Online ISSN: 2249-4618
Print ISSN: 0975-5888

Global Journal of Medical Research: B

Pharma, Drug Discovery, Toxicology and Medicine

Hydrochlorothiazide Diuretic

Delivery of Macromolecular Drugs

Highlights

Neurotoxic or Neuroprotective

Vasoconstrictor and Antihistaminic

Discovering Thoughts, Inventing Future

VOLUME 15 ISSUE 2 VERSION 1.0

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Volume 15 Issue 2 (Ver. 1.0)

Open Association of Research Society

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Registration No.: 430374
Import-Export Code: 1109007027
Employer Identification Number (EIN):
USA Tax ID: 98-0673427

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Contents of the Issue

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology and Medicine
Volume 15 Issue 2 Version 1.0 Year 2015
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Delivery of Macromolecular Drugs using Microsphere Technology

By Shabna, Sijo Pattam, Vimal Mathew & Sujith Varma

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Introduction- Resent years have witnessed development of protein- based therapeutic agent as the main focus of biotechnology industry. Progress made in biotechnology, genomics and combinatorial chemistry have led to the discovery of a wide variety of active moiety for specific therapeutics application. However, the common problems associated with these active moieties such as poor stability, low solubility, high potency etc, have paved way for developing a new method of drug delivery system. Considerable attention was made for the development of new drug delivery technology in recent research. The reason for developing a new drug delivery system is to apply in some clinical situations, where a constant drug delivery rate is insufficient, like delivery of insulin for patients with diabetes mellitus, gastric acid inhibitors for ulcer control, anti arrhythmic for patients with heart rhythm disorders, nitrates for patients with angina pectoris, birth control, immunization, cancer chemotherapy, selective β-blockade and general hormone replacement. The treatment for these clinical conditions could be optimized through the use of a novel delivery system (NDDS) (1). For delivering genetically engineered pharmaceuticals like peptides and proteins to the site of action, without incurring biological inactivation, need new system of delivery. Targeting the active moiety for better therapeutic efficacy can improve patient compliance by reducing the size and number of doses. Over the past decades major development were made in systemic delivery of protein and peptides by oral, transdermal and pulmonary routes (2-3).

GJMR-B Classification : NLMC Code: QV 55

Strictly as per the compliance and regulations of:

Delivery of Macromolecular Drugs using Microsphere Technology

Shabna [α], Sijo Pattam [σ], Vimal Mathew [ρ] & Sujith Varma [ω]

I. Introduction

Resent years have witnessed development of protein- based therapeutic agent as the main focus of biotechnology industry. Progress made in biotechnology, genomics and combinatorial chemistry have led to the discovery of a wide variety of active moiety for specific therapeutics application. However, the common problems associated with these active moieties such as poor stability, low solubility, high potency etc, have paved way for developing a new method of drug delivery system. Considerable attention was made for the development of new drug delivery technology in recent research. The reason for developing a new drug delivery system is to apply in some clinical situations, where a constant drug delivery rate is insufficient, like delivery of insulin for patients with diabetes mellitus, gastric acid inhibitors for ulcer control, anti arrhythmic for patients with heart rhythm disorders, nitrates for patients with angina pectoris, birth control, immunization, cancer chemotherapy, selective β-blockade and general hormone replacement. The treatment for these clinical conditions could be optimized through the use of a novel delivery system (NDDS) (1). For delivering genetically engineered pharmaceuticals like peptides and proteins to the site of action, without incurring biological inactivation, need new system of delivery. Targeting the active moiety for better therapeutic efficacy can improve patient compliance by reducing the size and number of doses. Over the past decades major development were made in systemic delivery of protein and peptides by oral, transdermal and pulmonary routes (2-3).

The controlled release technology aims to deliver the drug overcoming the difficulties associated with traditional methods of administration. Controlled delivery technology utilizes devices such as polymer based disks, microparticles or pallets, rods, which can encapsulate the drug and release in a controlled manner for a prolong period of time. Among the various devices for the controlled release, biodegradable polymer microspheres are the one most used, and can be administered by injecting into the blood stream via intramuscular injection, subcutaneous, oral or by inhalation (4). Polymeric materials are the most diverse class of materials and offer benefits to patient health care and treatment (5). Very few of these systems have reached the market and its reason may be due to the failure in addressing the fundamental concepts of pulsatile delivery regardless of the route of administration.

Micropsheres are defined as homogenous, monolithic particles with size ranging from 1-1000 μm. They are employed as drug carriers for controlled release. Microspheres are also referred to as microparticles. Microsphere technologies have significant importance in biomedical application. Delivery of therapeutic moiety by microspheres will improve the therapeutic efficacy by providing localization of the active substance at the site of action, and thereby prolonging the release of drugs. Sensitive drugs like proteins and peptides may be protected against chemical and enzymatic degradation when the drugs are enclosed in microspheres (6-7). Microspheres are prepared from natural and synthetic materials. Different microspheres are commercially available in market like glass microspheres, polymer microspheres, and ceramic microspheres and are used for different applications.

Delivering therapeutic moiety inside the body utilizes polymeric microspheres as the carrier (8). The polymeric microspheres can be biodegradable or non biodegradable. Non biodegradable microspheres when injected inside can cause carrier toxicity when used over a long period of time however; biodegradable microspheres tend to exclude these problems and are better suited for parentral applications. Biodegradable microspheres are prepared either from synthetic and natural polymers, and the main requirement for such products is that the degradation products should be nontoxic. The natural biodegradable polymers such as polysaccharides and proteins undergo biodegradation by enzymatic degradation in the body; synthetic polymers undergo biodegradation by utilizing the hydrolysable linkage like esters, amide, urea, and urethanes. In the past few decades more biodegradable polymers have been utilized for the development of effective delivery of drugs such as DNA, protein and incorporation of these agents can prevent the degradation in vivo and in vitro there by improve the therapeutic effect and prolong the biological activity (9-

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10). Currently biodegradable polymers like dextran, chitosan, starch, alginate, and pullulan are used for incorporation of macromolecular drugs. Although many synthetic biodegradable polymers were developed for various biomedical applications, use of natural biodegradable polymers is a better choice due to their abundance in nature, biocompatibility and modifiability (11). Among the natural biodegradable polymers, protein based polymers such as gelatin, collagen, albumin and polysaccharides- based polymers like (chitosan, hyaluronic acid, starch, and dextran) are used for drug delivery. The drug delivery based on polymer prepared from polysaccharide are gaining more important due to their cost-effectiveness, wide range of physicochemical properties, flexibility in obtaining desired release profile and ease in modification for specific applications and have wide regulatory acceptance(12). These polymers besides their application in drug delivery system, also used in various pharmaceutical formulations.

II. Microsperes as a Carrier System for Drug Molecules

Several devices are used for controlled release of drug molecules, The most commonly used are biodegradable polymeric microspheres, nanoparticles, microcapsules [13-14]. These delivery devices are highly useful because they can be administered to a variety of locations in vivo via a syringe needle [13-14]. The microspheres can be incorporated with drug molecule small molecules, proteins and nucleic acid. These delivery devices have high bioavailability and show good biocompatibility, which is capable of sustaining the release of drug molecule for a longer period of time. Many drug molecules could be incorporated on biodegradable microspheres regardless of their molecular weights and water solubility using different manufacturing techniques [15-19].

III. Different Types of Microspheres used in Drug Delivery System

Magnetic microspheres are an important type of drug delivery system and have the ability to localize the drug concentration at the site of action. Magnetic responses are received by the magnetic carriers in response to a magnetic field from incorporated materials which are used in magnetic microspheres like chitosan, dextran etc [20]. The magnetic microspheres are the supramolecular particles, which are small (<4 μm) can circulate through the capillaries. The magnetic microspheres are susceptible (ferromagnetic) to get captured into micro vessels and later get dragged into the adjacent tissue with the help of magnetic fields. In magnetic microspheres some portions of the freely circulating drug molecules can be replaced by incorporating smaller amount of magnetically targeted drug. The magnetic microspheres can be prepared by different processes continuous solvent evaporation process (CSE) by phase separation emulsion polymerization method (PSEP). Therapeutic magnetic microspheres are utilized for delivering chemotherapeutic agents to liver tumour and other drugs like proteins and peptides for drug target [21]. Magnetic microspheres can also be used for the diagnostic purpose that can be used for imaging liver metastases [22].

The oral controlled drug delivery system is one of the most promising route because of the low cost and high level of patient compliance. The effective oral drug delivery may depend on several factors like, gastrointestinal transit time of the dosage form, gastric emptying process, release of drug from the dosage form and finally the site of absorption. The gastric emptying process is one of the variables, which depends on the type of dosage form and the fed and the fasted state of stomach. The normal gastric residence time is between 5 minutes to 2 hours. In empty stomach the transit of dosage forms takes place by the electrical activity in the stomach and the interdigestive myoelectric cycle or migrating myoelectric complex. The retentive systems can remain in the gastric region for several hours and there by prolong the gastric residence time of drugs [23]. Prolongation of the gastric retention can improve the bioavailabity of the drug, improves solubility for those drugs which show poor solubility at high pH and also reduce drug wastage. Floating type microspheres are one such group having bulk density lower than the gastric fluid and remain buoyant in stomach. The floating microsphere does not affect the gastric emptying time and the release of drug is initiated at the desired rate. Floating drug delivery system can be divided into effervescent systems and non-effervescent systems. The mechanism by which the floating microsopheres release the drug is when the microspheres come in contact with gastric fluid the polymer forms a colloidal gel barrier, which controls the rate of fluid penetration into the device resulting in drug release. When exterior surface of the delivery system dissolves, a gel layer will be maintained by the hydration of the adjacent hydrocolloid layer. The buoyancy of the microspheres is initiated by the entrapment of air by the swollen polymer [25-26]. The floating type microspheres prepared from acrylic resins, eudragit, cellulose acetate, polyethylene oxide, polystyrene floating balloons and gelucire floating granules are the recent developments in this category.

Microspheres with bioadhesion property are another group, which can be utilized for drug targeting to a particular region of the body for a prolonged period of time. The term mucoadhesion was coined for the adhesion of polymers with the surface of mucosal layer. The adhesion takes place via interfacial forces between drugs to the membrane by using the sticking property of

water soluble polymers. The adhesion between polymers attached to the mucin layer of mucosal tissue is an example of bioadhesion[27]. The mucoadhesion is used when mucosal layer, which is present in number of regions which include urogenital tract, airways, GIT, ear, nose and eye. Hence these sites can be utilized as potential sites for bioadhesive system. The mucoadhesive drug delivery system can be used for oral, nasal, buccal, vaginal, rectal and ocular route of administration. These microspheres exhibit prolonged resident time and offers intimate contact with the absorption site and offer better medicinal action [21].

Radioactive microspheres are the groups which can emit beta or gamma radiation either alone or in combination. These microspheres are available in wide range of biocompatible glass compositions such as aluminosilicate, borate, silicate and borosilicate. The ideal characteristic required for radioactive microspheres are bioabsorbability or bio-inertness and they can be in the size range of 10-30 nm. These microspheres are injected to the arteries and get localized to the tumor of interest. The radioactive microspheres can deliver high radiation dose to the target area without causing any side effect to the normal surrounding tissues.

The floating microspheres also called hollow microspheres and are referred to as the gastro-retentive drug delivery system by non effervescent approach. The floating microspheres have low bulk density than the gastric fluid and helps to remain buoyant in stomach without affecting the gastric emptying rate. Floating microspheres are spherical empty particles without a core and are free flowing powders consisting of proteins or synthetic polymers with a size range of 1-1000 μm. The release of drug from the floating microspheres takes place slowly resulting in increase gastric retention with reduced fluctuations in plasma drug concentration (28-29). These types of microspheres are prepared by solvent diffusion and evaporation methods to create a hollow inner core. The characterization of floating microspheres can be done based on micromeritic properties such as particle size distribution, tapped density, true density, flow properties, compressibility index, scanning electron microscopy, in vitro floatability studies, in vitro drug release studies and stability studies etc.

IV. Preparation of Microspheres

Varieties of techniques have been developed for the preparation of microspheres to be used as drug delivery system-combinations of phase separation or precipitation, emulsion/solvent evaporation (30-36), and spraying methods (37-41). The control of the particle size and size distribution can be initiated by varying the fabrication parameters. The incorporation of the drug on to microspheres can be done by several different ways depending on the properties of the drug molecule. A self assembled polydisperse porous microspheres preparation was studied and was prepared by self assemble of three peptides containing various conformationally flexible and rigid γ-amino acids. The three peptides used for the self assembly are peptide 1, which adopts an extended backbone confirmation. The peptide 2 will form a turn like structure and peptide 3 can adopt a kink-like conformation. These peptides are consistent with increase rigidity of the N-terminaly γ-amino acids. These peptides in solid state in methanol-water system (19:1) solution they assemble and form polydisperse porous microspheres. The SEM images have revealed that microspheres have a diameter range from 500 nm-1μm (42). The most common method especially at the lab scale is emulsion-solvent extraction/evaporation methods. In this process a polymeric solution containing the drug to be encapsulated are emulsified in a non-solvent phase (continuous phase) containing the stabilizer. The emulsions are then prepared by any of the physical methods adopted such as homogenization and sonication(43). The components are chosen in such a way that the solvent is slightly soluble in the non-solvent. Once the emulsification is affected the solvent is extracted into the continuous phase and allowed to evaporate, while the non-solvent may penetrate into the polymeric droplets. The loss of solvent will help the disperse phase to get enriched in polymer until the droplets get harden to become particle. The microspheres so formed are then filtered, washed and lyophilized. Microspheres containing Aceclofenac are prepared by emulsion solvent evaporation techniques by using sodium PVP as emulsifying agent and eudragit as polymer (44).

Emulsion cross linking method is also another method for fabricating the microspheres. A typical example for microspheres prepared by this method include chitosan microspheres, in which chitosan gel in dispersed in toulune containing span 80 as emulsifying agent and resulting w/o emulsion are crosslinked by glutaraldehyde. The microspheres obtained were then washed with acetone and touluene, later collected as free flowing powder (45). The microspheres can also be prepared by Co-acervation phase separation method. The first step involved in Co-acervation method is formation of three immiscible phases namely- liquid manufacturing vehicle, core material and coating material. The core material (drug) were added on a coating polymer solution and is made immiscible in the liquid state by using one of the techniques like changing temperature, addition of salt, addition of non solvent, inducing polymer-polymer interaction and finally addition of incompatible polymer to the polymer solution. The polymeric coating material in liquid form is then deposited on to core material and finally the micropsheres were rigidized by cross linking,

desolvation or thermal treatments (46-47). The spray drying techniques for preparing microspheres, involves the dispersion of the core material on a liquefied coating material and later the mixture are sprayed in an environment for effecting solidification of coating followed by rapid evaporation of solvent. The spray drying is a rapid process, but sometimes may loose crystalinity due to the fast drying process (48). A novel quasi-emulsion solvent diffusion method was developed for preparing a controlled-release microsphere made of acrylic polymer containing ibuprofen. The procedure involves an ethanol solution of ibuprofen and acrylic resin was mixed in an aqueous medium with stirring. The fine dispersion of ethanolic droplet such as coacervates formed in the aqueous media is later solidified gradually to form microspheres during agitation (49). The microspheres prepared by multiple emulsion method, involves the dispersion of the powdered drug in polymeric solution. The dispersion was then emulsified by using ethyl cellulose solution in ethyl acetate. The primary emulsion so formed was then re-emulsified in aqueous medium to get discrete microspheres (48).

Another technique adopted for the preparation of microsphere is ionic gelation, which involves the addition of drug in an aqueous polymeric solution with continous stirring. The resulted mixture was added drop wise to solution containing calcium/aluminum compounds and chitosan solution in acetic acid. The microspheres formed were kept in original solution for 24 hrs for internal gellification and later separated by filtration (48).

References Références Referencias

1. Kost J, Langer R, 1991. Responsive polymeric delivery systems, Adv Drug Delivery Rev, 6, 19-50.
2. Wallance B M, Lasker J S, 1993. Stand and delivery getting peptide drugs into the body, Science, 260:912-913.
3. Patton J, 1998. Breathing life into protein drugs, Nature Biotechnology, 16: 141-143.
4. Freiberg S, Zhu X, 2004. Polymer microspheres for controlled drug release. Int J Pharm, 282: 1-18.
5. Thrombre A G, Cardinal J R, 1990. Encyclopedia of Pharmaceutical technology, Vol.2, P.61, Swarbrick J, Boylan J C. eds., Marcel Dekker, New York.
6. Okada H, Toguchi H, 1995. Biodegradable microspheres in drug delivery. Crit Rev Ther Drug Carrier System, 12:1-99.
7. Crotts G, Park T G, 1998. Protein delivery from poly (lactic-co-glycolic acid) biodegradable micro-spheres: release kinetics and stability issues, J Microencap, 15:699-713.
8. Davis SS, Illum L, McVie JG, Tomlinson E, Eds, 1984. Microspheres and Drug Therapy: Pharmaceutical, Immunological and Medical Aspects, Elsevier, Amsterdam.
9. Hans ML, Lowman AM (2002) Curr Opin Solid State Mater Sci 6:319.
10. Vasir JK, Reddy MK, Labhasetwar V (2005) Curr Nanosci 1:47.
11. Naira LS, Laurencin CT (2007) Prog Polym Sci 32:762.
12. Liu Z, Jiao Y, Wang Y, Zhou C, Zhang Z (2008) Adv Drug Deliv Rev 60:1650.
13. Jain, R. A. The manufacturing techniques of various drug loaded biodegradable poly (lactide-coglycolide) (PLGA) devices. Biomaterials 2000, 21, 2475-2490.
14. Berkland, C.; King, M.; Cox, A.; Kim, K.; Pack, D. W. Precise control of PLG microsphere size provides enhanced control of drug release rate. J. Control. Release 2002, 82, 137-147.
15. Felder Ch, B.; Blanco-Prieto, M. J.; Heizmann, J.; Merkle, H. P.; Gander, B. Ultrasonic atomization and subsequent polymer desolvation for peptide and protein microencapsulation into biodegradable polyesters. J. Microencapsul. 2003, 20, 553-567.
16. Kiyoyama, S.; Shiomori, K.; Kawano, Y.; Hatate, Y. Preparation of microcapsules and control of their morphology. J. Microencapsul. 2003, 20, 497-508.
17. Sinha, V. R.; Trehan, A. Biodegradable microspheres for protein delivery. J. Control. Release 2003, 90, 261-280.
18. Sinha, V. R.; Goyal, V.; Bhinge, J. R.; Mittal, B. R.; Trehan, A. Diagnostic microspheres: an overview. Crit Rev Ther Drug Carrier Syst 2003, 20, 431-460.
19. Wang, J.; Chua, K. M.; Wang, C. H. Stabilization and encapsulation of human immunoglobulin G into biodegradable microspheres. J. Colloid Interface Sci. 2004, 271, 92-101.
20. Li, S.P., Kowalski C.R., Feld K.M., Grim W.M., Recent Advances in Microencapsulation Technology and Equipment, Drug Dev Ind Pharm.1988; 14: 353-376.
21. www.pharmainfo.net/reviews/bioadhesivemicrospheres-review, 24th Nov 2010 Patel JK,Patel RP, Amin AF, Patel MM, 4(6),12/16/2006.
22. Shanthi N.C., Dr.Gupta R., Mahato K.A., Traditional and Emerging Applications of Microspheres: A Review, International Journal of Pharm Tech Research. 2010; 2(1):675-681.
23. Rangasamy M, Parthiban KG and CM. Floating Drug Delivery System: A Review. Journal of Scientific Speculations and Research 2010; 1(2):1–8.
24. Najmuddin M., Ahmed A., Shelar S., Patel V.,Khan T., Floating Microspheres of Ketoprofen: Formulation and Evaluation, International Journal of Pharmacy and Pharmaceutical sciences. 2010; 2 (Suppl2): 83-87.

