1 and R2−R1 to measure spasticity. The R2 is the passive range of motion measured during slow passive stretch. The R1 is the angle of muscle reaction measured during fast passive stretch, and occurs in a particular angle of 'catch' from hyperactive stretch reflex. Large and small differences between R2 and R1 indicate spasticity and muscle contracture, respectively. Quality of muscle reaction during fast passive stretch is also graded based on 0–4 scores and is defined as the MTS scores.

The aim of this study was to analyse the interrater reliability of Modified Ashworth scale and Modified Tardieu Scale in children with Spastic Cerebral Palsy using Tactile Stimulation.

METHOD

Participants

30 children were randomly selected and recruited for the study from the department of physiotherapy from the out-patient department of Jyoti Rao Phule Subharti College of Physiotherapy, Meerut. 23 participants were identified with spastic Cerebral Palsy (All topographical variations i.e., hemiplegic, diaplegic, triplegic, paraplegic and quadriplegic) 4 of which dropped out from the study owing to various reasons whereas 5 others were rejected from the study for having not met with the inclusion criteria (other types of CP i.e., ataxic, athetoid, mixed and flaccid).

Inclusion Criteria

1. Patients suffering from spastic cerebral palsy (All topographical variations i.e., hemiplegic, diaplegic, triplegic, paraplegic and quadriplegic).
2. Age group 6 years to 12 years.
3. All etiology where given prefence so as to gain a wide range of patients (Hypoxic Ishchaemic Encephalopathy, Hyperbilirubinaemia, Post trauma, Post seizures, etc).
4. Consent was given by patient party.

Exclusion Criteria

1. All the other type of cerebral palsy (athetoid, ataxic, mixed and flaccid).
2. Patient party withdrew or did not give consent.
3. Ages not below 6 years and above 12 years of age.

Raters

Two raters both of whom are physiotherapists undergoing post-graduation in physiotherapy in Neurology from Jyoti Rao Phule Subharti College of Physiotherapy. Both have handled such cases and are intimately aware of the use and interpretation of both the scales. Both physiotherapists have been trained by neurophysiotherapists having more ten years of experience in the field.

Tools and Testing

The tools used in the study were GMFM-66, Modified Ashworth Scale and Modified Tardieu Scale.

Gross Motor Function Measure (GMFM) is an assessment tool designed and used to evaluate changes in gross motor function with interventions in children with cerebral palsy. It was first developed in 1997 as a five level clinical classification system. Items that span the spectrum of gross motor activities are (a) Lying and Rolling (b) Sitting (c) Crawling and Kneeling (d) Standing (e) Walking, Running and Jumping.

The GMFM-66 is a subset of the original 88 items identified through Rasch analysis, Items are ordered in terms of difficulty and a unit of change has the same meaning throughout the scale ranging 0 to 100.

The GMFM-66 provides information on the level of difficulty of each item thereby providing information to assist with realistic goal settings.

The Modified Ashworth Scale is a universally accepted scale used to measure hypertonicity. It is a six point numerical scale. It is as follows:

Table 1: Modified Ashworth Scale

Grade	Modified Ashworth Scale
0	No increase in muscle tone
1	Slight increase in muscle tone, with a catch and release or minimal resistance at the end of the range of motion when an affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested as a catch, followed by minimal resistance through the remainder (less than half) of the range of motion
2	A marked increase in muscle tone throughout most of the range of motion, but affected part(s) are still easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

The Modified Tardieu Scale quantifies muscle tone at specified velocities and has been suggested as superior to Ashworth Scale for assessment of neural vs. peripheral contributions of spasticity[12-14]. The scale is given in the below table:

Table 2: Modified Tardieu Scale

Grade	Modified Tardieu Scale	
0	No resistance throughout the course of the passive movement.	
1	Slight resistance throughout the course of passive movement, with no clear catch at precise angle.	
2	Clear catch at precise angle, interrupting the passive movement followed by release.	
3	Fatigable clonus (<10s when maintaining pressure) occurring at precise angle.	
4	Infatiguable clonus (>10s when maintaining pressure) occurring at preciseangle.	
V1 As slow as possible		R1 Angle of catch seen at Velocity V2 or V3

V2 Speed of the limb segment falling.	R2 Full range of motion achieved when muscle is at rest and tested at V1 velocity.
V3 As fast as possible (> natural drop)	

Adapted from Bohannon and Smith and Boyd et al
Note: V1 is used to measure the passive range of motion (PROM). Only V2 and V3 are used to rate spasticity.