25. Chickering DE, Jacob JS, Matho WE.Reactive Polymers 1995 ;(25):189-206.
26. Soppimath KS, Kulkarni AR, Aminabhavi TM. Drug Dev. Ind Pharm 2001; 27(6): 507-15.
27. J. R. Robinson, Rationale of bioadhesion/ mucoadhesion. In Bioadhesion Possibilities and Future Trends. Gurny R, Junginger, HE, Eds, Wissenchaftliche verlag Gesellschaft, Stuttgart. (1990). 13-28.
28. Najmuddin M., Ahmed A., Shelar S., Patel V., Khan T., Floating Microspheres of Ketoprofen: Formulation and Evaluation, International Journal of Pharmacy and Pharmaceutical sciences. 2010; 2(Suppl2):83-87.
29. Hirtz J. The git absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol 1985; 19:77- 83.
30. M.A. Beboit, B. Baras, and J. Gillard. Preparation and characterization of protein-loaded poly(ε-caprolactone) microparticles for oral vaccine delivery. Int. J. Pharm., 184:73–84, 1999.
31. L.Y. Chu, R. Xie, J.H. Zhu, W.M. Chen, T. Yamaguchi, and S.I. Nakao. Study of SPG membrane emulsi- fication processes for the preparation of monodisperse core-shell microcapsules. J. Colloid Interface Sci., 265: 187–196, 2003.
32. S.C. Lee, J.T. Oh, M.H. Jang, and S.I. Chung. Quantitative analysis of polyvinyl alcohol on the surface of poly (D,L-lactide-co-glycolide) microspheres prepared by solvent evaporation method: effect of particle size and PVA concentration. J. Control. Rel., 59:123–132, 1999.
33. G.H. Ma, Z.G. Su, S. Omi, D. Sundberg, and J. Stubbs. Microencapsulation of oil with poly(styrene-N, Ndimethylaminoethyl methacrylate) by SPG emulsification technique: Effect of conversion and composition of oil phase. J. Colloid Interface Sci., 266:282–294, 2003.
34. G. Wei, G.J. Pettway, L.K. McCauley, and P.X. Ma. The release profiles and bioactivity of parathyroid hormone from poly(lactic-co-glycolic acid) micro-spheres. Biomaterials, 25:345–352, 2004.
35. Y.Y. Yang, T.S. Chung, and N. Ng. Morphology, drug distribution, and in vitro release profiles of biodegradable polymeric microspheres containing protein fabricated by double-emulsion solvent extraction/evaporation method. Biomaterials, 22(3):231–241, 2001a.
36. A. Supsakulchai, G.H. Ma, M. Nagai, and S. Omi. Preparation of uniform titanium dioxide (TiO2) polystyrene-based composite particles using the glass membrance emulsification process with a subsequent suspension polymerization. J. Micro-encapsul., 20:1–18, 2003.
37. S. Freitas, H.P. Merkle, and B. Gander. Ultrasonic atomization into reduced pressure atmosphere–envisaging aseptic spray-drying for microen-capsulation. J. Control. Rel., 95:185–195, 2004.
38. P. He, S.S. Davis, and L. Illum. Chitosan microspheres prepared by spray drying.Int. J. Pharma., 187:53–65, 1999.
39. L. Mu and S.S. Feng. Fabrication, characterization and in vitro release of paclitaxel (Taxolr) loaded poly (lactic-co-glycolic acid) microspheres prepared by spray drying technique with lipid/cholesterol emulsifiers. J. Control. Rel., 76:239–254, 2001.
40. F. Quaglia, G. De Rosa, E. Granata, F. Ungaro, E. Fattal, and M.I. La Rotonda. Feeding liquid, non-ionic surfactant and cyclodextrin affect the properties of insulin-loaded poly (lactide-co-glycolide) microspheres prepared by spray-drying. J. Control. Rel., 86:267–278, 2003.
41. F.J. Wang and C.H. Wang. Sustained release of etanidazole from spray dried microspheres prepared by non-halogenated solvents. J. Control. Rel., 81:263–280, 2002.
42. Maity S K, Bera S, Paikar A, Pramanik A, Haldar D, Fabrication of microspheres from self-assembled γ-peptides, Cryst Eng Commm, 2013, 15, 5860-5866.
43. S. Cohen, T. Yoshioka, M. Lucarelli, L.H. Hwang, and R. Langer. Controlled delivery systems for proteins based on poly (Lactic/Glycolic Acid) micro-spheres. Pharma. Res., 8(6):713–720, 1991.
44. Trivedi P., Verma A.M.L., Garud N.,Preperation and Charecterization of Acclofenac Microspheres, Asian Journal of pharmaceutics. 2008; 2(2): 110-115.
45. Sujith Varma, C Sadasivan, A Long acting biode-gradable controlled delivery of chitosan micro-spheres loaded with tetanus toxoide as model antigen, Biomedicine and Pharmacotherapy. 68 (2014), 225-230.
46. H G Bungenberg de Jong, Kruvt, Prog Kungl. Ned.Acad. Wetensch., 32(1929), 849-856, through, Swapan Kumar Ghosh,Functional Coatings and Microencapsulation: A General Perspective, P.16.
47. H G Bungenberg de Jong, in: Colloid science (Ed.H.R.Kruyt), Elsevier, 1949, P.232-258, through, Swapan Kumar Ghosh, Functional Coatings and Microencapsulation:A General Perspective,P.16.
48. Mathew Sam T., Devi Gayathri S., Prasanth V.V., Vinod B; NSAIDs as microspheres, The Internet Journal of Pharmacology .2008;6(1).
49. Kawashima Y, Niwa T, Handa T, Takeuchi H, Iwamoto T, Itoh K, Preparation of Controlled release microspheres of ibuprofen with acrylic polymers by a novel quasi-emulsion solvent diffusion method. J Pharm Sci, 1989; 78(1):68-72.

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Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology and Medicine
Volume 15 Issue 2 Version 1.0 Year 2015
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Marijuana: Neurotoxic or Neuroprotective?

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Abstract- Chronic marijuana intake was known to induce morphological changes to the brain impairing memory and learning ability. However, several studies demonstrated the protective effect of marijuana post-brain traumas. This article reviews studies that strengthen our horizon to understand the effects of marijuana smoking in brain. This review predicts that optimum use of marijuana or pure marijuana compound can be beneficial or detrimental depending on the consumed dose.

Keywords: *marijuana, cannabinoids, neuroprotective, neurotoxic.*

GJMR-B Classification : *NLMC Code: QW 630.5.N4*

Strictly as per the compliance and regulations of:

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I. Introduction

Marijuana is the dried leaves, flowers, stems, and seeds from the plant *Cannabis sativa*. It has a several psychoactive chemicals along with a relatively well-characterized delta-9-tetrahydro-cannabional (Δ^9-THC). Marijuana can also be concentrated in a resin called hashish or a black sticky liquid called hash oil.It is the most common illicit drug in the United States. Even though federal government considers marijuana as a Schedule I substance, several states have legalized it for medicinal and recreational use (www.drugabuse.gov).

Numerous compounds are produced when marijuana is smoked, which may have acute or chronic effect. G protein-coupledcannabinoid (CB) receptors are involved to respond acute effects of cannabinoids and the development of tolerance. CB1 receptors are predominantly available in the hippocampus, striatum, and cerebellum in the brain (Ameri 1999).Another cannabinoid receptor, CB2, is mostly found in spleen, which has only about 44% nucleotide sequence similarity with CB1 receptor(Ameri 1999).

Even though marijuana is the most common street drug, it has been employed as a therapeutic drug. There are well-proofed potential medicinal actions of marijuana, such as antiemetic, analgesia, anticonvulsant, and lower intraocular pressure (Hollister 1986).However, psychological effects, development of tolerance, and the abuse potential of marijuana have discouraged their medicinal use. In addition, the public debate exists whether or not marijuana should be legalized. Thus, it is the aim of this review to present the effect of marijuana and its psychoactive components on brain and evaluate if it is neuroprotective or neurotoxic.

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II. Neurological Effects

Although marijuana have shown direct cellular effects on a number of organ systems such as immune system, liver, reproductive system, and digestive system, major behavioral and pharmacological effects involve the central nervous system (CNS)(Ameri 1999). The behavioral effects of marijuana may vary depending on dose and route of administration, expectations of subjects, and individual vulnerability to certain effect. Marijuana at low doses generally produces euphoric, relaxation, and stimulatory effects, and at higher doses they exert predominantly depression(Lukas et al. 1995). Acute marijuana is associated with impaired functioning in cognitive and performance tasks such as reaction time, learning perception, motor coordination and attention (Court 1998; Heishman et al. 1997). Multiple studies have implicated that marijuana deficits short-term memory, whichmeditate CB1 receptors(Heyser et al. 1993; Lichtman and Martin 1996).

One biological effects of Δ^9-THC is their ability of inhibiting pain transmission(Martin et al. 1996), potentially involving neuronal pathway of κ opioid receptors with distal or converging pathway of cannabinoid receptors(Ameri 1999; Calignano et al. 1998).

Multiple studies suggest that marijuana possess antiepileptic properties in animal seizure models and human patients (Carlini and Cunha 1981; Karler and Turkanis 1981). Available evidences predictedthe antiepileptic property of marijuana is due to its interaction with the glutamatergic transmission in the central nervous system (Feigenbaum et al. 1989).

III. Marijuana-Induced CNS Modification: Neurotoxic or Neuroprotective?

Multiple studies revealed neuroprotective and neurotoxic effects of marijuana in animal models or human systems. It was shown to induce beneficial or detrimental effects at cellular level(Bash et al. 2003; Sarne and Keren 2004).

Many epidemiological studies have demonstrated that chronic use of marijuana deteriorates cognitive functions, specific impairment of attention, memory, and executive function (Pope and Yurgelun-Todd 1996; Schweinsburg et al. 2008; Solowij et al. 1995). Interestingly, unlike ethanol, cognitive impairment caused by marijuana is not clearly dose-dependent.

However, chronic (at least several months) marijuana exposure may cause long-term impairment (Pope and Yurgelun-Todd 1996).A major psychoactive ingredient of marijuana, Δ^9-THC, persistently reduced maze learning ability in rats(Fehr et al. 1976; Stiglick and Kalant 1982; Stiglick et al. 1984). Similar results were detected in rats with hippocampal lesions, suggesting the possibility of neurotoxic effects of marijuana in the hippocampus (Morris et al. 1982). In addition, neuronal death and reduced synaptic density and dendritic length of pyramidal neurons were measured in the hippocampus of chronic marijuana administered rats(Landfield et al. 1988; Lawston et al. 2000). Furthermore, THC induced neuronal death in the neuronal cell lines, cultured hippocampal neurons or hippocampal slices(Chan et al. 1998). Chan et al. presented evidences of Δ^9-THC inducing apoptosis of hippocampal neurons by shrinking neuronal bodies and nuclei as well as DNA fragmentation (Chan et al. 1998). Furthermore, the neuronal cell loss is assumed to be responsible for impairment in memory after long-lasting consumption of marijuana. 10 and 1 μM THC are found to induce 50% hippocampal neuronal death in 2 hr and 5 days, respectively (Chan et al. 1998). In a separate report, marijuana was considered to produce toxic encephalopathy in young humans (Court 1998).

In contrast to the above reports, marijuana induces the expression of endocannabinoid 2-arachidonoyl glycerol (2-AG), which reduced brain edema and infarct volume following severe closed head injury(Sarne et al. 2011). In addition, CB1 and CB2 receptors agonist Bay 38-7271 demonstrated neuroprotective properties in traumatic brain injury and focal ischemic rat models (Sarne et al. 2011; Sarne and Keren 2004). Additionally, the role of endogenous cannabinoid system is suggested to be neuroprotective (Guzman et al. 2001; Mechoulam et al. 2002). Multiple *in vitro* studies have reported protection of neurons in culture by cannabinoid agonists acting through CB1 receptors(Shen and Thayer 1998). Also, CB1 receptor acting cannabinoid agonists protected hippocampal neurons from synaptically- mediated excitotoxicity (Abood et al. 2001). Furthermore, the cannabinoid agonist CP-55, 940 protected cortical neurons from glutamatergic excitotoxicity by CB1 receptor-mediated voltage-dependent calcium channels inhibition (Hampson and Grimaldi 2001). Other synthetic cannabinoid WIN55 and 2122 administered daily (twice, 2 mg/kg) to rats increased hippocampal granule cell density and dendritic length in the CA3 pyramidal cell layer (Chan et al. 1996).

Some studies did not show any effect of marijuana in central nervous system. An MRI study found no evidence of cerebral atrophy or regional changes in tissue volumes among 18 current, frequent, adult marijuana users compared to 13 adult non-users (Block et al. 2000). A study claimed ultrastructural changes in septum and hippocampal in rhesus monkeys by marijuana smoking(Harper et al. 1977; Heath et al. 1980), however, subsequent larger study failed to show effect of marijuana in the histopathology of monkey brain (Scallet 1991). The neuroprotective or neurotoxic effect of marijuana is potentially determined by the amount inhaled or ingested as shown in Fig. 1.

IV. Summary

The increasing legalization of marijuana for medical and recreational use renewed the interest in its potential effect on health and therapeutic applications. Marijuana, THC, and other cannabinoid agonists all have a common problem of a narrow therapeutic window between clinical benefits and the unwanted psychic side-effects. Further elaborated studies at multiple doses for short- and long- term consumption is essential prior to conclude beneficial or detrimental effect of marijuana in the central nervous system.

References Références Referencias

1. Abood ME, Rizvi G, Sallapudi N, McAllister SD. 2001. Activation of the CB1 cannabinoid receptor protects cultured mouse spinal neurons against excitotoxicity. *Neuroscience letters* **309** (3):197-201.
2. Ameri A. 1999. The effects of cannabinoids on the brain. *Progress in neurobiology* **58**(4):315-348.
3. Bash R, Rubovitch V, Gafni M, Sarne Y. 2003. The stimulatory effect of cannabinoids on calcium uptake is mediated by Gs GTP-binding proteins and cAMP formation. *Neuro-Signals***12**(1):39-44.
4. Block RI, O'Leary DS, Ehrhardt JC, Augustinack JC, Ghoneim MM, Arndt S, Hall JA. 2000. Effects of frequent marijuana use on brain tissue volume and composition. *Neuroreport* **11**(3):491-496.
5. Calignano A, La Rana G, Giuffrida A, Piomelli D. 1998. Control of pain initiation by endogenous cannabinoids. *Nature* **394** (6690):277-281.
6. Carlini EA, Cunha JM. 1981. Hypnotic and antiepileptic effects of cannabidiol. *Journal of clinical pharmacology* **21**(8-9 Suppl):417S-427S.
7. Chan GC, Hinds TR, Impey S, Storm DR. 1998. Hippocampal neurotoxicity of Delta9-tetrahydro-cannabinol. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **18** (14):5322-5332.
8. Chan PC, Sills RC, Braun AG, Haseman JK, Bucher JR. 1996. Toxicity and carcinogenicity of delta 9-tetrahydrocannabinol in Fischer rats and B6C3F1 mice. *Fundamental and applied toxicology : official journal of the Society of Toxicology* **30** (1):109-117.
9. Court JM. 1998. Cannabis and brain function. *Journal of paediatrics and child health* **34** (1):1-5.
10. Fehr KA, Kalant H, LeBlanc AE. 1976. Residual learning deficit after heavy exposure to cannabis or alcohol in rats. *Science* **192** (4245):1249-1251.

11. Feigenbaum JJ, Bergmann F, Richmond SA, Mechoulam R, Nadler V, Kloog Y, Sokolovsky M. 1989. Nonpsychotropic cannabinoid acts as a functional N-methyl-D-aspartate receptor blocker. *Proceedings of the National Academy of Sciences of the United States of America* **86** (23):9584-9587.
12. Guzman M, Sanchez C, Galve-Roperh I. 2001. Control of the cell survival/death decision by cannabinoids. *Journal of molecular medicine* **78** (11):613-625.
13. Hampson AJ, Grimaldi M. 2001. Cannabinoid receptor activation and elevated cyclic AMP reduce glutamate neurotoxicity. *The European journal of neuroscience* **13** (8):1529-1536.
14. Harper JW, Heath RG, Myers WA. 1977. Effects of Cannabis sativa on ultrastructure of the synapse in monkey brain. *Journal of neuroscience research* **3**(2):87-93.
15. Heath RG, Fitzjarrell AT, Fontana CJ, Garey RE. 1980. Cannabis sativa: effects on brain function and ultrastructure in rhesus monkeys. *Biological psychiatry* **15**(5):657-690.
16. Heishman SJ, Arasteh K, Stitzer ML. 1997. Comparative effects of alcohol and marijuana on mood, memory, and performance. *Pharmacology, biochemistry, and behavior* **58**(1):93-101.
17. Heyser CJ, Hampson RE, Deadwyler SA. 1993. Effects of delta-9-tetrahydrocannabinol on delayed match to sample performance in rats: alterations in short-term memory associated with changes in task specific firing of hippocampal cells. *The Journal of pharmacology and experimental therapeutics* **264** (1): 294-307.
18. Hollister LE. 1986. Health aspects of cannabis. *Pharmacological reviews* **38** (1):1-20.
19. Karler R, Turkanis SA. 1981. The cannabinoids as potential antiepileptics. *Journal of clinical pharmacology* **21**(8-9 Suppl):437S-448S.
20. Landfield PW, Cadwallader LB, Vinsant S. 1988. Quantitative changes in hippocampal structure following long-term exposure to delta 9-tetrahydrocannabinol: possible mediation by glucocorticoid systems. *Brain research* **443** (1-2):47-62.
21. Lawston J, Borella A, Robinson JK, Whitaker-Azmitia PM. 2000. Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2. *Brain research* **877** (2):407-410.
22. Lichtman AH, Martin BR. 1996. Delta 9-tetrahydrocannabinol impairs spatial memory through a cannabinoid receptor mechanism. *Psychopharmacology* **126** (2):125-131.
23. Lukas SE, Mendelson JH, Benedikt R. 1995. Electroencephalographic correlates of marihuana-induced euphoria. *Drug and alcohol dependence* **37** (2):131-140.
24. Martin WJ, Hohmann AG, Walker JM. 1996. Suppression of noxious stimulus-evoked activity in the ventral posterolateral nucleus of the thalamus by a cannabinoid agonist: correlation between electrophysiological and antinociceptive effects. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **16** (20):6601-6611.
25. Mechoulam R, Panikashvili D, Shohami E. 2002. Cannabinoids and brain injury: therapeutic implications. *Trends in molecular medicine***8**(2):58-61.
26. Morris RG, Garrud P, Rawlins JN, O'Keefe J. 1982. Place navigation impaired in rats with hippocampal lesions. *Nature* **297**(5868):681-683.
27. Pope HG, Jr., Yurgelun-Todd D. 1996. The residual cognitive effects of heavy marijuana use in college students. *Jama* **275**(7):521-527.
28. Sarne Y, Asaf F, Fishbein M, Gafni M, Keren O. 2011. The dual neuroprotective-neurotoxic profile of cannabinoid drugs. *British journal of pharmacology* **163** (7):1391-1401.
29. Sarne Y, Keren O. 2004. Are cannabinoid drugs neurotoxic or neuroprotective? *Medical hypotheses* **63** (2):187-192.
30. Scallet AC. 1991. Neurotoxicology of cannabis and THC: a review of chronic exposure studies in animals. *Pharmacology, biochemistry, and behavior* **40** (3):671-676.
31. Schweinsburg AD, Brown SA, Tapert SF. 2008. The influence of marijuana use on neurocognitive functioning in adolescents. *Current drug abuse reviews* **1**(1):99-111.
32. Shen M, Thayer SA. 1998. Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. *Molecular pharmacology* **54** (3):459-462.
33. Solowij N, Michie PT, Fox AM. 1995. Differential impairments of selective attention due to frequency and duration of cannabis use. *Biological psychiatry***37**(10):731-739.
34. Stiglick A, Kalant H. 1982. Residual effects of prolonged cannabis administration on exploration and DRL performance in rats. *Psychopharmacology* **77**(2):124-128.
35. Stiglick A, Llewellyn ME, Kalant H. 1984. Residual effects of prolonged cannabis treatment on shuttle-box avoidance in the rat. *Psychopharmacology* **84** (4):476-479.

Figure Legend

Figure 1. Marijuana dose determines beneficial or detrimental effect of marijuana consumption. Research so far indicated that low dose of marijuana has beneficial and neuroprotective response. However, higher marijuana dose stimulate psychoactive impairment as well asmemory and attention deficits, potentially due to its neurotoxic effect.

Figure

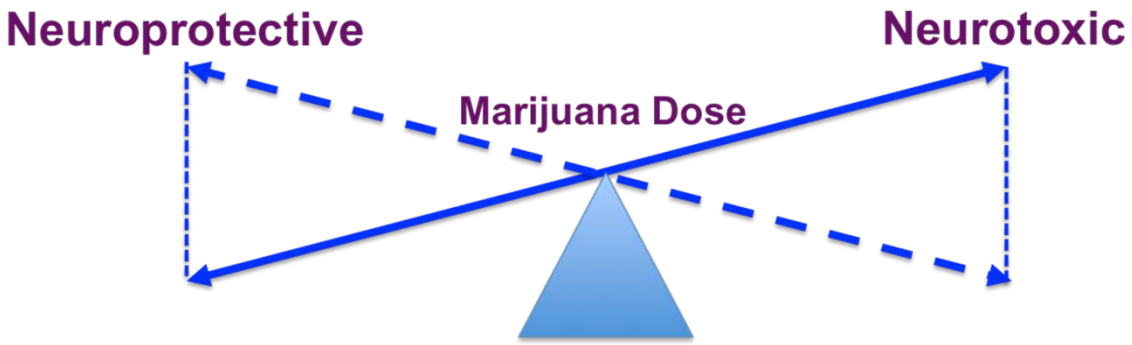

Fig. 1

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology and Medicine
Volume 15 Issue 2 Version 1.0 Year 2015
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Non Adherence and its Contributing Factors to Anti-TB Drug in Children's at Adama Referral Hospital, Oromia, Ethiopia

By Kelifa Osman Yusuf, Muluneh Fromsa Seifu, Belayneh Kefale Gelaw, Esayas Tadesse Gebremariam & Mustefa Ahmed Mohammed

Ambo University, Ethiopia

Abstract- *Objective:* The objective of this study was to assess of factors affecting adherence of pediatric TB patients to anti TB drugs in Adama referral hospital.

Methodology: Retrospective cross sectional study has been conducted from March 19th to May 20th, 2014 to assess factors affecting adherence of pediatrics TB patients to anti TB drugs in Adama referral hospital. Data collection format was used to collect data from available data sources such as patients' medical cards and DOT registration book. Simple random sampling technique has been used in this research and data was presented in table and categorized and analyzed by using SPSS computer software package.

Keywords: *pediatric patients, adama, adherence, TB patients.*

GJMR-B Classification : *NLMC Code: WF 360*

Strictly as per the compliance and regulations of:

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Result: Among 91 patients 42(46.1%) were males and 49(53.8%) were females. And 16 (17.6%) of patients were below 5 years of age, 30(32.96%) and 45(49.5%) of patients were between age of 6-10years and between11-15 years of age, respectively. Among all pediatrics patients 59(64.83%) of them adhered to treatment program while 27(29.67%) patient defaulted (not adhered to) the treatment program. But for 5(5.5%) patients at end of program it was not known whether they defaulted or completed the treatment. At the end of treatment program 14(15.38%) of patients were cured while 6(6.6%) of the patients were not cured due to either MDRTB development or relapse, and 6(6.6%) of the patient were died. The most common factor identified to affect pediatrics adherence to anti TB medication were parents' knowledge of TB, parents relationship with provider, presence or absence of other reason like feeling better, forgetfulness and residence area.

Conclusion: As this study shows 29.67% of patients did not adhere to their treatment program. Also, this study shows that adherence of pediatric patients to their medication is not only affected by patient taking medication as prescribed but also by parent knowledge of TB, parent relationship with provider, presence or absence of other reason like feeling better, forgetfulness and residence area.

Keywords: pediatric patients, adama, adherence, TB patients.

I. Introduction

a) Background Information

Tuberculosis is an infectious disease caused by mycobacterium tuberculosis which is transmitted through the air, by ingesting infected milk or meat and it is both preventable and curable disease. People who have pulmonary tuberculosis can infect other through droplet infection when they cough, sneeze, and talk. If TB is detected early and fully treated, people with disease quickly become non infectious and eventually cured (1).

The WHO in its global plan to stop TB report that poor treatment has resulted in evolution of mycobacterium TB strain that do not respond to treatment with standard first line combination of anti TB drug. Emergency of multi drug resistant TB, extensive drug resistant TB, HIV associated TB and weak health system are the major challenge to TB control program globally (2).

One of the greatest challenges facing most TB program is that of patient who do not complete their TB treatment for one or more reasons such as patient are not only at risk of relapsing ,but also they may develop resistances to one or more potent first line TB drug ,such as isoniazid (INH),rifampcin(RMP) Pyrazinamide (PZA), ethambutol (ETH)and streptomycin(2).

Out of approximately one million estimated case of TB in children world wide,75% occur in the 22 high burden countries and majority of children with smear positive TB who are <15 years of age were in Africa and south east Asia. In low income countries childhood TB is associated with malnutrition, poverty, over-crowding, higher death rate and lower treatment success rate (3).

Although the true burden of childhood TB is not well known, it is one of the 10 major causes of childhood mortality with estimated annual death of 74,000_130,000. Ethiopia is one of 22 high burden countries in which TB is the second leading cause of death ,it is estimated that children contribute to 16% of national TB burden. Childhood TB is marker of recent transmission in population; moreover, children are the primary victims of poor TB control programs and TB is significant childhood morbidity and mortality in the country (4).

Adherence to long term therapy is a multi-dimensional phenomenon determined by the interplay of five set factors namely social and economical factor, health care team, conditional related factor, therapy and patient related factor (6).

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Poor adherence to treatment of chronic disease including TB is a worldwide problem of striking magnitude, however patient with TB are expected to have adherence level greater than 90% in order to facilitate cure .The failure for cure increase the risk of development of drug resistance TB and further spread in community which in turn increase morbidity and mortality (5)

In sub sub-Saharan Africa there is high rate of loss to follow up of TB patient that range from 11.1% - 29%. Ethiopia is one of the seventh countries that reported lower rate of treatment success and patient who take TB treatment irregularly and unreliable way are at greatly increased risk of treatment failure(5).

b) Statement of the Problem

Compliance to TB treatment continues to be one of the major obstacles that TB control program worldwide have to deal with, especially in developing countries (7). Poor compliance and defaulting anti TB treatment contribute to the increase of multi drug resistant mycobacterium tuberculosis (8). In addition, comprehensive studies on resistance to anti TB drug in children are lacking, because they are not included in global survey. Surveillance of anti TB drug resistance during 1995-2007 among children from south Africa showed a significant increase in resistance to INH and RMP from 2.3%-6.7%. Drug-resistance among children has been documented in clinical trial of both pulmonary and extra pulmonary tuberculosis (4). Therefore, children under treatment for TB who default from treatment are at risk for clinical deterioration and complication and can continue to be infectious to other and at risk of premature death (11).

Furthermore, mortality from tuberculosis is highest in early childhood due to children non adherence to TB treatment (4). Approximately one million children develop active TB annually comprising 30%-40% of the total TB case load in high burden countries, out of this 75% occur in high burden countries of whom 450,000 die each year, even though there is highly effective medication (12). According to 2012 WHO report estimate, half of million children ill with tuberculosis in 2011 of which nearly 64000 children die of TB, even though there is effective medication(9).

In Ethiopia, even though TB drug are given free of fee TB continues to be major cause of TB related child hood death (10). In developing countries including our country large number of family have no balanced diet for their child normal growth? In these types of children when they are infected with mycobacterium tuberculosis with underlying malnutrition, they develop drug side effect such as drug intolerance and vomiting in intensive phase of the treatment which result in child non adherence to their treatment. In this type of countries poor adherence is major concern of child hood TB treatment and usually less than one third of participant to the treatment program complete full course of poorly supervised treatment (13).

Treatment is challenging since no pediatric drug formulations are currently commercially available and with a long and burdensome disease, especially in the case of MDR-TB when treatment can take up to two years, adherence to treatment is difficult for patients and their families. Children lack the emotional resources to cope with the disease on their own and rely heavily on practical and emotional support from their care giver. (14)

II. Significance of the Study

The result of this study would identify the major problems that account for children non adherence to their medication and TB relapse. It also notifies the development of MDR TB in children who are being treated and who will be treated at Adama hospital. The finding of this study also gives an insight to health professional about major factors affecting the children adherence to their anti TB drug treatment schedule. If it is implemented, also it will improve children cure rate and minimize death from MDR TB in children. Once the factors are identified, then targeted strategies to address them can be formulated. The finding may also be used to formulate strategies to improve quality of care for TB pediatric patient.

a) Objective

General objective

- To assess factors affecting children adherence to anti TB drug in Adama referral hospital, East Shewa Ethiopia

Specific objective

- To determine the magnitude of non adherence in children attending anti-TB drug in Adama referral hospital
- To determine reasons for MDR TB in children
- To determine factors affecting children adherence to anti TB drugs in Adama referral hospital
- To assess factors contributing to children defaulting TB treatment program

III. Methodology

a) Study Area

Adama is one of the towns of Oromia regional state, East Shewa zone and located 99Km far from Addis Ababa. There are different governmental and non-governmental institutions in the town such as 8 health Centers, one referral hospital, one general hospital, 50 private clinics, and 105 pharmacies. The study was conducted in Adama hospital medical college on pediatrics patients who had attended TB treatment program from September 2002 EC-September 2006 EC. Adama hospital was established & started its full

function in 1965. The hospital is now providing several health services including TB treatment program for the community.

b) Study Design

In this research a cross sectional study based on retrospective data was conducted by reviewing patient`s DOT registration book and patient medical charts. The study period had been from April 1 to May 20, 2014.

c) Source Population

All pediatric patients' s DOT registration book and medical charts of who had attended TB treatment program in the previous five year from 2002 E.C-2006 E.C

d) Study Population

All sampled pediatric patients s DOT registration book and medical charts of who had attended TB treatment program at TB clinic for the past five year from 2002 E.C-2006 E.C were included.

e) Inclusion and Exclusion Criteria

All medical charts of pediatrics patients below sixteen years old were included and all adult TB patients above fifteen years old were excluded from the study.

f) Sample Size Determination

The proportion to be studied was (p) =10% of the population, allowed deviation was ''w' 'which was 5 % and confidence interval was 95% therefore minimum sample size required was obtained by the formula:

$n=z^2p\ (1\text{-}P)/W^2$

$n= (1.96)^2 0.1x0.9/(0.05)^2$

n=138 sampled for the study

but because N was relatively small adjustment was made for the above ''n'' required by the following formula

n/(1+n/N)

=138/(1+138/1500)

=126 Patient were included

g) Sampling Technique

In this study simple random sampling was used.

h) Study Variables

Independent Variables

a) Socio-demographic characters

- Age
- Sex
- address
- quality of service
- parent educational status
- parent socioeconomic status

Dependent Variables

- Adherence/non adherence to the treatment
- Defaulting the treatment
- MDRTB development

i) Data Processing and Analysis

After data was collected, it was categorized and analyzed using SPSS computer soft ware package. And the result was summarized and presented in table and written form.

j) Data Quality Control

To ensure data quality, data collection technique and format was pretested at study area in 5% of sample population of the same source population.

k) Ethical Consideration

Permission letter or ethical clearance was obtained from college of medical and health science department of pharmacy and was given to Adama hospital administrative office and permission was obtained from administrator. In addition the patients' information was kept confidentially.

l) Operational Definition

Adherence = extent to which the patient take their medication as prescribed by physician

Non adherence = not taking medication as prescribed

Defaulting = discontinuing taking medication

Tuberculosis = disease caused by mycobacterium tuberculosis

IV. Result

In this study 126 pediatric TB patients' medical charts were sampled from 1500 medical charts of pediatrics TB patient population using simple random sampling. Among whom 35 patients were transferred to other health institution for close follow up of DOT therapy. Thus, 91 pediatrics medical charts were analyzed.

Table 5.1 : demonstrate demographic characteristics and patient sources of sample population

Variable		frequency	Percent
Sex	Male	42	46.1%
	Female	49	53.8%
Age	0-5	16	17.6%
	6-10	30	32.96%
	11-15	45	49.5%
New to program	YES	86	94.5%
	NO	5	5.5%

Among 91 patients 42(46.1%) were males and 49(53.8%) were females, the association between sex and patients completion of the treatment was identified by calculating "p" value for both variables and the association was found to be insignificant 0.66 (>0.05). 16(17.6%) of patients were below 5 years of age, 30(32.96%) and 45(49.5%) of patients were between age of 6-10 years and between age of 11-15 years, respectively. The association between age of patients and treatment completion behavior of the patients was obtained to be statistically insignificant (p = 0.87 at 0.05 level of significance).

In this study 86(94.5%) of the patients were new for treatment program while 5(5.5%) of patients had attended the treatment program before they were readmitted to the treatment program.

Out of all pediatrics TB patients analyzed 52(57.1%) of patients were treated for extra pulmonary TB while the rest 39(42.82%) of patients were treated for pulmonary TB. The association between type of TB and treatment completion behavior was obtained to be insignificant (p=0.769).

Table 5.2 : Demonstrates initiation missed dose, phase in which dose was missed ,duration for which dose was missed, side effect, type of side effect ,other reason and defaulting behaviors of patient

Variable		Frequency	Percent
Initiation missed dose per week	none	68	74.5%
	One dose	1	1.1%
	Two dose	10	10.99%
	Three dose	9	9.9%
	Four dose	3	3.3%
Side effect	yes	26	28.6%
	Unknown	65	71.42%
Type of side effect	none	64	70.33%
	Vomiting and headache	13	14.28%
	Nausea	1	1.1%
	Hepatotoxicity	8	8.78%
	Vomiting and nausea	5	5.49%
Other reason	Feeling better	15	16.48%
	Forget	4	4.39%
	Missed	2	2.19%
Phase in which dose was missed	Initiation	17	18.7%
	Continuous	19	20.87%
Duration for which dose was missed	None	64	70.33%
	Two week-one month	14	15.4%
	Two month-four month	13	14.3%
Default	yes	22	24.17%
	No	66	72.52%
	unknown	3	3.3%

In initiation phase 17(18.7%) of the patients were recorded to missed their dose up to two weeks of initiation phase because of side effect or other reason while 19(20.87)of the patients default the treatment in continuous phase due to other reason like feeling better, forgetfulness, being far away and due to missing. But statistical p value (0.857) indicates that there was no association between presence of side effect and treatment completion behavior of patients. But other reasons like feeling better, forget fullness and death together with treatment completion behavior had association (p=0.00).

The side effect of anti TB medication was identified in 26 (28.6%) of patients and not identified in 65 (71.42%) of the rest patients. The most common identified drug related side effect were vomiting and nausea in 18(19.78%) of patients, followed by hepatotoxicity in 8(8.7%). The other reasons for which most of the patients missed their dose were feeling better in15 (16.48%) of the patients, forget in 4(4.39%) of the patients and being far away in 2(2.19%) of the patient. Most of these reasons were very common in continuous phase of treatment program. The patient who defaulted treatment program for two weeks –one month were 14(15.4%) while 13(14.3%) of the patient discontinued their medication for two months-four months. There was statistically significant association between defaulting and treatment completion with (p=0.00).

Table 5.3 : demonstrate type of TB the patient was treated for, patient co morbid condition, type of ART the patient had been taking and MDRTB status of the patient.

Variable		Frequency	Percent
Co morbid condition	HIV	20	21.97%
	DM	5	5.49%
	No other condition	66	72.52%
Type of TB	Pulmonary	39(42.85)	42.85%
	Extra pulmonary	52(57.1)	57.1%
ART medication	None	71	78%
	D4T+3TC+EFV	11	12.1%
	TNF+3TC+EFV	9	9.9%
MDRTB	Yes	7	7.69%
	No	14	15.38%
	Unknown	70	76.92%

The most common co morbid condition reported in these patients were HIV in 20(21.97%) of pediatric TB patients who analyzed for the study and DM in 5(5.49%) of the patients. Among the patients who had HIV as underlying disease to tuberculosis 11(55%) of patients were treated with D4T+3TC+EFV and 9(45%) of the patients were treated with TDF+3TC+EFV regimen. Statistical p-value that indicates association between co morbid condition and treatment completion was 0.868 indicating insignificant association.

MDRTB was identified in 7(7.69%) of the patients, while 14(15.38%) of the patients were cured and 70(76.92%) of the patients were not reported whether they had MDRTB or not. The statistical association between adherence and MDRTB was found to be insignificant (p=0.121).

Table 5.4 : demonstrates parent TB knowledge, parent relation with provider, economic status and patient health status at the end of treatment program and completion status.

Variable		Frequency	Percent
Parent economy	No any information	91	100%
Parent TB knowledge	Good	58	63.73%
	Poor	20	21.97%
	Unknown	13	14.28%
Parent relation with provider	Good	56	61.54%
	Poor	22	24.17%
	Unknown	13	14.28%
Patient health at end of the treatment	Cured	14	15.38%
	Not cured	6	6.6%
	Missed	6	6.6%
	Unknown	65	71.43%
Did the patient complete the treatment course	Yes	59	64.83%
	No	27	29.67%
	Unknown	5	5.5%

The knowledge of parents of TB patients for 58(63.73%) were good while poor for 20(21.97%), and those whose parent's TB knowledge status was unknown were 13(14.28%) of the patient. The statistical association between adherence and parents' TB knowledge was (p=0.000). Parents of 56(61.54%) patients had good relationship with health care providers of the program while parents of 22(24.17) patients had poor relation with health care provider and parents relation with provider for 13(14.28%) of pediatrics patients was unknown. The statistical association between patient adherence and parent relation with service provider was significant (p=0.00). At the end of treatment program 14(15.38%) of patients were cured while 6(6.6%) of the patients were not cured and 6(6.6%) of the patients died. However, patients health at the end of the program were not known for 65(71.43%) of patients. The statistical association between adherence and patient's health status at the end of treatment program was found to be significant (p=0.00). Among all pediatrics TB patients 59(64.83%) were successfully complete (adhere to) treatment program while 27(29.67%) patient default ed treatment program (non adhere) and for 5(5.5%) patient at end of program whether they complete or not were not known.

Table 5.5 : Relationship of patient address to treatment completion

		Completeness				P value
Address		yes	no	unknown	total	
	Urban	43	17	5	65	
	Rural	16	10	0	26	

Out of patients who attended treatment from urban area 66% completed their treatments while 26% of patients from urban area did not. But 61% of patients from rural area completed the treatment while 38.4% of patient did not complete the treatment. The statistical association between adherence and address was obtained to be insignificant (p= 0.220).

V. Discussion

In this study 46.1% of patients were found to be males while 53.8% of the patients were females, this result is similar with study conducted in Kenya in which 44.9% of the patients were males and 55.1% of the patient was females (15). In this study there was no significant association between sex, age and patient's adherence to their medication. This result is also consistent with finding of the study conducted in Kenya (15). In addition, it is similar with result reported by study conducted in Nigeria (18). Both studies concluded that there was no significant association between age, sex and patient adherence to medication. This could be due to the fact that in pediatric patients adherence is highly dependent on care giver of the patients (15). The result of this study showed that extra pulmonary TB was found to be more common in patients when compared with pulmonary TB, 57.1% and 42.82%, respectively. This result was not reported in study conducted in different countries. This indicates that diagnosis of TB in children is made at advanced stage of TB in pediatrics patient in Adama referral hospital. Furthermore, there was no statistically significant association (p = 0.76) between type of TB and patient adherence to their medication. This means that there is no difference in adherence to medication between the types of TB.

The patients who completed the treatment course at the end of the program were 64.83% while 29.67% of the patients defaulted the treatment, because caregiver may thought that their children were cured or due miss. This result is in line with a study conducted in Uganda which reported similar non adherence (25% of the study population) (17). Among these patients those whose sputum result recorded for three consecutive months showed that they were cured, were 15.38% while 6.6% of patients failed to be cured. 6.6% of patients died while they were on treatment. And those for which their health status was not known at end of treatment program were 64.83%. This result is not consistent with study conducted in Nigeria where higher cure rate and lower failure rate were reported (17). But it is consistent with result reported in retrospective study conducted in Ethiopian rural hospital in 2010 in which almost similar defaulter rate (16.8%) was reported, but the patients who died were lower than that obtained in this study (12).

Adherence in this study (64.83%) is slightly lower than that reported in study conducted on children registered for TB treatment at 23 health centers (85%) in Addis Ababa, but lower death rate (3.3%) of patients was reported (4). But it is in contrast with study conducted in Egypt in which lower adherence (16%) and higher non adherence (51%) of studied patients were reported (16).

As this study indicates vomiting and headache in 19.68% of the patients and hepatotoxicity in 8.78% of patients were found to be the most common drug related side effects which appear on patients in initiation phase. This result is in contrast with the result reported in study conducted in Nigeria in which hepatotoxicity (72.1%) and nausea and vomiting (25%) of the side effects reported in the patients (18). But according to the finding of this study, there was no significant association between treatment completion and presence of side effect. This means presence or absence does not bring difference in the extent treatment completion (18).

The finding of this study shows 24.17% of the patients defaulted the treatment program in continuous phase due to feeling better in (16.48%), forget in(4.39%) and missed(died) in 2.19% of patients. Similar result was reported by the study conducted in Uganda (17). As the above finding shows other reasons like feeling better, forgetfulness and miss had significant association with adherence of the patients, this is also in contrast with what has been obtained in study conducted in Kenya which showed that there was no significant relationship between side effect and adherence to anti TB medication (15).

The finding of this study also showed that the most common co morbid conditions were HIV in 21.97% and DM in 5.49% of studied patients. There was no significant association between co morbid condition and adherence. However, the patient who had been taking ART had good adherence to medication than non HIV co morbid patients, because their family might think that

their children would die if they discontinue taking anti TB drug as they were told by service providers. This result was similarly reported in study conducted in Uganda (17).