Procedure

30 children were randomly selected from the department of Physiotherapy, of which 14 participants fulfilled the inclusion criteria as well gave their consent for participation in the study. The participants and their caregivers were explained in detail about the objective of the study and the intervention that would be employed.
The raters performed their assessments discretely and a half hour gap was given between the two assessments. The order of assessment and sequence of muscle testing by two was sequenced. The muscle testing sequence was in order of Hip Adductors then Hamstring followed by the Plantar flexors.

Table 3: Starting joint positions and Velocities

Muscle	Position	Velocity
Hip Adductors, Knee Extended	Hips and Knee Extended	V3 for R1 V1 for R2
Hip Adductors, Knee Flexed	Hip Extended, Knee flexed by 90˚	
Knee Flexors, Hip Extended	Prone lying, hip extended.	
Plantar flexors, Knee Extended	Knee fully extended	
Plantar flexors, Knee Flexed	Knee fully flexed by 90˚	

The testing was performed with the child being emotionally stable & devoid of any anxiety, excitement or fear as any emotional distress may exaggerate muscle tone. The documentation of each raters was shared or discussed by both raters.
Each child then underwent therapeutic intervention as predecided by the raters.

Table 4: Interventions made in the study

Sl. No.	Intervention	Dosimetry	Duration
1	Gentle Rocking and Shaking Exercises using Swiss Ball	3 sets; 10 repetitions in each set	-
2	Slow Stroking	5 repetitions with 30 second interval in between	10 minutes
3	Prolonged Stretch	3 sets; 30 second hold with 3 repetitions in each set.	-
4	Neutral warmth	-	10-20 minutes

(Ref. CASH'S Textbook of Neurology for Physiotherapists, 4th Ed.)

Data Analysis

Measurements by different raters overthe same child on day one and day seven were used to determine the interrater reliability. The interrater reliability was calculated for the Modified Ashworth Scale scores & Modified Tardieu Scale scores. EZR statistical software was used to analyse the data collected. Paired t-test was applied to determine the effectiveness of the therapy. Pearson's coefficient for correlation was applied to determine the interclass reliability between the two raters.

Table 5: Analysis of the data collected

Scale	Muscles	Correlation coefficient range pre and post		p values of paired t-test	
		Rater 1	Rater 2	Rater 1	Rater 2
MAS	Hip Adductors	0.904-0.991	0.687-0.966	0.823	0.136
	Plantar flexors	0.922-0.992	0.856-0.986	0.165	0.275
	Hamstrings	0.913-0.991	0.856-0.986	0.104	0.0823
MTS	Hip Adductors	0.054-0.946	0.79-0.978	0.0823	0.336
	Plantar flexors	0.79-0.978	0.358-0.915	0.336	0.0823
	Hamstrings	0.632-0.958	0.559-0.948	0.0823	0.0823

Result & Conclusion

Fourteen children with a mean age of 8 years 9 months (range 6 years 3 months to 11 years 7 months) were included. Eight of them were male and six were female. Ten children had spastic diplegic cerebral palsy, and four had triplegic cerebral palsy. Three of the children belonged to level II in the Gross Motor Function Classification System and eleven to level III. Children were rated twiceThe second ratings were done 1 week followed by seven days of therapeutic intervention. The Modified Ashworth Scale and Modified Tardieu Scale scores were distributed across the entire scales (Table 5). No child reported any discomfort during the testing procedure. The correlation coefficient for MAS and MTS for the targeted muscles has been given above (table 5). ICC for MAS obtained were excellent (between 0.75-1.00). However for MTS the results obtained were between moderate to good (fair being- 0.40-0.59 while good being 0.60-0.74). Hence, the results for correlation between the two raters obtained were reliable. However, the effectiveness of the therapy was non-optimistic (p value >0.05, which was considered standard).

Discussion

Fosang et al concluded that the interrater reliability ofthe Modified Tardieu Scale was better than that of the ModifiedAshworth Scale, none of the interrater intraclass correlation coefficients (of the Modified Ashworth Scale score or theModified Tardieu Scale score) in their study reached the acceptable level of 0.75[15].
Winnie Ka Ling Yam et al concluded that the intraclass correlation coefficients of Modified Ashworth Scales and Modified Tardieu were low and did not reach the acceptable limit of 0.75[16].
In our study the correlation coefficient for MAS and MTS for the targeted muscles has been given above (table 5). ICC for MAS obtained was excellent (between 0.75-1.00). However for MTS the results obtained were between moderate to good (fair being- 0.40-0.59 while good being 0.60-0.74). Hence, the

results for correlation between the two raters obtained were reliable. However, the effectiveness of the therapy was non-optimistic (p value >0.05; table 5, which was considered standard).