MDRTB was found in 7.69% of patients. According to the finding of this study there was no association between MDRTB development and adherence to medication as it was shown by p value (p=0.121 CI=95%). It might be due to poor adherence of patients to their medication or patients were caught by MDRTB from other patients. As the finding of this study shows there was no significant association between parent monthly income and patient adherence to anti TB medication. This result is in line with finding reported in study conducted in Kenya which states that family average monthly income had no statistically significant association with patient adherence to their medication (15). This was because TB treatment was given free and readily available to all patients.

As one can observe from the finding of this study the patients whose caregiver had TB knowledge (like nature of the disease, the effect of discontinue the treatment and the effect of irregular medication taking behavior) had good adherence to their medication when compared to patient whose care giver had poor TB knowledge, and there was statistically significant association between parent TB knowledge and adherence to medication .This result is in contrast with finding reported in Kenya which state that caregiver knowledge of TB had no significant association with adherence to medication (15). But it is consistent with study conducted in Uganda (17).

It was found that pediatric patients whose care giver had good relation with service provider had good adherence when compared with patient whose parent had poor relation with service provider. In addition, the quality of services has been shown to have significant association with adherence to the medication. This might be due to the parents were getting advice properly from health service providers. This finding is, however, in contrast with what reported in study conducted in Kenya which states that there was no statistically significant association between pattern of health care and patient adherence to medication (15).

In this study, even though higher defaulter were obtained in patients attended treatment from rural area when compared with those attended treatment from urban area, there was no significant association between address and adherence of patients to their medication (p=0.220, CI, 95%). This finding is in line with study conducted in Uganda (17). It is also consistent with finding reported in Kenya (15)

VI. Conclusion and Recommendation

a) Conclusion

This study shows that adherence of pediatric patients to their medication is not only affected by patient taking medication as prescribed but also parents' knowledge of TB, parents' relationship with health providers, presence or absence of other reasons like feeling better, forgetfulness and residence area . As the finding of this study shows presence of underlying disease like HIV have no effect on adherence of patient to anti TB drug. The parent monthly income also have no effect on adherence of the patient to anti TB medication .The result of this study indicate that MDRTB and TB relapse were most common in patients with poor adherence to their medication.

b) Recommendation

- Health professionals should give special consideration for parents of children who come from rural area and parents should be informed and made aware about TB because pediatrics adherence to their medication is highly dependent on parent's TB knowledge.
- Unlike adult patients children do not know the effect of discontinuing their medication; therefore treatment adherence of pediatrics patient should be monitored only by health professionals even during continuous phase of the treatment.
- Health status of pediatrics patient should be checked at least every two months.
- Side effect and other reasons which account for missing the dose should be monitored early so that children will adhere more to their medication.
- Adama hospital TB clinic should be staffed by qualified health personnel so that pediatrics patients will get high quality of service.
- Health professionals should focus on how to create awareness about factor affecting adherence in the community.
- Parents should be educated about the causes and the effects of TB, and possible adverse reactions of the medication, and the importance of children completing their medication according to the treatment plan.

Abbreviation and Acronyms

DOT = directly observed therapy
EDR TB = extended drug resistant tuberculosis
ETH = Ethambutol
HIV = human immune deficiency virus
INH = Isoniazid
MDR TB = multi drug resistant tuberculosis
PZA = pyrazinamide
RMP = rifampcin
SRP = streptomycin
TB = Tuberculosis
WHO = world health organization
D4T = stavudine
3TC = lamivudine
EFV = efaverenz
TDF = tenofovir

VII. Acknowledgement

We are very grateful to our college staff members for unreserved guidance and constructive suggestions and comments from the stage of proposal development to this end. We would like to thank Ambo University for supporting the budget which required for this research. Finally our deepest gratitude goes to Adam Referral Hospital staffs, which helped and allowed us in collecting and gathering data.

Funding: Ambo University

Conflict of interest: None declared

Ethical approval: Approval and permission was sought from Ethical Review Board of College of Medicine and Health Sciences of Ambo University

References Références Referencias

1. Kudakwashe Ch. Factor affecting compliance to tuberculosis treatment in Andra Kanvango region in Namibia, Journal of compliance to TB treatment, 2010, and 5-6.
2. Rieder, L. H. Interventions for tuberculosis control and elimination; journal of International Union against Tuberculosis and Lung Diseases, 2002, 5.
3. Soumya Swaminatha and Banu rekha. Burden of child hood tuberculosis and DOT in childhood in India, journal of medical science, 2010,6-7
4. Dereje hailu ,et al. Child hood tuberculosis and its treatment out come in Addis Ababa, Journal of BMC, Pediatrics 2014,14:61 doi.10.1186/1471-2431-14-61
5. Akilew, Kefyalew and mulugeta Belay. Non adherence to anti TB treatment November 11, 2013,DOI: 10.1371/journal. pone. 0078791;1
6. Bernand N Muture, Mergaret N Keraka, Peter K Kimu. Factor associated with defaulting from treatment among tuberculosis patient in Nairobi provinces, Journal of BMC Public Health 2011, 11:696 doi:10.1186/1471-2458-11-696
7. Tessema, B, Muche, A, Bekele, A, Reissig, D, Emmrich, F and Sack, U. Treatment outcome o f tuberculosis patients at Gondar University Teaching Hospital, Northwest Ethiopia, 2009. A five year retrospective study. Biomedical Central journal 9:371;1-2
8. B Castlen Vovo.A review of compliance to anti tuberculosis treatment and risk factors for defaulting treatment in Sub Saharan Africa, journal of African Health Science ; Dec 2010;v.10(4),1-3
9. Alyysa Finlay. et al.Patient and provider level risk factor associated with defaulting from tuberculoisis treatment South Africa 2002,1-2
10. Ibrahim Ali, Yimtubeznash Woldeamnuel, Amha Mekasha, Markos Abebe, Demissew Beyene, Shiferaw Bekele Abraham Aseffa. Drug Resistant Pattern of M. tuberculosis Among TB Suspected Children at Tikur Anbesa Specialized Hospital, Ethiopia, 2011:1-4
11. WHO report. Burden of TB on children 2012:14-15
12. Ramos, et al. Childhood and adult tuberculosis in rural hospital south east Ethiopia, Journal of BMC, public health, 2010,10:215
13. B.J Maris, et al. The burden of child hood tuberculosis in south Africa,Journal of public health 2005,4:35
14. Tajakistan ministry of health. Improving pediatric TB care inTajakistan, report of 2013:3-5
15. Dr Mario Nyamokami Ongayo ,etal. Determinant of adherence to anti TB drug among pediatrics TB patient in urban Kenya, journal of pharmacology 2011,1-2
16. Aida Mohey Mohammed .Adherence of children to INH preventive therapy in Alexandria, Egypt journal of community medicine 2010:5-7
17. Monica G Amuha,1 Paul Kutyabami,1 Freddy E Kitutu,1 Richard Odoi-Adome, 1 and Joan N Kalyango. Non-adherence to anti-TB drugs among TB/HIV co-infected patients in Mbarara Hospital Uganda: Prevalence and associated factors, Afr Health Sci. Aug 1, 2009; 9(Suppl 1): S8–S15. PMCID: PMC2890989
18. Bello S.I and Itiola O.A. drug adherence among tuberculosis patient in university of Ilorin teaching hospital, Nigeria, African journal of pharmacy and pharmacology. vol. (4) pp (109-114) march 2010.

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology and Medicine
Volume 15 Issue 2 Version 1.0 Year 2015
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Formulation & Evaluation of Eye Care Solution of Vasoconstrictor and Antihistaminic Drug for Conjuctivitis

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Abstract- The purpose of present research work was to formulate and evaluate eye care solution of Naphazoline hydrochloride (Vasoconstrictor) and Pheniramine maleate (Antihistaminic) drug for allergic conjunctivitis. The optimum values of responses for viscous eye care solution formulation was found to be 97.6 cps viscosity, 1759 cps mucoadhesion index and 96.67 % CDR for naphazoline hydrochloride and 93.34% CDR for pheniramine maleate. These could be obtained at lower levels of NaCMC and higher level of HPMCE4M (0.25/0.6%w/w respectively).These viscous eye care solution showed acceptable physicochemical properties. The optimized formulation was found to be stable in one month study and providing prolonged release of the drug over an 8 hr period. Irritation study on rabbit eye revealed that it was non-irritant. All the rabbits' eyes were normal by the end of 5 hour without any redness. There were no other adverse affects on the eyes throughout 8 hours study. This proves that optimized formulations of viscous eye care solution were very effective against common allergic conditions.

Keywords: *naphazoline hydrochloride, Pheniramine maleate, HPMC E4M, conjunctivitis.*

GJMR-B Classification : *NLMC Code: QV 701*

Strictly as per the compliance and regulations of:

Formulation & Evaluation of Eye Care Solution of Vasoconstrictor and Antihistaminic Drug for Conjuctivitis

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Abstract- The purpose of present research work was to formulate and evaluate eye care solution of Naphazoline hydrochloride (Vasoconstrictor) and Pheniramine maleate (Antihistaminic) drug for allergic conjunctivitis. The optimum values of responses for viscous eye care solution formulation was found to be 97.6 cps viscosity, 1759 cps mucoadhesion index and 96.67 % CDR for naphazoline hydrochloride and 93.34% CDR for pheniramine maleate. These could be obtained at lower levels of NaCMC and higher level of HPMCE4M (0.25/0.6%w/w respectively).These viscous eye care solution showed acceptable physicochemical properties. The optimized formulation was found to be stable in one month study and providing prolonged release of the drug over an 8 hr period. Irritation study on rabbit eye revealed that it was non-irritant. All the rabbits' eyes were normal by the end of 5 hour without any redness. There were no other adverse affects on the eyes throughout 8 hours study. This proves that optimized formulations of viscous eye care solution were very effective against common allergic conditions. We have successfully developed viscous eye solution for allergic conjunctivitis which contains 0.25 % NaCMC and 0.60 % HPMCE4M .It was well tolerated and could be used to prolong the therapeutic effectiveness of drug. The developed system is thus a viable alternative to conventional ophthalmic formulations.

Keywords: naphazoline hydrochloride, Pheniramine maleate, HPMC E4M, conjunctivitis.

I. Introduction

Sustained and controlled delivery of drugs to the ocular tissues continue to remain a major objective for formulation scientists and engineers in light of the emergence of more potent drugs and biological response modifications with limited biological half-lives. In ophthalmic drug delivery, in the front of the eye, the major hurdles of optimum drug bioavailability include rapid turnover, lacrimal drainage, reflex blinking and drug dilution by tears. Another physiological constraint is the limited permeability of cornea resulting into low absorption of ophthalmic drugs. A major portion of the administered dose drains into the nasolacrimal duct and thus can cause unwanted systemic side effects. Additionally, the rapid elimination of the drug through the punctum results in a short duration of the therapeutic effect resulting in a frequent dosing regimen. A significant challenge for the formulation is to circumvent these protective barriers of the eye without causing permanent damage to the tissue. Due to these physiological and anatomical barriers, only a very small fraction of the drug, usually 1-5% or even less of the instilled dose, is effectively absorbed. Frequent instillations of eye care solution are necessary to maintain a therapeutic drug level in the tear film or at the site of action. The frequent use of ophthalmic solutions may induce toxic side effects and cellular damage at the ocular surface. Moreover, once-a-day or twice-a-day formulations would like to improve patient compliance.

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a) Materials

Naphazoline hydrochloride, Pheniramine maleate, HPMC E4M, NaCMC, Benzalkonium chloride, Sodium chloride, NaoH.

II. Methods

To prepare viscous eye care solution, different concentrations of HPMC E4M and NaCMC as per 3^2 factorial design were used. In order to obtain clear viscous solutions, accurately weighed HPMC E4M and NaCMC were dispersed and thoroughly hydrated in about 30 ml of the required amount of WFI. The dispersion was vigorously stirred and heated to 80–90°C, until the solution became clear. Then add weighed quantity of Sodium Chloride, Disodium Edetate, Disodium Hydrogen Phosphate, Sodium Hydroxide and at last add weighed quantity of drugs and Benzalkonium Chloride in about 40-50% of the required amount of WFI. Add this mixture to the dispersion of polymers while stirring. Adequate WFI was then added to obtain the required volume. The viscous solutions prepared with the excipients were sterilized at 121°C in autoclave for 20 min. Afterward, aqueous solutions were sterilized by filtration through 0.22 μm sterile filter. The same formulation was prepared into simulated tear fluid in place of WFI.

III. Experimental Design

Experimental designs are frequently used to establish an empirical relationship in terms of a mathematical model between dependent variables, and a number of factors or independent variables. To study all the possible combinations of all factors at all levels, a

two factor, three level full factorial design was constructed and conducted in a fully randomized order. The experimental design consists of total 9 experiments. The concentration of HPMC E4M (X_1) and concentration of NaCMC (X_2) was selected as formulation (independent) variables. The factor levels were chosen from the knowledge obtained from the preliminary studies. All other formulation and process variables were kept invariant throughout the study. Table 2 Summarizes the 9 experimental runs studied and their factor combinations and translation of the coded levels to the experimental units employed during the study. The viscosity (Y_1), Mucoadhesion index (Y_2), cumulative percentage drug released after 8 hrs. (Y_3) were studied as response variables (dependent variables).Design-Expert software (V.8.0.7.1, Stat-Ease Inc.) was used for the generation of the mathematical models.

Table 1 : Variables and their levels in 3^2 factorial designs

Independent Variables	Levels		
	Low	Medium	High
X_1 = Concentration of HPMC E4M (% W/V)	0.5	0.55	0.6
X_2 = Concentration of NaCMC (% W/V)	0.25	0.4	0.5
Transformed values	-1	0	1
	Y_1 = Viscosity(cps)		
Dependent variables	Y_2 = Mucoadhesive Index		
	Y_3= Drug Release in 8 hr(%CDR)		

Table 2 : Factor combination as per chosen experimental design and translation

Trial No.	Coded Factor	
	X_1 Conc.of HPMC E4M (%w/v)	X_2 Conc. Of NaCMC (%w/v)
F1	1	1
F2	1	0
F3	1	-1
F4	0	1
F5	0	0
F6	0	-1
F7	-1	1
F8	-1	0
F9	-1	-1

a) Evaluation Parameters

i. *Clarity*

Clarity test was done by visual inspection of each container and by measuring the refractive index using refractometer at 25°c.

ii. *PH*

PH of prepared viscous eye care solution was measured with pH meter.

iii. *Viscosity*

Viscosity of batches F1-F9 by Brookfield viscometer at different RPM. By plotting graph of RPM vs. viscosity, flow pattern was checked.

iv. *Osmolarity*

The osmolarity of optimized sterilized viscous eye care solution was determined with a vapor pressure osmometer at room temperature.

v. *Mucoadhesion Tes*

Mucin dispersion method was used to measure mucoadhesion index. *Mucin Dispersion (MUC):* MUC (15%w/v) was prepared by dispersing required amount of Mucin powder -into phosphate buffer (*pH* 7.4) and kept on magnetic stirrer at 600 rpm for 24 hrs for complete hydration and measured it viscosity (ηm). To study the mucoadhesive interaction, 5 ml of polymer dispersion (ηp) and 15 ml of MUC was mixed and determined its viscosity (ηt) at 37°±1°C at shear rates D of 12.5, 25, 50, and 100 s^{-1} . An interaction between polymer and mucin should be seen as a synergistic effect in the rheological properties, which means that the rheological response of the Polymer/MUC mixture should be larger than the sum of the rheological responses of the single components polymer and mucin. Therefore, it is essential to rheologically characterise the single components as well as the polymer/MUC mixture.

vi. *Sterilization Study*

Membrane filter of 0.2-μm porosity was used for sterilization by filtration in μm aseptic area. The suitability of both methods of sterilization in the present study was tested by determining drug content of representative eye solution formulation of (aqueous based) before and after subjecting to sterilization by the respective method. Aqueous base solutions were prepared with 1 % drug and other excipients filled in vials and sealed. These vials were autoclaved for 20 minutes. In some other vials, solutions were filled by filtration through 0.2μm Millex, Millipore filter.

vii. *Sterility testing*

The sterility testing of the viscous eye care solution was performed for the aerobic, anaerobic bacteria and fungi by using alternative thioglycolate medium (ATGM) and soyabean casein digest medium (SBCD). The positive control (growth promotion), negative control (sterlity) test was also conducted. Bacillus subtilis was used as a test organism in the case of aerobic bacteria test. Bacterio desvulgatus was used as a test organism in case of anaerobic bacteria test and candida albicans in fungi test. Incubation was carried in all cases and growth was checked. All the samples were inoculated separately in to ATGM and SBCD media and incubated at 35°C and 20-25°C, respectively for 7 days. Similarly unsterilized samples of films were also inoculated separately in to ATGM and SBCD media and incubated at 35°C and 20-25°C, respectively for 7 days. A control evaluation was also carried out.

viii. *Antimicrobial Test*

The test was performed according to USP. Cultures of bacteria [Escherichia coli (ATCC 4352), Pseudomonas aeruginosa (ATCC 9027), Staphylococcus aureus (ATCC 6538)] and fungi [Aspergillus niger (ATCC 16404) and Candida albicans (ATCC 10231)] were grown on solid agar media and soyabean casein digest media respectively. The test microorganism cultures were diluted with sterile WFI to obtain 10^{-6} CFU/ml as per USP. All the cultures were transferred into 5 test tubes containing 10ml prepared eye drops(solution) and 0.1% prepared cultures in each. Initial counts were noted. These solutions were poured into petri plate containing Soya bean Casein Digest Agar Medium for bacterial cultures and Sabouraud Glucose Agar Medium for fungi. Keep them into incubator at 32.5±2.5°C and 22.5±2.5°C for bacteria and fungi respectively. Record the numbers of colony of microorganism at 7th, 14th and 28th day. Check the criteria for preservative effectiveness for their acceptable range.

ix. *Invitro Diffusion study*

The Franz diffusion cell was used for studying the in vitro release of the viscous eye care solution(drops). A cellulose acetate membrane (Dialysis membrane with 25 mm diameter) was adapted to the terminal portion of the cylindrical donor compartment. 2.5 mL viscous eye drops containing drug, sufficient for establishing sink conditions for the assay was placed into the donor compartment. The receptor compartment contained 15 mL of Phosphate buffer solution of pH 7.4 maintained at 37°C under mild agitation using a magnetic stirrer. At specific time intervals, aliquots of 3mL will be withdrawn and immediately restored with the same volume of fresh phosphate buffer. The amount of drug released was assessed by measuring the absorbance at 261.6 nm and 272.4nm for Naphazoline and Pheniramine respectively using UV spectrophotometers. In order to analyze the drug release mechanism, in vitro release data was fitted into a zero-order, first order, Higuchi, And Korsmeyer-peppas model.

x. *Animal study*

– Test for irritation
– Antiallergy activity of the prepared formulations of Naphazoline Hydrochloride and Pheniramine Maleate

xi. *Stability*

To assess the drug and formulation stability, stability studies was done according to ICH guidelines. Optimized formulation was kept in the stability chamber at specified temperature and humidity (40°±10°C and 75%RH) for one month. The chemical stability of the formulation was assessed by the estimation of the percentage drug remaining in the formulation and physical stability was evaluated by monitoring any change in pH, viscosity and appearance.

IV. Result and Discussion

Development of first order derivative spectroscopy method for simultaneous determination of NH and PM:-
Selection of wavelength for simultaneous estimation of NH and PM :-

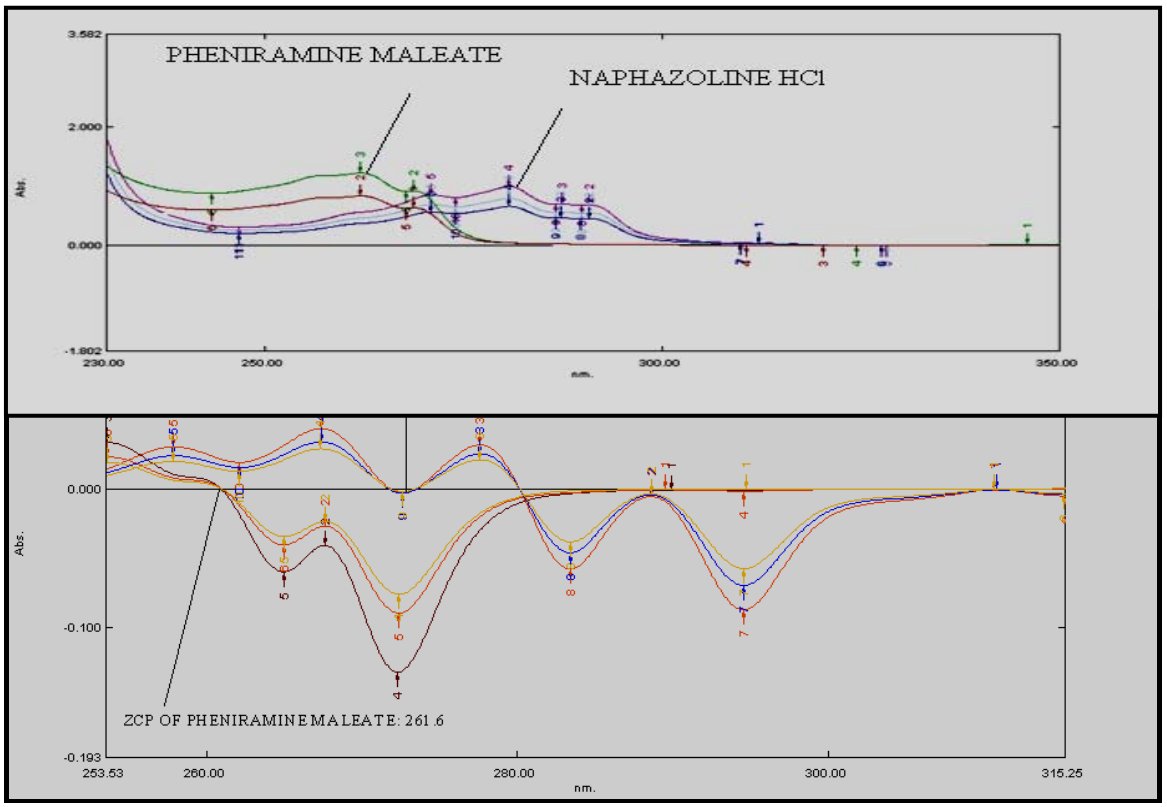


Figure 1

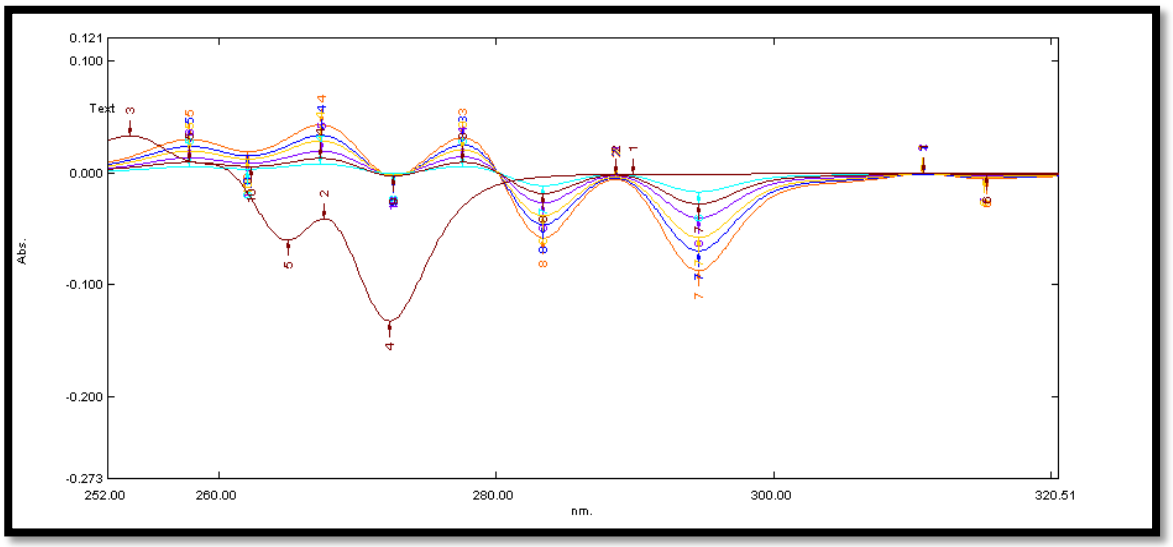


Figure 2

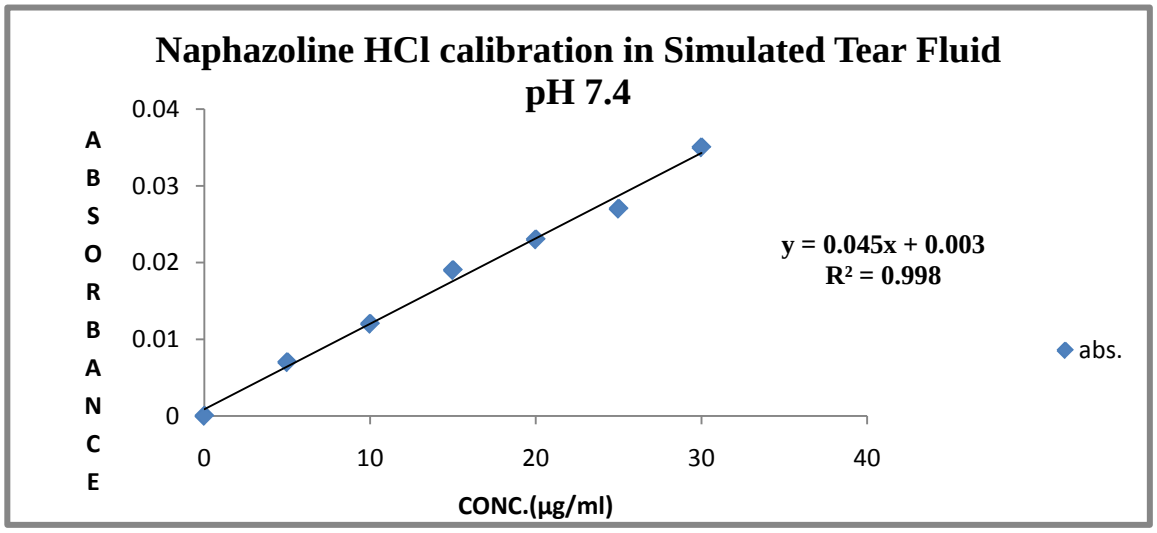


Figure 3

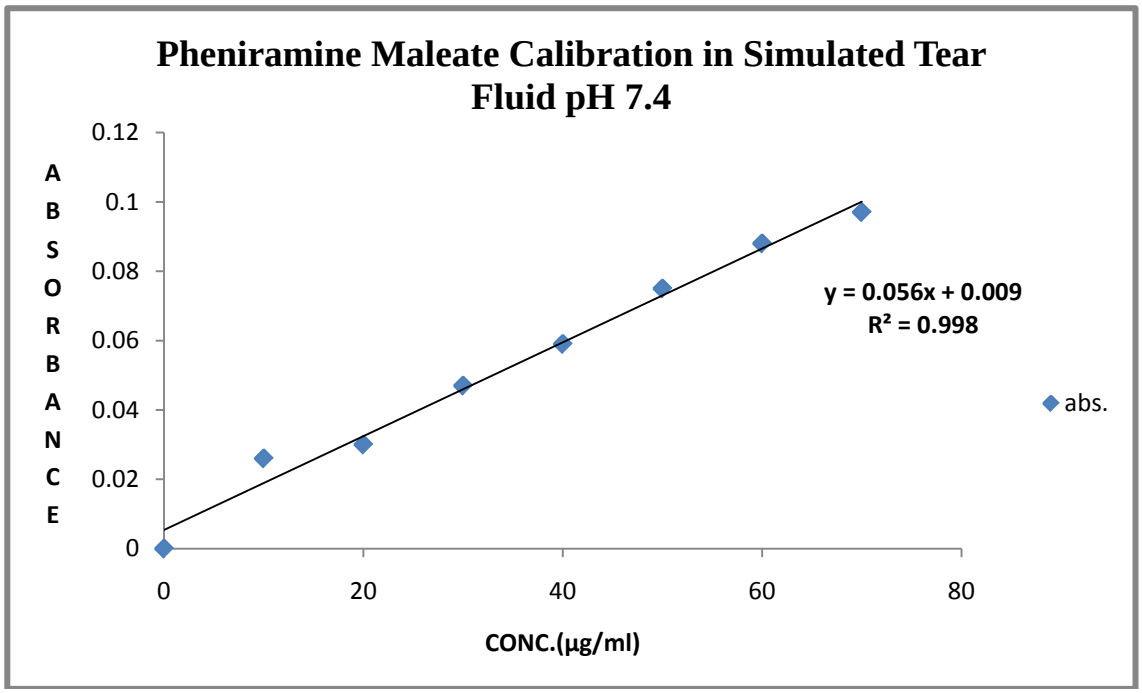


Figure 4

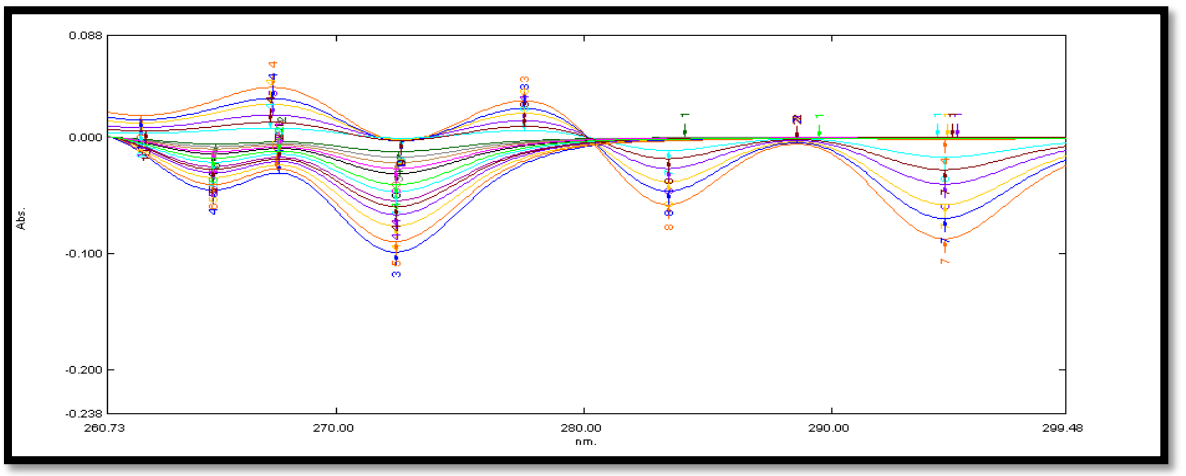


Figure 5 : FTIR spectra of physical mixture-II (Naphazoline Hydrochloride + Pheniramine Maleate + HPMC E4M + NaCMC)

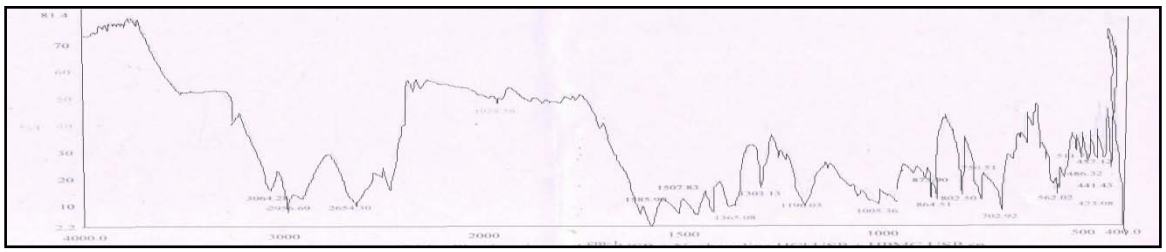


Figure 6

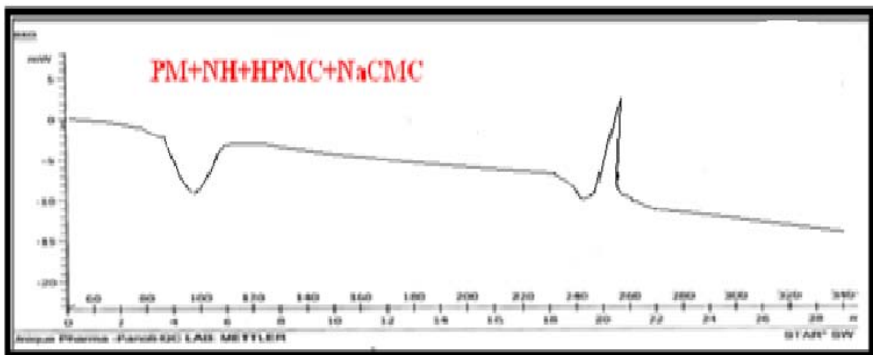


Figure 7 : DSC thermogram of physical mixture-III (Naphazoline Hydrochloride + Pheniramine Maleate + HPMC E4M + NaCMC)

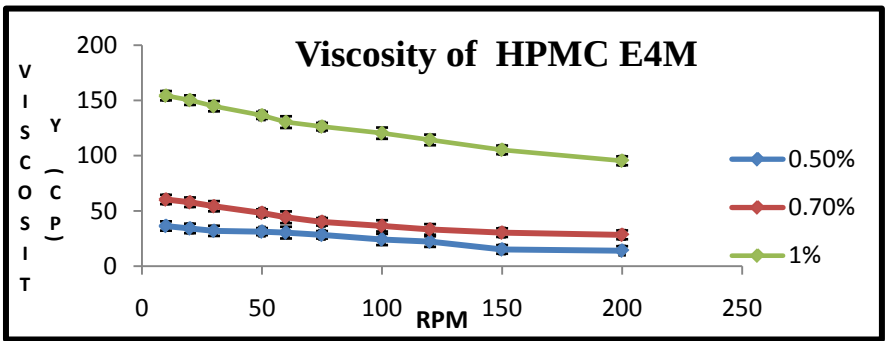


Figure 8

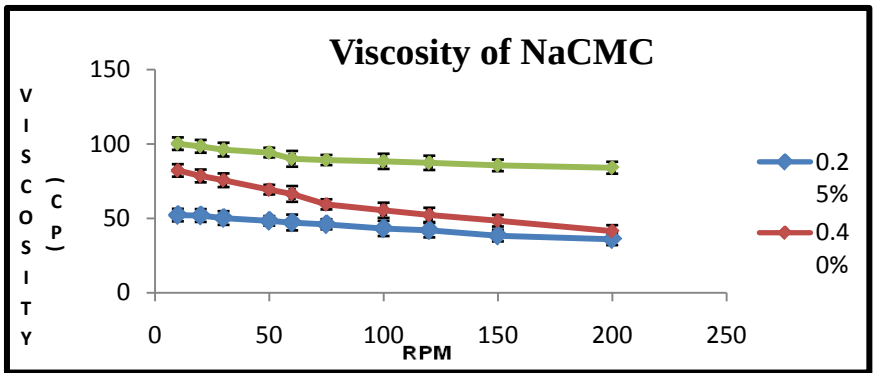
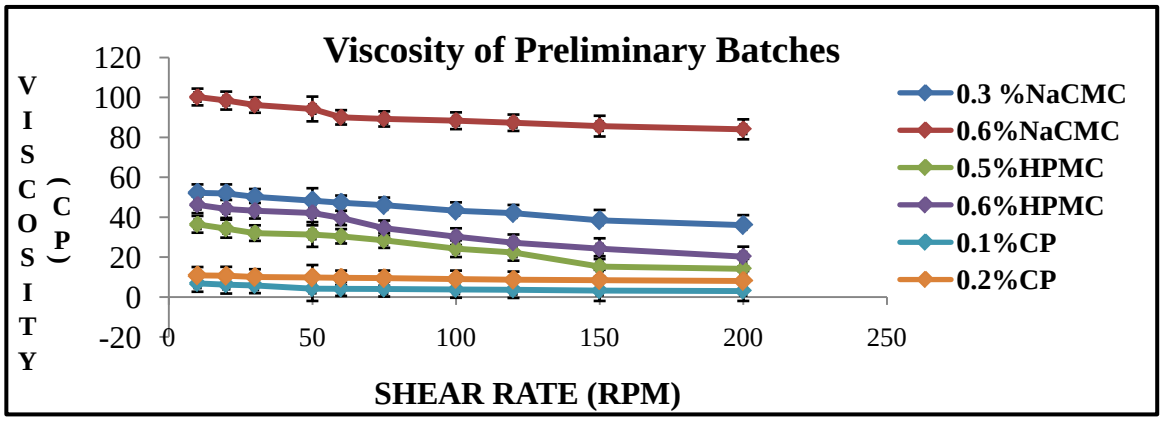


Figure 9



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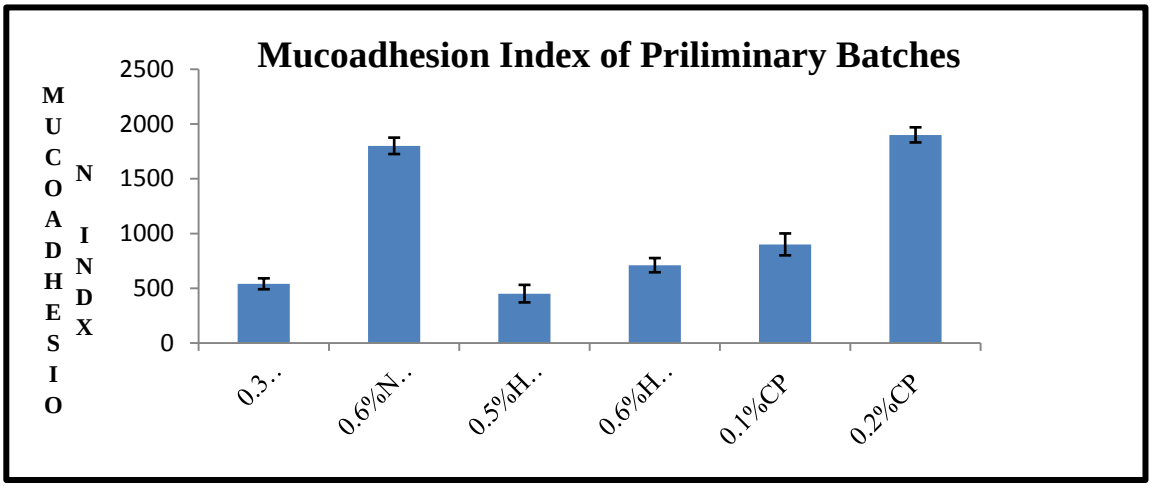