Extraneous factors, such as the emotional status of the child or pain that could contribute to variability were specifically identified and care was taken to avoid such circumstances.The emotional instability of the child had been eliminated by specific instructions in our testing procedure, and no child reported any pain or discomfort. To improve scoring methods, strict standardization of the position and procedure was used in our study. The starting limb position, neutral positioning of the head, and the number and velocity of testing movement were specified to reduce variability arising from reflex excitability and viscoelasticity of soft tissues and joints.However, it would be interesting to undertake further studies to see if standardization (e.g., preceding activities, interval between testing movements, force used, and external standardization with three-dimensional movement analysis) might improve the chances of reliability further. To resemble the clinical setting,we distributed written guidelines and included the scales andinstructions in the recording forms. Further studies should be performed to identify what type of training to raters might further increase the interrater reliability of the scale. In summary, the interrater reliability of the Modified Ashworth Scale and the Modified Tardieu Scale was good.

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References

1. Stavsky M, Mor O, Mastrolia SA, Greenbaum S, Than NG and Erez O (2017) Cerebral Palsy—Trends in Epidemiology and Recent Development in Prenatal Mechanisms of Disease, Treatment, and Prevention. Front. Pediatr. 5:21. doi: 10.3389/fped.2017.00021.
2. Abolhasani H, Ansari NN, Naghdi S, et al. Comparing the validity of the Modified Modified Ashworth Scale (MMAS) and the Modified Tardieu Scale (MTS) in the assessment of wrist flexor spasticity in patients with stroke: protocol for a neurophysiological study. BMJ Open 2012;2:e001394. doi:10.1136/bmjopen-2012-001394
3. Lance JW. The control of muscle tone, reflexes, and movement: Robert Wartenberg Lecture. Neurology 1980;30:1303–13.
4. J.W. Lance, Pathophysiology of spasticity and clinical experience with baclofen, in: Spasticity: Disordered Motor Control, J.W. Lance, R.G. Feldman and W.P. Koella, eds, Year book, Chicago, 1980, pp. 185–204.
5. Goldstein EM. Spasticity management: an overview. *J Child Neurol*2001;16(1):16-23.
6. Sanger TD, Delgado MR, Gaebler-Spira D, et al. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics*2003;111(1): e89-97.
7. AlirezaShamsoddini*1, PhD; Susan Amirsalari2, MD; Mohammad-Taghi Hollisaz1, MD; Alireza Rahimnia3, MD; Amideddin Khatibi-Aghda1, MD 1Exercise Physiology Research Center, 2Department of Pediatric Neurology, 3Department of Orthopedic Surgery, Baqiyatallah University of Medical Sciences, Tehran, Iran Iran J Pediatr Aug 2014; Vol 24 (No 4), Pp: 345-351.
8. Bohannon RW, Smith MB: Interrater reliability of a modified Ashworth scale of muscle spasticity. PhysTher 1987;67:206–207.
9. Boyd RN, Barwood SA, Ballieu CE, Granham HK: Validity of aclinical measure of spasticity in children with cerebral palsy in adouble-blinded randomized controlled clinical trial, abstract. DevMed Child Neurol 1998;40(Suppl 78):7.
10. Van Wijck FMJ, Pandyan AD, Johnson GR, Barnes MP. Assessing motor deficits in neurological rehabilitation: Patterns of instrument usage, Neurorehab Neural Rep 2001;15:23-30.
11. F.Li[1], Y.WU[2], X.LI[2]; Test-retest reliability and inter-rater reliability of the modified Ashworth and the modified Tardieu Scale in hemiplegic patients with stroke: [1]Department of rehabilitation, Huashan Hospital Fudan University, Shanghai, China [2]Department of rehabilitation First Rehabilitation Hospital of Shanghai, China.
12. Patrick E, Ada L. The Tardieu Scale differentiates contracture from spasticity whereas the Ashworth Scale is confounded by it. ClinRehabil 2006; 20: 173–182.
13. Fleuren JF, Voerman GE, Erren-Wolters CV, Snoek GJ, Rietman JS, Hermens HJ et al. Stop using the Ashworth Scale for the assessment of spasticity. J NeurolNeurosurg Psychiatry 2010; 81: 46–52.
14. Haugh AB, Pandyan AD, Johnson GR. A systematic review of the Tardieu Scale for the measurement of spasticity. DisabilRehabil 2006; 28: 899–907.
15. Fosang AL, Galea MP, McCoy AT, et al: Measures of muscle and joint performance in the lower limb of children with cerebral palsy. Dev Med Child Neurol 2003;45:664–670.
16. Winnie Ka Ling Yam, FHKAM (Paediatrics); Milan So Mei Leung, PDipPT: Interrater Reliability of Modified Ashworth Scale and Modified Tardieu Scale in Children With Spastic Cerebral Palsy. J Child Neurol 2006;21:1031–1035.

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