Figure 11

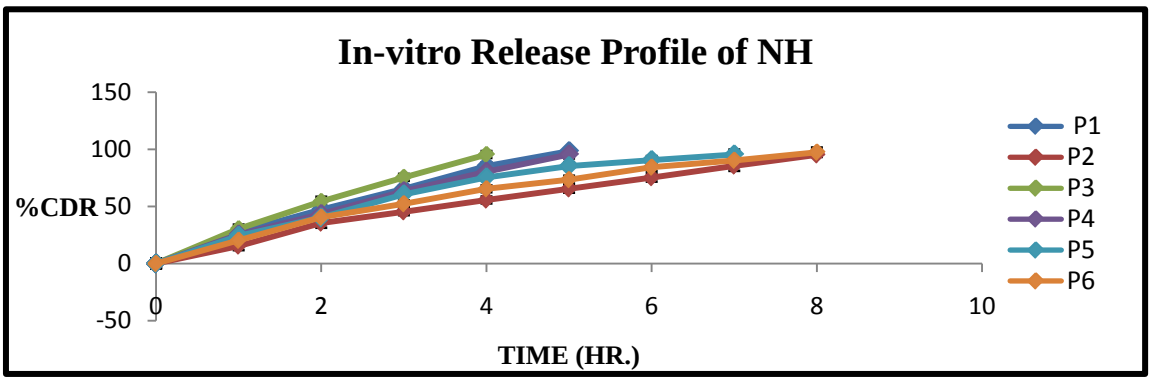


Figure 12

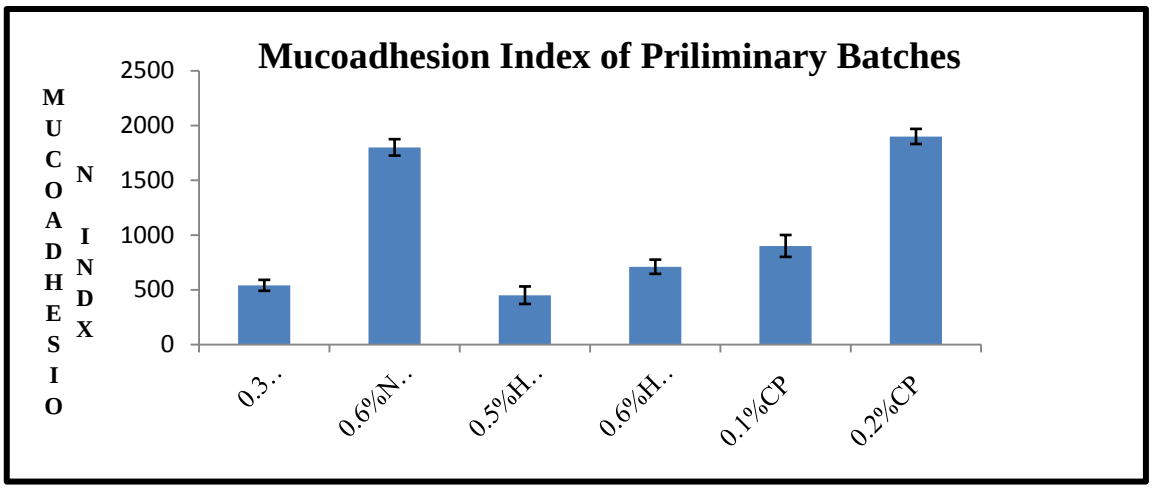


Figure 11

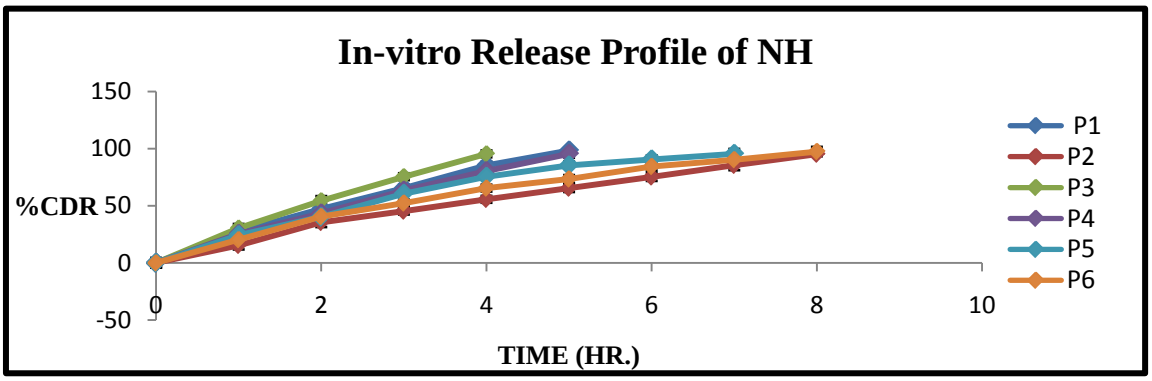


Figure 12

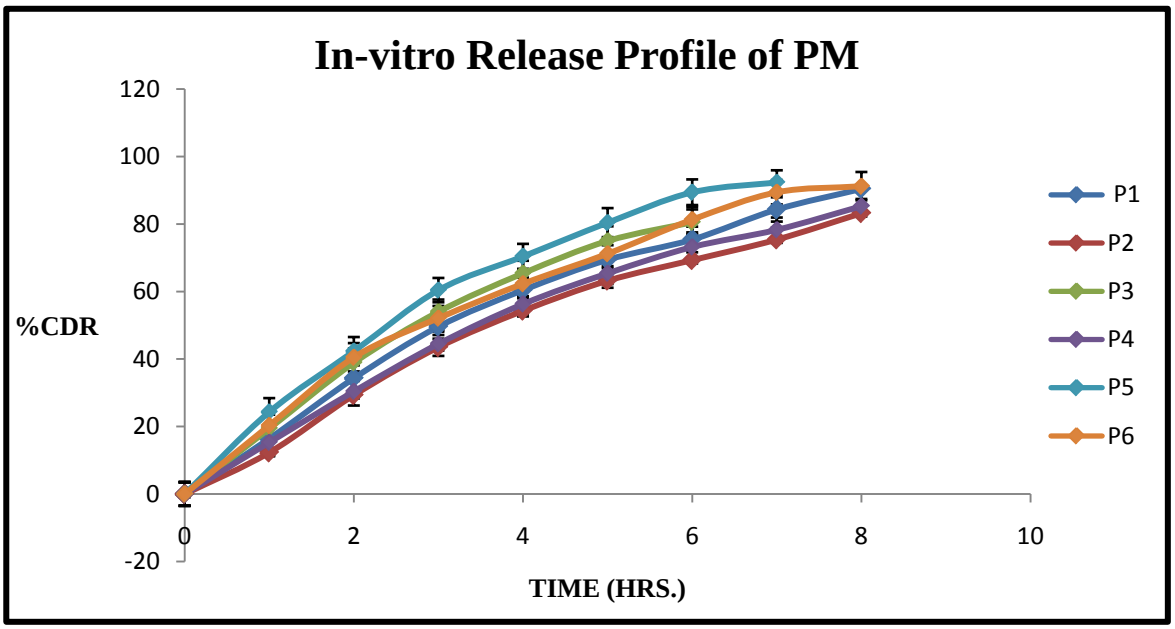


Figure 13

Table 3 : Composition of NaphazolineHCl / PheniramineMaletae viscous eye care solution

Name of components	Amount (%w/v)
Naphazoline Hydrochloride(NH)	0.0265
Pheniramine Maleate(PM)	0.315
NaCMC	0.25-0.5
HPMCE4M	0.5-0.6
Sodium Chloride	0.68
Benzalkonium chloride	0.01
Disodium Edetate	0.1
NaOH	To adjust pH
WFI/STF/Phosphate Buffer pH 7.4	Up to 100ml

Table 4 : Viscous eye drops physical characterization (X ± S.D.)

Batch	Clarity	pH (n= 3)	Refractive Index
F1	Slightly translucent	7.40±0.02	1.469±0.001
F2	Clear	7.40±0.01	1.431±0.001
F3	Clear	7.41±0.01	1.356±0.001
F4	Slightly translucent	7.40±0.01	1.465±0.002
F5	Clear	7.40±0.03	1.358±0.002
F6	Clear	7.40±0.01	1.341±0.001
F7	Slightly translucent	7.41±0.01	1.471±0.001
F8	Clear	7.41±0.02	1.341±0.002
F9	Clear	7.40±0.01	1.334±0.001

a) pH

The pH values for all formulations were shown in **Table 4**. The pH was within acceptable range (6.8 to 7.4) and would not cause any irritation upon administration of the formulation.

b) Refractive index

Refractive index of tear fluid is 1.340 to 1.360. (Hussein et al.2009) It is recommended that eye care solution should have refractive index values not higher than 1.476. **Table 4** depicts that Naphazoline hydrochloride and Pheniramine maleate viscous eye care solution had refractive index values ranging from 1.443 to 1.334 which are within the recommended values. Data reflected that no visual problem may cause in patient after administration of formulation.

c) Viscosity

The longer contact time and effectiveness of the formulation in the eye is probably dependent not only on its mucoadhesive properties, but also on its viscosity and bulk rheological properties. Viscosity data of all the batches are shown in figures. Viscosity study in phosphate buffer 7.4 pH and in simulated tear fluid was carried out. From the rheograms shown in **Fig. 14 & 15** and respectively was found that viscosity in both the medium remain same. From the data, it was found that batches F1, F4 and F7 shows very high viscosity due to highest concentration of NaCMC; was not selected as they were too viscous to instill properly into the eye. While, batches F6, F8 and F9 shows low viscosity due to lowest concentrations 0.5% HPMC, was not selected as aim of this study was to increase the viscosity of the formulations developed for residence time in ocular globe. Batches F3, F5 and F7 showed satisfactory viscosity. Each batch showed non-newtonian (dilatant) flow behaviour without any hysteresis. Non-newtonian solutions offer less resistance to movement of the eyelids over the globe and, therefore, are expected to be more comfortable in the eye than Newtonian solutions. By using the viscolysers like HPMC and NaCMC, viscosity of the prepared eye care solution was increased which gives longer contact time to the ocular globe. Therefore frequency of the instillation is decreased, which improves patient compliance. This increasing shear rate mimic ocular shear rates associated with normal blinking which is extremely wide, ranging from 0.03-28500S^{-1}.

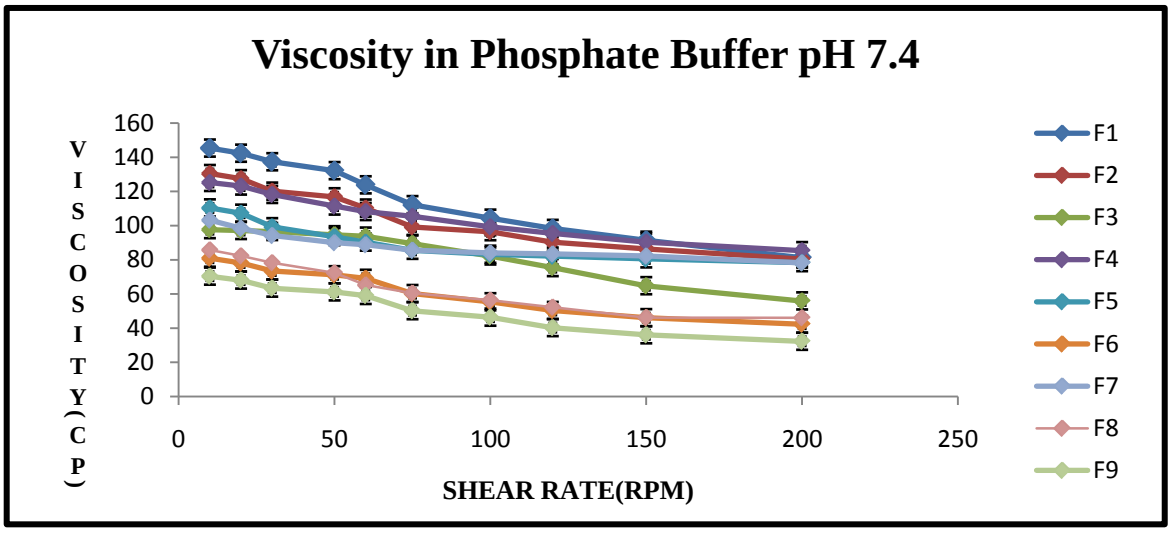
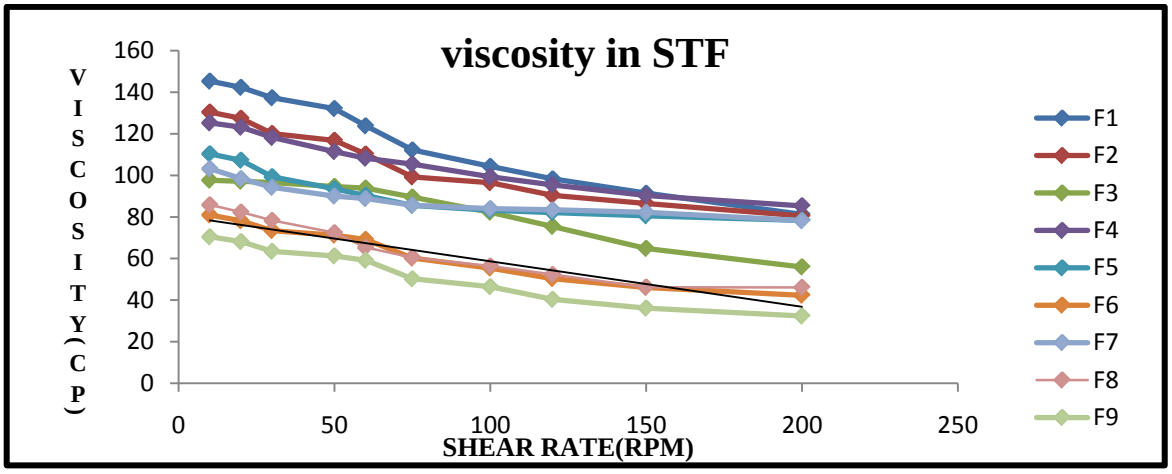


Figure 14



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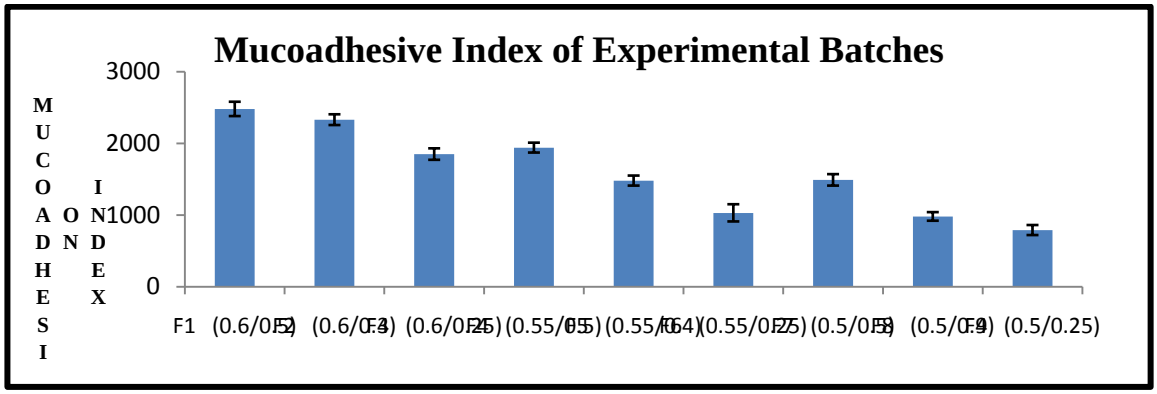


Figure 16

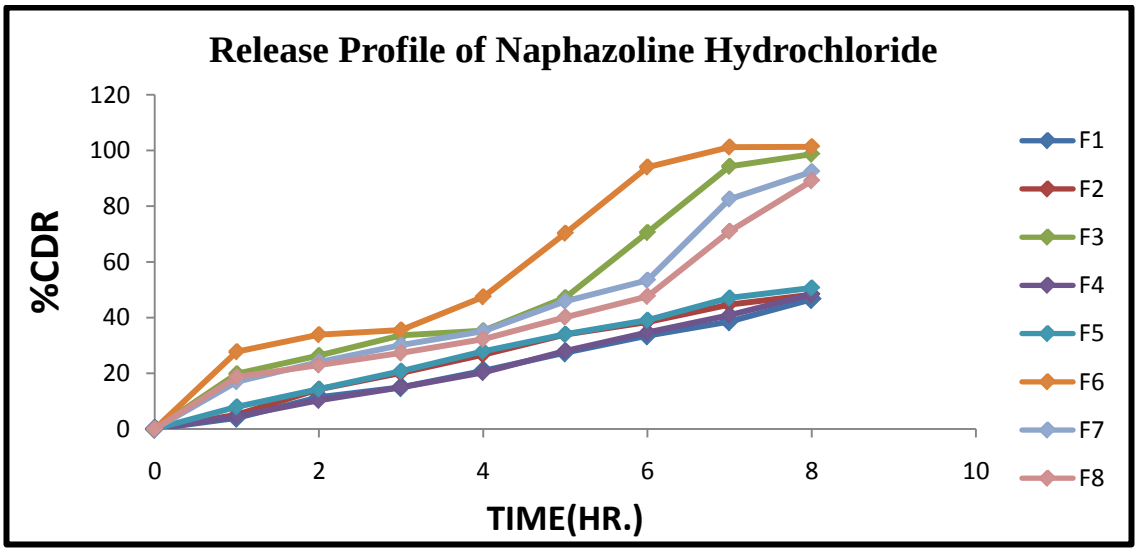
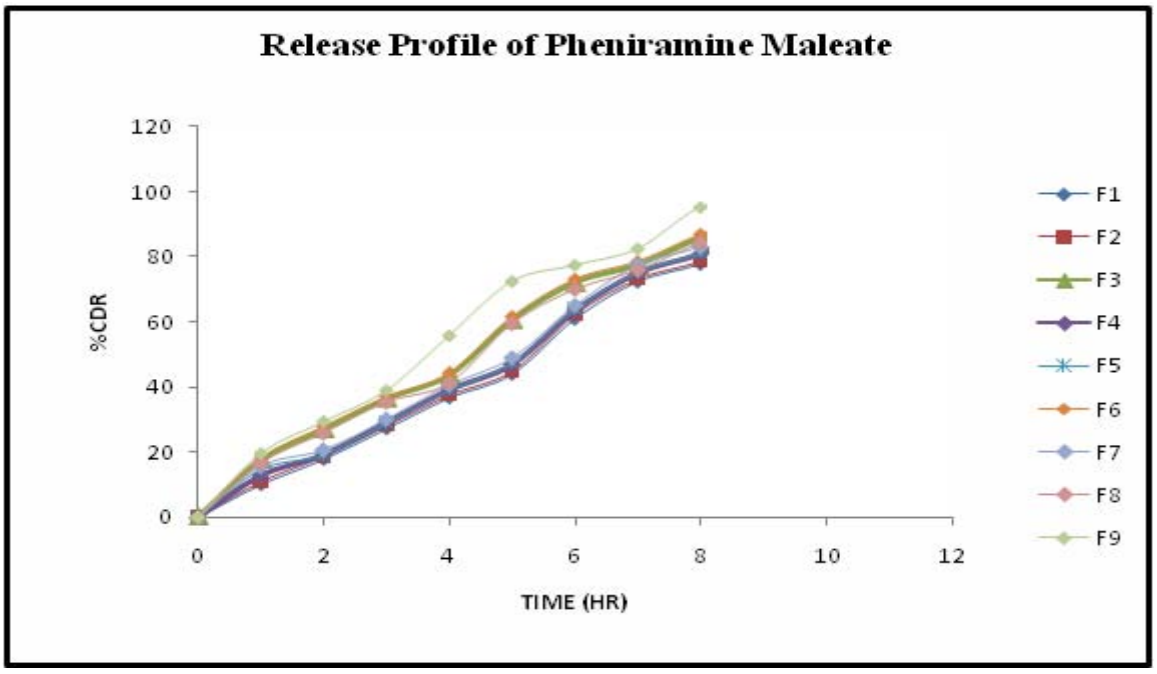


Figure 17



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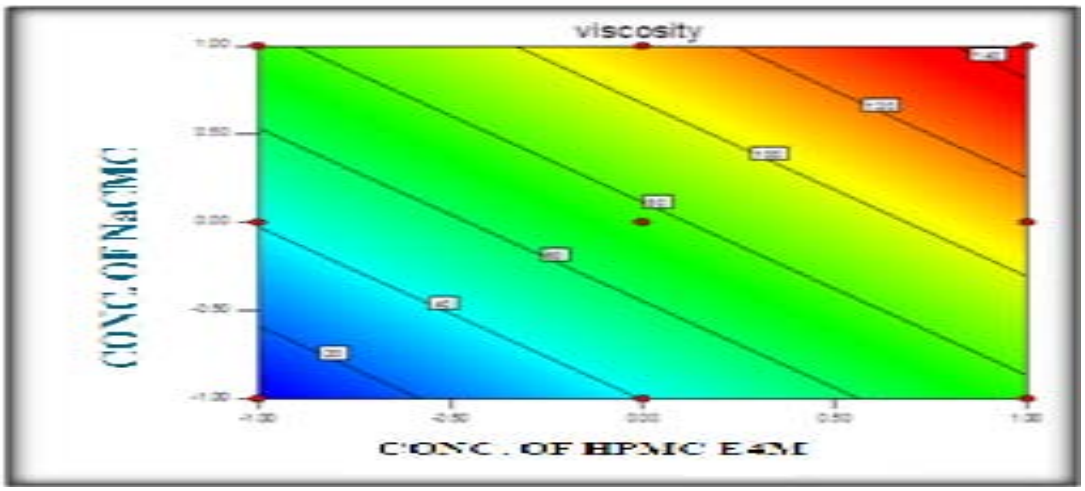

Figure 19

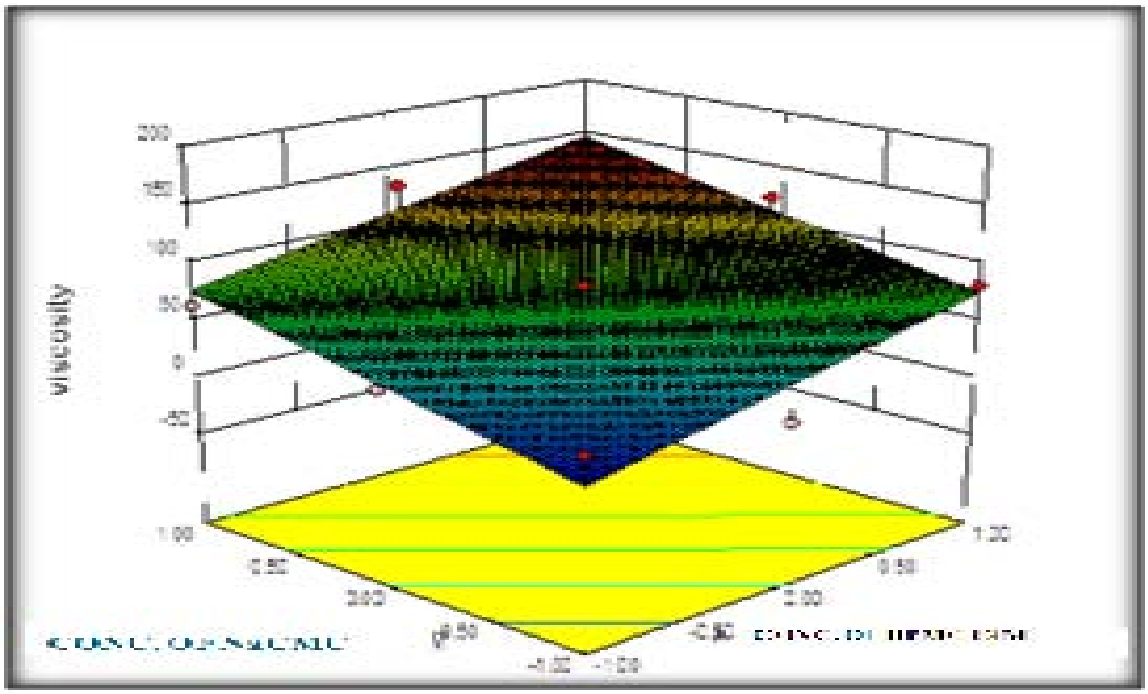

Figure 20

Contour plot (a) and response surface (b) plot showing the relationship between various level of polymer (HPMC E4M & NaCMC) on viscosity

d) Sterilization and Sterility testing

Results of sterility test of optimized batches in both the media are shown in **Table 5.** It indicated absence of turbidity in media after 21 days of incubation period. This indicates absence of any contamination.

Table 5 : Sterility testing of optimized batch

Batch	Media		Result
	ATGM	SBCD	
F*	Clear	Clear	Complies

ATGM–Alternative Thio glycolate media; SBCD – Soya bean casein digest media

e) Antimicrobial efficacy testing (AET)

AET was done to evaluate the efficiency of preservative. Data shown in **Table 6** depicted that fungi Candida albicans and Aspergillus niger show inhibition in growth after 7th, 14th and 28th day from initial count. The microbial count for bacteria (Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus) is shown in **Table 7** and as per USP there should be 1 log reduction after 7 days, 3 log reductions after 14 days and no growth in population as compare to 14th day after 28 days. In case of fungi, as per USP, there should be no growth/inhibition for AET. Optimized batch was obeyed the similar pattern of reduction in population as per standard limit and complies with the results.

Table 6 : Microbial count of fungi at specified time interval for AET

Culture	Batch	Initial	7th day	14th day	28th day
Candida albicans	F*	15×10^{6}	85×10^{5}	46×10^{4}	33×10^{3}
Aspergillus Nniger	F*	9×10^{6}	34×10^{5}	52×10^{4}	12×10^{3}

Table 7 : Microbial count of bacteria at specified time interval for AET

Culture	Batch	Initial	7th day	14th day	28th day
Escherichia Coli	F*	25×10^5	18×10^4	300	253
Pseudomonas aeruginosa	F*	19×10^5	11×10^4	287	218
Staphylococcus aureus	F*	22×10^5	13×10^4	240	198

f) Osmolarity

The Osmolarity of the ophthalmic preparation should be in the range of 310-350 mOsmol/kg to avoid irritation. Osmolarity of optimized batches was found to be in the range and shows 325 mOsmol/kg which was within the acceptable tonicity range of the eye to avoid ocular irritation.

g) Animal Study

Table 8 : Ocular Irritation test for Optimized Batch and Marketed Formulation

FORMULATION	RABBIT A						RABBIT B					
TIME (HR.)	1	2	3	4	5	6	1	2	3	4	5	6
F*	N	N	N	N	N	N	-	-	-	-	-	-
CONTROL	N	N	N	N	N	N	-	-	-	-	-	-
OPCON A	-	-	-	-	-	-	N	N	N	N	N	N
CONTROL	-	-	-	-	-	-	N	N	N	N	N	N

S- Severe itching / irritation, M-Mild itching / irritation, N- No itching / irritation Stability

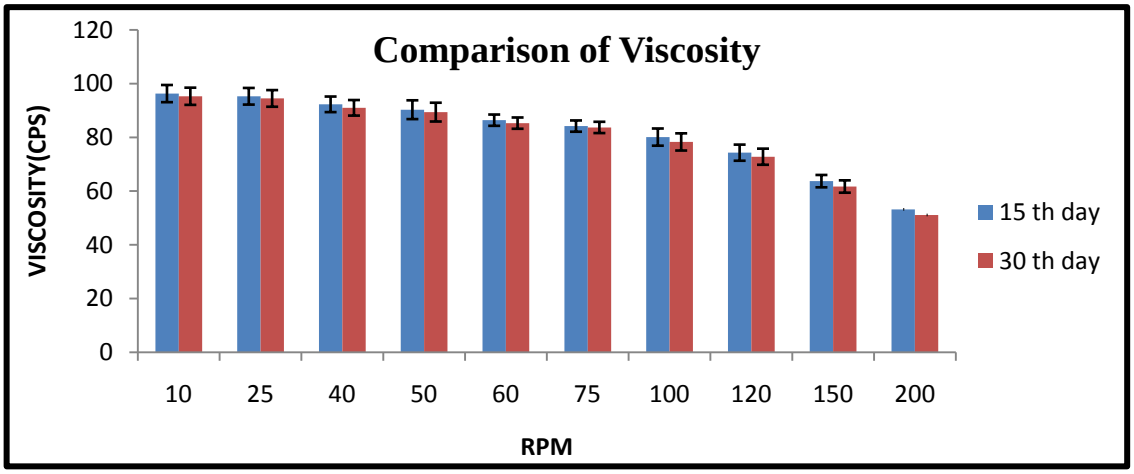

Figure 21

Table 9 : Change in pH, Assay of NH, PM and Assay of BKC data over time (Stability Study)

Days	pH*	Assay of NH (% w/v)*	Assay of PM (% w/v)*	Assay of BKC (% w/v)*
15	7.4 ± 0.02	99.60±0.54	99.34±0.34	99.79±0.64
30	7.41 ± 0.01	99.41±0.83	98.76±0.43	99.58±0.90

**Value Expressed as Mean ± SD (n=3)*

V. Conclusion

Thus, on the basis of all the studies we can conclude that the batch having naphazoline hydrochloride and pheniramine maleate along with 0.59 % of HPMC E4M in the combination with 0.26 % NaCMC viscous solution may be considered as a promising for ophthalmic drug delivery.If the aforementioned formulation will scaled-up to manufacturing level, it will be used for potential sustained release effect for the allergic conjuctivitis.

References Références Referencias

1. Bisca M, "Current therapy of allergic conjunctivitis", Current Therapeutic Research 58, 828-841, 1997.
2. Ali YA and Lehmussaari K, "Industrial perspective in ocular drug delivery", Advanced Drug Delivery Reviews 58, 1258–1268, 2006.
3. Rathore et al, ''An overview and advancement in ocular drug delivery systems", International Journal of Pharmaceutical Science & Research 46, 11-23, 2010.
4. Eva M.del Amo and Atourtti, ''Current and future ophthalmic drug delivery systems, A Shift to the posterior segment, Drug Discovery Today, 13,135-143, 2008.
5. Maurice DM and Mishima SP, "Ocular pharmacokinetics", Handbook Of Experimental Pharmacology,15th Edition, Springer-Verlag, Berlin-Heidelberg Publication, pp.19-116, 1984.
6. Ripal gaudana And Saih A.N "Recent perspectives in ocular drug delivery-expert review", Pharmaceutical Research, 26, 1197-1216, 2009.
7. Maria D.Moya-Ortega et al, ''Dexamethasone eye drops containing alpha cyclodextrin-based nanogels", International Journal of Pharmaceutics, (44), 507-515, 2013.
8. Ansari MJ and Kohli, "Microemulsion as potential drug delivery system", Pdaj. Pharma Science Techno, 62, 66–79, 2008.
9. Kassem MA and Abdelrahman AA. "Nanosuspension as an ophthalmic delivery system for certain glucocorticoid drugs", Int. J. Pharm, 340, 126–133, 2007.
10. Hathout RM and Mansour S. "Liposomes as an ocular delivery system for acetazolamide: in-vitro and in vivo studies. Aaps Pharm scitech, 8, 1, 2007.
11. Vandammeand TF and Brobeck L. "Poly (amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide". J. Control Release, 4, 13-14, 2007.
12. Kaur IP and aggarwal D. "Vesicular systems in ocular drug delivery". Int. J. Pharm 2, 15-20, 2010.
13. Bourges JL and Gautier SE. "Ocular drug delivery targeting the retina and retinal pigment epithelium using polylactide nanoparticles". Invest. Ophthalmol. Vis. Sci, 44, 3562–3569, 2003.
14. Bourges JL and Behar-Cohen F. "Intraocular implants for extended drug delivery: therapeutic applications". Adv. Drug Delivery Review, 58, 1182–1202, 2006.
15. Sigurdsson HH and Stefansson E. "Topical and systemic absorption in delivery of dexamethasone to the anterior and posterior segments of the eye". Acta. Ophthalmol. Scand. 85, 598–602, 2007.
16. Gulsenand D and Chauhan A. "Ophthalmic drug delivery through contact lenses". Invest Ophthalmol Vis Science, 45, 2342–2347, 2004.
17. Hitesh Sharma, ''A novel approach sustained ocular drug delivery: In-situ Gel", International Journal of Research in Pharmacy and Life Science, 1(2), 121-124, 2013.
18. Mark A. Babizhayev et al, "Current ocular drug delivery challenges for N-acetyloxcarnosine: novel patented routes and modes of delivery, design for enhancement of therapeutic activity and drug delivery relationships". Recent Patents on Drug Delivery & Formulation, 18, 229-265, 2009.
19. Parkinson TM and Mundasad M. "Tolerance of ocular iontophoresis in healthy volunteers". J. Ocul. Pharmacol. Therapy, 19, 145–151, 2003.
20. Joossand K and Chirmule N. "Immunity to adenovirus and adeno-associated viral vectors: implications for gene therapy" .Gene Therapy, 10, 955–963, 2003.
21. Rathore KS and Nima RK, "An insight into ophthalmic drug delivery system", International Journal of Pharmaceutical Science and Drug Research, 47, 1-5, 2009.
22. The Handbook of Ocular Disease Management.
23. Santa J and Mark BA "Allergic conjunctivitis: update on pathophysiology and prospects for future treatment"
24. United State Pharmacopeia and National Formulary (USP 30), "Naphazoline Hydrochloride Monograph", pp 2707.
25. United State Pharmacopeia and National Formulary (USP 30), "Pheniramine Maleate Monograph", pp 2917.
26. Annickludwig, "The use of mucoadhesive polymers in ocular drug delivery", Advanced Drug Delivery Reviews, 7, 1595-1639, 2005.
27. Van Santvliet and Ludwig AK, "Influence of the physico-chemical properties of ophthalmic viscolysers on the weight of drops dispensed from a flexible dropper bottle", European Journal of Pharmaceutical Sciences, 95, 339–345, 1999.
28. Soumendra sahoo et Al., "Mucoadhesive nanopolymer – a novel drug carrier for topical ocular drug delivery", European Journal of Scientific Research, 46, 401-409, 2010.
29. Raymond C Rowa and Siân C Owen, "Handbook of Pharmaceutical Excipients", 6thedn, The Pharmaceutical Press, pp 118-121, 2006.
30. Sahoo Soumendra et. al. "Tamarind seed polysaccharide: a versatile biopolymer for mucoadhesive applications", Journal of Pharmaceutical and Biomedical Sciences, 8 (20), 2010.
31. Raymond C Rowa and Siân C Owen, "Handbook of Pharmaceutical Excipients", 6thedn, The Pharmaceutical Press, pp 314-315, 326-329, 2006.
32. Raymond C Rowa and Siân C Owen, "Handbook of Pharmaceutical Excipients", 6thedn, The Pharmaceutical Press, pp 159-161, 2006.

33. Unlu N and Ludwig A, ''A comparative rheological study on carbopol viscous solutions and evaluation of their suitability as the ophthalmic vehicle and artificial tears, Pharma Act, 67(1), 5-10, 1992.
34. Vianna Lopez et al., "A poloxamer/chitosan in situ forming gel with prolonged retention time for ocular delivery", European Journal of Pharmaceutics and Biopharmaceutics, 75, 186–193, 2010.
35. Barretta GU and Nazzi S. "Synergistic interaction between TS-polysaccharide and hyaluronic acid: implications in the formulations of eye drops". International Journal of Pharmaceutics.2011, 395,122–131.
36. Sibelbozdag and Koraygum, "Formulation and In-vitro evaluation of cysteamine hydrochloride viscous solution for treatment of corneal cystinosis", European Journal of Pharmaceutics and Biopharmaceutics, 2008, 70, 260–269.
37. Jack VG, "Pheniramine maleate/naphazoline hydrochloride ophthalmic solution and olopatadine hydrochloride ophthalmic solution in the conjunctival allergen challenge model", Clinical Therapeutics, 2005, 27.
38. Attwood D. et al, "In-situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride", International Journal of Pharmaceutics , 2001, 229.
39. Kaur IP et al., "Formulation and evaluation of ophthalmic preparations of acetazolamide", International Journal of Pharmaceutics 2000 ,199, 119–127.
40. Felt O. et al, "Topical use of chitosan in ophthalmology: tolerance assessment and evaluation of precorneal retention", International Journal of Pharmaceutics 1999, 180, 185–193.
41. Forming Jingcai, Eye preparation for treating medicine, US Patents 03132242.5,2004.
42. Jeffrey Hutterer, Method and composition for treatment of skin conditions, US Patents PCT/US2005/010269,2005.
43. John Denick, Zhenze Hu, Ophthalmic compositions including glycerin and propylene glycol, US Patents US 08/794,690,1998.
44. Farnes et al., Ketorolac tromethamine compositions for treating ocular pain,US Patents 12/396,131,2009.
45. Orest Olejnik, Fred W.Wendel, Ophthalmic formulation, US Patents US 081329,808,1997.
46. Krisriino kyyronen and Arrourrri, "Improved ocular: systemic absorption ratio of timolol by viscous vehicle and phenylephrine", Investigative Ophthalmology & Visual Science, 1990, 15, 798-806.
47. Sibelbozdag and Koraygum, "Formulation and In-vitro evaluation of cysteamine hydrochloride viscous solution for treatment of corneal cystinosis", European Journal of Pharmaceutics and Biopharmaceutics, 2008, 70, 260–269.
48. Patel PB and Shastri DH, " Development and evaluation of pH triggered in-situ ophthalmic gel formulation of ofloxacin" ,American Journal of Pharmtech Research., 2011, 1, 430-445.
49. Kulkarni SV and Sandeep HN." Effect of a single drop of latanoprost ophthalmic gel on intra ocular pressure in the treatment of glaucoma". International Journal of Pharmaceutical Sciences. 2010, 2, 429-435.
50. Hussein OA and Salama HA, "Nanoemulsion as a potential ophthalmic delivery system for dorzolamide hydrochloride", AAPS Pharmscitech. 2009, 10, 808-819.
51. Sibelbozdag and Koraygumu, "Formulation and In-vitro evaluation of cysteamine hydrochloride viscous solution for treatment of corneal cystinosis", European Journal of Pharmaceutics and Biopharmaceutics, 2008, 70, 260–269.
52. Matthias O and Sigrid K, "Polyacrylic acid/polyvinylpyrrolidone bipolymeric systems.i. Rheological and mucoadhesive properties of formulations potentially useful for the treatment of dry-eye-syndrome", European Journal of Pharmaceutics and Biopharmaceutics, 1999, 47, 113–118.
53. Jansook P and Stefánsson E, "Cyclodextrin solubilization of carbonic anhydrase inhibitor drugs: formulation of dorzolamide eye drop microparticle suspension", European Journal of Pharmaceutics and Biopharmaceutics, 2010, 76, 208–214.
54. Sunisha Kulkarni et al, ''Solubility enhancement of water insoluble drug for ophthalmic formulation", Int. J. of Drug Delivery,3[2011],141-118.
55. Bourlais CL and Acar L, " Ophthalmic drug delivery systems recent advances". Progress In Retinal And Eye Research. 1998, 17, 33-58.
56. Zignani M and Tabatabay C. "Topical semi-solid drug delivery: kinetics and tolerance of ophthalmic hydrogels". Adv Drug Deliv Rev .1995, 16, 51-60.
57. Colo GD and Zambito Y. "Selected polysaccharide at comparison for their mucoadhesiveness and effect on precorneal resident of different drugs in rabbit model." Drug. Dev. and Ind. Pharmacy. 2009, 35, 941-949.
58. Mayol L and Quaglia F, "A novel poloxamers/hyaluronic acid in situ forming hydrogel for drug delivery: rheological, mucoadhesive and in vitro release properties". European Journal of Pharm and Biopharms. 2008, 70, 199–206.
59. Masteikova R and Chalupova Z. "Stimuli-sensitive hydrogels in controlled and sustained drug delivery". Medicina. 2003, 39, 19-24.
60. Shetty GN and Charyulu RN, "A study on stability and in-vivo drug release of naphazoline and antazoline in situ gelling systems for ocular delivery", Int J of Pharm Bio Sci 2013, 4(1), 161 – 171.

61. Sankara V et al, "In-vivo evaluation of dexamethasone sodium phosphate nanoparticles for post cataract treatment", Pharmacologyonline 2009, 8, 822-828.

Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology and Medicine
Volume 15 Issue 2 Version 1.0 Year 2015
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Problems of using Hydrochlorothiazide Diuretic in Adult Diabetic Patient in Diabetic Clinic of Adama Hospital Medical College, East Shoa Zone, Oromia Regional State, Ethiopia

By Omer Aliyi, Mohammed Hussien & Belayneh Kefale
Ambo University, Ethiopia

Abstract- *Back ground:* Diabetes mellitus (DM) is a group of common metabolic disorders that share the phenotype of hyperglycemia. Half century ago hydrochlorothiazide has been associated with a diagnosis of diabetes in hypertension treatment containing hydrochlorothiazide during long term therapy. This explained by association between glucose, potassium, and hydrochlorothiazide induced hyperglycemias and plasma insulin level. The objective of this study was to assess the problem associated with use of hydrochlorothiazide among adult diabetic patient in diabetic clinic of AHMC.

Methodology: A cross sectional study was carried out by reviewing patient information sheet and physician diagnosis card with a period from March, 25-May, 28, 2014. Data was collected from patient information sheet and physician diagnosis card by using check list and collected data was analyzing by using SPSS-20.

Keywords: *hyperglycemia, high and low insulin response, hypokalemia.*

GJMR-B Classification : *NLMC Code: WD 200*

Strictly as per the compliance and regulations of:

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Abstract- ***Back ground:*** Diabetes mellitus (DM) is a group of common metabolic disorders that share the phenotype of hyperglycemia. Half century ago hydrochlorothiazide has been associated with a diagnosis of diabetes in hypertension treatment containing hydrochlorothiazide during long term therapy. This explained by association between glucose, potassium, and hydrochlorothiazide induced hyperglycemias and plasma insulin level. The objective of this study was to assess the problem associated with use of hydrochlorothiazide among adult diabetic patient in diabetic clinic of AHMC.

Methodology: A cross sectional study was carried out by reviewing patient information sheet and physician diagnosis card with a period from March, 25-May, 28, 2014. Data was collected from patient information sheet and physician diagnosis card by using check list and collected data was analyzing by using SPSS-20.

Result: In this study population the total of 1,200 patient cards with hypertension and type-2 diabetes were observed, from which only 60 patient have a problem associated with hydrochlorothiazide diuretic. Among these patient 55 % were female and 38.3 % were in the age group of 40-50 years and mean age was 51 years. Most of patient, 82% patient had increased FBS after HCT administration and around 90% of patient had decreased FBS after HCT discontinuation. Among the total number of the cases only in 5% showed high response to insulin and 37% low response to insulin. Most of the patient around 70% develop problem associated with HCT within start to six month.

Conclusion: In general in this study indicated that elevated fasting serum glucose level was the main problem associated with the use of HCT in adult diabetic patient.

Keywords: hyperglycemia, high and low insulin response, hypokalemia.

I. Introduction

a) Background Information

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.

DM is classified on the basis of the pathogenic process that leads to hyperglycemias, as opposed to earlier criteria such as age of onset or type of therapy. The two broad categories of DM are designated type 1 and type 2. Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes progress. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) represent pre diabetic stage. In Ethiopia type 2 DM was more predominating than type 1 DM (1).

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 285 million in 2010. Based on current trend the International Diabetes Federation projects that 438 million individuals will have diabetes by the year 2030. Accordingly there are about 12 million DM patient found in Africa and around 1.5 million found in Ethiopia in particular. Although the prevalence of both type 1 and type 2 DM increasing worldwide, the prevalence of type 2 DM is rising much more rapidly, presumably is because of increasing obesity, reduced activity levels as countries become more industrialized, and the aging of the population (1).

Thiazide diuretics have been available for the treatment of hypertension since the late 1950s, and reports of thiazide-associated hyperglycemia began appearing shortly thereafter. However, benzothiadiazine derivatives (hydrochlorothiazide most commonly) continue to be recommended as first-line therapy for hypertension without regard to metabolic status that resulted in diabetic's exacerbation. (2). Although there is not uniform agreement on the long-term significance of diuretic-induced diabetic, the controversy seems more about the relative benefits from improved BP control offset by the consequences of worsening metabolic status related to the thiazide diuretic. These patients are those likely to receive hydrochlorothiazide diuretics for decades, and the implications of diuretic-induced diabetes may not be fully understood in those

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patient taking hydrochlorothiazide for relatively short-term period of time.(3)

Metabolic effects of hydrochlorothiazide that can have a negative impact on diabetic risk profile include alterations in lipids, hypokalemia, impairment of glucose metabolism, and, therefore, the occurrence of type 2 diabetes by increasing hepatic insulin resistance. Early evidence emerged in the 1960s demonstrating aggravation of pre-existent type 2 diabetes mellitus in patients treated with hydrochlorothiazide diuretics. Since then, the adverse metabolic effects of hydrochlorothiazide diuretics have been demonstrated in a number of researches. There is also positive relation between thiazide-induced hypokalemia and the incidence of type 2 diabetes, most probably via the inhibitory effect of low potassium on insulin secretion. (4, 5)

Although hydrochlorothiazide and thiazide-like diuretics are indispensable drugs in the treatment of hypertension, their role as first-line or even second-line drugs is a provoking debate that Doctors are faced with a difficult dilemma whenever they prescribe a HCT in diabetics, because of emergence of elevated FBS (4). This also compromises the efforts of the health care system, policy makers and health care professionals in improving the health of the populations. In Ethiopia, particularly in the study area, little is known about the problem of HCT therapy in DM patients and associated factors. Therefore, the aim of this study will be to assess the problem and associated factors to hydrochlorothiazide therapy in adult diabetic patient visiting Adama Hospital Medical College.

b) Statement of the problem

After introduction of hydrochlorothiazide in all over Ethiopia this diuretics associated with several potentially deleterious metabolic adverse effect and other complication attributed to problem of HCT therapy in diabetes. Among the major problem of HCT use in diabetics the frequently encountered one are diuretic induced hyperglycemia, hypokalemia and increased insulin resistance were the dominant ones. (6) Diuretics induced hyperglycemia can increase the risk of diabetic exacerbation which associated with a higher risk of all-cause mortality rate, for example, the incidence of coronary artery disease was 64% higher in the subjects who developed elevated FBS was the problem of HCT use in DM patient (3). The risk of thiazide-induced diabetes is also dose dependent such that at 25-mg hydrochlorothiazide (HCT) there is substantial risk of impairing the glucose response. Since a high-dose HCT diuretic has a negative effect on glucose metabolism, it may be related to hypokalemia that can be corrected by potassium supplementation or combination of thiazide with ACE inhibitor or potassium-sparing agents might prevent thiazide-induced diabetes (7).

The other common problem of HCT Diuretics in diabetic adult patient may be hypokalemia that cause several other adverse reactions, potentially leading to discontinuation. Potassium is thought to play a key role in glucose homeostasis. Potassium is involved in the release of insulin as well as insulin-mediated glucose uptake into skeletal muscle. Both serum potassium depletion and glucose level elevation are common in patients treated with thiazide-type diuretics. Each 0.5 meq/L decrease in serum potassium during the 1st year of treatment was associated with a 45% higher adjusted diabetes risks that from decreased insulin secretion. Widespread use of low-dose thiazide can prevent this hypokalemia effect, but no information is available regarding the effects of low dose HCT diuretics on insulin action. Furthermore, hypokalemia can impair glucose metabolism by reducing insulin secretion and insulin sensitivity (6).

The other problem associated with HCT use in adult DM patient is increased resistance to insulin. The mechanism traditionally associated with this increased risk of diuretic-associated diabetes mellitus was a reduction in serum potassium. Any medication that worsens insulin sensitivity, i.e., HCT diuretics will hasten the development of diabetes mellitus in those with impaired fasting glucose. However exact relationship between hypokalemia and worsening of insulin resistance is unclear but appears most pronounced in those with preexisting impaired glucose tolerance. There is evidence that prevention of hypokalemia with K^+ supplementation or potassium-sparing agents lessens the degree to which plasma glucose increased (8).

c) Significance of the study

The results of this study contribute to increase the awareness of health care providers particularly physicians on the issue of prescribing HCT diuretic in adult diabetes patient and may aid them to develop strategies for improvement HCT diuretic induced hyperglycemia.

With increasing access to problem of HCT diuretic in adult diabetic patient in our country, there is an opportunity to better understand the benefit and limitation of HCT in DM clinic of AHMC. Data on the problem of HCT diuretic in adult diabetic patient in our country are scarce, so data can potentially provide good strategic approach in deciding problem of using HCT diuretic in adult diabetic patient in our country. It also provides important assistance to concerned organization especially for health institution.

This study also helps the different organization like government organization and non government organization [NGO] to use the result of the study in decision making related HCT in diabetic. The main aim of this study is to add to the existing body of knowledge about the problem associated with use of HCT in adult DM patient and lifestyle modifications necessary to

maintain diabetes control, and to propose strategies that will assist policy makers and clinicians with diabetes management decisions

d) Objective of the Study

i. *General objective*

The general objective of this study was to assess the problem associated with use of hydrochlorothiazide among adult diabetic patient in diabetic clinic of AHMC

ii. *Specific Objective*

- To determine the number of patient who have developed a problem with using HCT in diabetes clinic of AHMC
- To describe the main problem associated with HCT in DM patient
- To identify type of the problem that resulted in dilemma of using HCT in DM patient

II. Methodology and Materials

a) Study area

Adama town is the capital city of Oromia regional state, Ethiopia and located 99Km from Addis Ababa. There are different governmental and non-governmental institution in town such as 8 health Center, one referral hospital, one general hospital, 86 private clinics, and 75 pharmacies.

The study was conducted in Adama hospital medical college on adult patients who have diabetics' and hypertension cases whose patient's card contain hydrochlorothiazide. AHMC has 200 beds for inpatient with five disciplines (Surgery, Internal medicine, pediatrics, Gynecology/Obstetrics and ophthalmology) with four pharmacies (OPD, ward, emergency and ART pharmacy). The hospital has about 465 workers of which 257 were health professionals. Adama hospital ranks second by patient intake next to Black lion hospital in Ethiopia.

b) Study Design and Period

A cross sectional study on retrospective data was conducted by reviewing patient information sheet and physician diagnosis card from March,25-May, 28, 2014.

i. *Population*

✓ Source population

The source populations for the study were all diabetic patients with hypertension that taking HCT during the follow up in DM clinic in of AHMC during previous one year from Sep. 2012 to May,9,2014.

c) Sample size and sample technique

The study includes all DM patients with hypertension and type 2 DM who develop a problem with HCT use from 1200 patient with hypertension and type 2 DM, so that no sampling technique was used.

d) Inclusion and Exclusion Criteria

The study includes all DM patients with hypertension who develop a problem with HCT use. The study exclude DM pediatric patient age group less than fifteen (15) years and DM patient who did not develop a problem with use of HCT.

Study Variable

✓ Dependent variable

- Fasting blood glucose level
- Hypokalemia
- Hyperglycemia
- Insulin response

✓ Independent variable

- Age
- Sex
- Educational status
- Marital status
- Income
- Residence
- Religion

e) Data collection

Data was collected from patient information sheet and physician diagnosis card by using check list.

f) Data processing and Analysis

After data have been collected it was categorized and analyzed by using SPSS-20.

g) Ethical consideration

Before data collection to conduct this study ethical approval was obtained from Ambo University College of medicine and health science research team leader and the letter was submitted to Adama referral hospital medical director office prior to the beginning of undertaking the study in the area

h) Quality assurance

Before starting of the actual data collection pre test was done on 5% of patient information sheets to ensure their completeness, validity, reliability and consistency.

i) Ope rational Définition

Hyperglycemia : Refers to blood glucose level > 126mg/dl

Hypokalemia: refers to serum potassium concenteration < 3.5 meq/L

Diuretic : are substance that remove fluides from the body by increasing urine out put

High response, Occur when FBS returned to normal with respect to insulin injection in diabetic patient using HCT.

Low response, Reduction of FBS by 10sin unit after insulin injection in diabetics' patient using HCT.

III. Results

In this study a total of 1200 patient card with hypertension and type 2 diabetes were observed, from which only 60 patient a problem associated with hydrochlorothiazide diuretic had. Among these patient 55 % were female and 38.3 % were in the age group of 40-50 years and mean age was 51 years (Table 1).

Table 1 : Age and sex distribution of study population in AHMC diabetes clinic, 2014

Age(years)			sex	
	frequency	percent	male	female
18-30	--	--	--	--
30-40	8	13.3%	--	8
40-50	23	38.3%	8	15
50-60	16	26.7%	9	7
>60	13	21.75%	10	3
Total	60	100	27	33

In this study the dose of hydrochlorothiazide diuretic that were prescribed in all 60 patient with hypertension and type 2 diabetics was 25mg daily, this dose was considered as high dose. During this study despite the necessity of lower dose, 12.5mg per day of hydrochlorothiazide in diabetic patient none of the patient (100%) were found to take this advisable lower dose (12.5mg).

Based on the data from the study the fasting plasma blood glucose level distribution of the patients since they start taking HCT was found with 5patients (8.33% of the patient) reported of having fasting plasma blood sugar greater than 250 mg/dl followed by 16.6%, 40%, and 35% of the patient reported to have fasting plasma blood sugar in the range of 90-100mg/dl, 100-150mg/dl and 150-250mg/dl respectively according to the following figure.

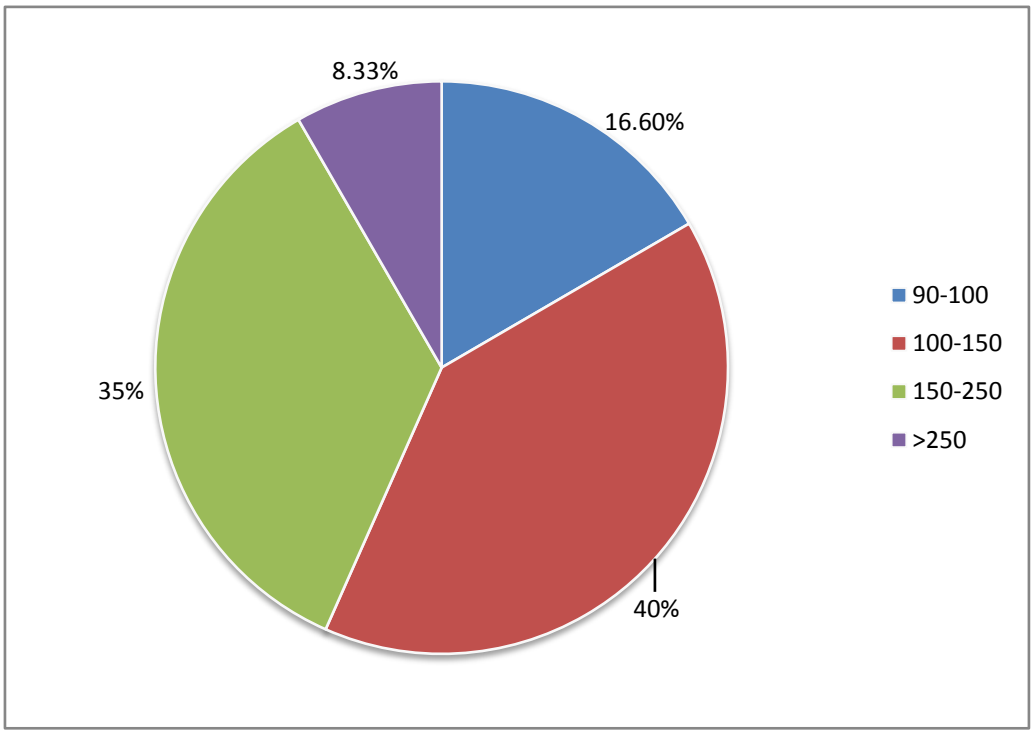

Figure 1: Fasting plasma blood glucose level at the start of HCT in AHMC diabetic clinic

Among 60 patient cards observed in DM clinic, around 49 (82%) patient cards were showed to have more increased fasting plasma glucose level after long term use of HCT than at the start of HCT. Only 2% of the patients were reported to have unchanged fasting blood sugar after long term use of HCT (Table 2).

Table 2 : Fasting plasma blood glucose level after long term use HCT in diabetic clinic of AHMC

FBS AFTER LONG USE of HCT	frequency	PERCENT
Increased	49	82 %
decreased	10	16.6 %
unchanged	1	2 %

However, after discontinuation of HCT, from 60 patient cards nearly 54(90%) of the patient resulted in more decreased FBS than when on HCT. (Table 3)

Table 3 : Fasting plasma blood glucose level after discontinuation of HCT in diabetic clinic of AHMC

FBS after HCT discontinuation	frequency	Percent
increased	3	5 %
decreased	54	90 %
unchanged	3	5 %

Response to insulin in the patient using HCT the response were reported as only 5(8.3%) patient were resulted in high response and 20 (33%) were resulted in low response while the rest 35(58%) of the patient were not taking insulin. Based on sex from 5 high responding patients 3 of them were female and from 20 low responding patients 11 of them were female.

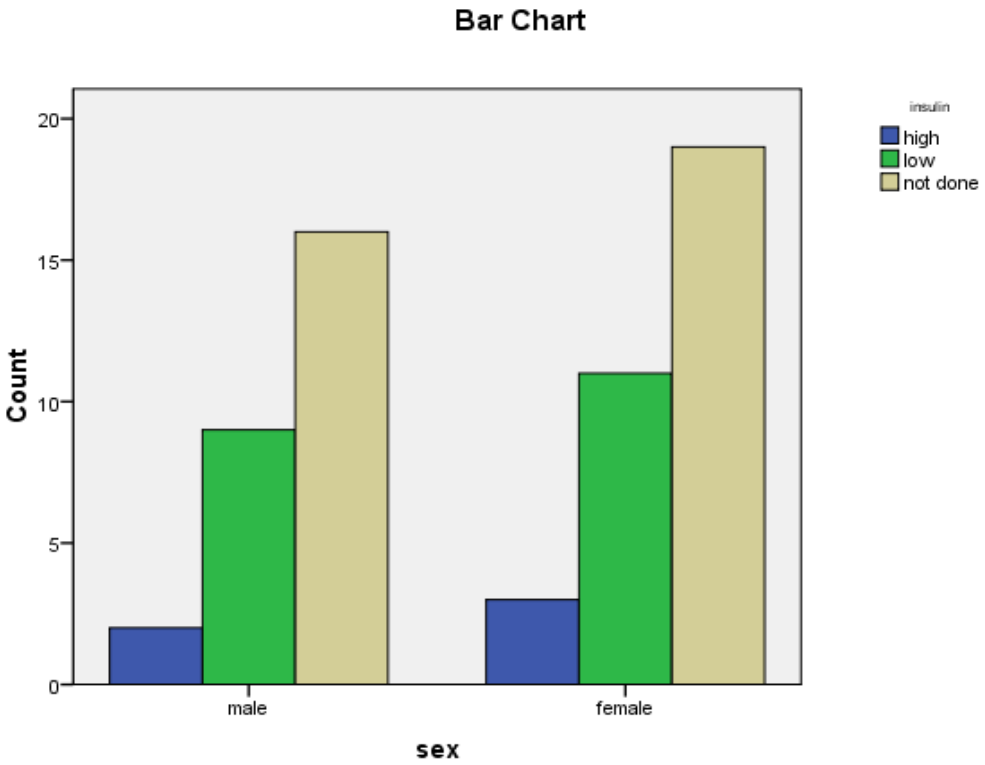

Figure 2 : responses to insulin in both male and female using HCT in diabetic clinic of AHMC

Time taken for HCT before it was resulted in increased FBS were reported as 70% of the patient were develop hyperglycemias within start to six month and 27% and 3% of the patient were develop hyperglycemias within 6 month -1 year and 1 year -2 year respectively. Regarding serum potassium electrolyte, in 100% of the study population no serum potassium electrolyte test was conducted in AHMC diabetic clinic.

IV. Discussion

The primary goal of studying the use of HCT in adult diabetic patient was to reduce the adverse metabolic effect associated it, improving patient quality of life and reducing diabetic related mortality and morbidity through proper monitoring of laboratory value related to HCT such as serum electrolyte, glucose level and insulin sensitivity. If we are to continue to use HCT in adult diabetic patient we must minimize adverse metabolic effect and one way to do that is to use lower doses. This study was in line with study done in Belfast university of United Kingdom.

The most common problem that associated with the use of HCT in adult diabetic patient was an increase in FBS (82%), followed by low response to insulin injection (37%) which indicates insulin resistance that occurred as a result of hypokalimia caused by hydrochlorothiazide. This is consistent with study done in university of Atlanta on male and female of age group of 17-65 year (9).

After discontinuation of HCT use in adult diabetic patient in AHMC from targeted study population around 90% of patient found to have decreased fasting serum blood glucose and only 5% of the patient found to have elevated serum blood glucose level after HCT discontinuation compared to 82% of the same study population with elevated serum blood glucose level before HCT discontinuation. Minor glucose elevation after HCT discontinuation may be due to non adherence to medication and error in laboratory result while decreased serum blood glucose level after HCT discontinuation was indicating that HCT was highly associated with hyperglycemias. This study is similar with recommendation of current national clinical guide line.

From study population 55% were female and 38.3% were in the age group of 40-50 years which is the age group mostly associated with HCT induced serum blood glucose elevation because of this age group is among the older age group associated with elevated serum glucose. According to this study the patients in the older age are more associated with HCT induced hyperglycemias than patient in the younger age in AHMC (38% v 8.33%) and this is because of risk factor for hyperglycemias is higher at this age group. This study was in line with the study done in America were younger and older age prevalence of HCT induced hyperglycemias is 6.7% and 43% respectively.

Regarding response to insulin in the diabetic patient using HCT, only 5% of the patient reveals high response to insulin therapy while 37% of the study population shows low response to insulin during this study and this higher resistance to insulin therapy during HCT therapy is most probably due to hydrochlorothiazide induced hypokalimia as a result of decreased serum potassium level which cause decreased insulin secretion or decrease insulin sensitivity. This study was in line with study done in Texas, USA.

Regarding the dose of hydrochlorthiazide 25mg dose per day was higher dose in diabetic patient that can be resulted in thiazide induced hyperglycemia in 82% of diabetic patient according to this study. This may be due to the greater serum potassium reduction with 25mg of hydrochlorothiazide than 12.5mg hydrochlorthiazide and Fasting serum insulin concentration was significantly increased after 12 weeks' treatment with Hydrochlorothiazide 25.0 mg but not with 12.5 mg. Endogenous glucose production was significantly higher after 25 mg compared with 12.5 mg HCT. This report was in line with the study done in Queen University of United Kingdom.

V. Conclusion

In general, the result of this study indicated that elevated fasting serum glucose level was the main problem associated with the use of HCT in adult diabetic patient among the study population. Decreased response to insulin and hypokalimia are the rest problem associated with HCT in adult diabetic patient. The dose of HCT above 12.5mg per day was associated with HCT induced diabetic complications.

VI. Recommendation

- Most problems associated with the use of HCT in adult diabetic patient require laboratory result for monitoring and follow up. Therefore, there should be enough qualitative and effective laboratory equipment and highly trained professional in Adama Hospital Medical College diabetic clinic
- Before prescribing HCT in diabetic patient the value of serum electrolyte should be done.
- This health facility required to have electrolyte measuring device.
- There should be adequate potassium supplementation in patient with diabetics using HCT.
- There should be monthly glucose tolerance test in patient with diabetics using HCT.
- All physician should prescribe the lower dose 12.5mg of HCT in adult diabetic patient in AHMC

Abbreviation and Acronymes

- HCT : hydrochlorothiazide
- DM : diabètes mellitus
- WHO : world Heath organisation
- AHMC : adama hospital medical collage
- ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)
- SHEP : Systolic Hypertension in the Elderly Program
- IGT: impaired glucose tolerance
- IFG: impaired fasting glucose
- F BS. Fasting serum blood glucose level

VII. Acknowledgements

We are very grateful to our college staff members for unreserved guidance and constructive suggestions and comments from the stage of proposal development to this end. We would like to thank Ambo University for supporting the budget which required for this research. Finally our deepest gratitude goes to Adama referral hospital staff workers who helped and allowed us in collecting and gathering data from the hospital.

Funding: Ambo University

Conflict of interest: None declared

Ethical approval: Approval and permission was sought from Ethical Review Board of College of Medicine and Health Sciences of Ambo University

References Références Referencias

1. Shie m. et al .Abnormality of carbohydrate and lipid metabolisms in patient with hypertension and diabetes. Arch intern medicine 1987; 147:1035-8.
2. Cutler J. et al. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive diureic treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2006; 166:2191–201.
3. Cutler JA. Et al. Thiazide-associated glucose abnormalities: prognosis, etiology, and prevention: is potassium balance the key? Hypertension. 2006; 48:198–200.
4. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. Hypertension. 2006; 48:219–24.
5. Verdecchia P. et al. Adverse prognostic significance of new diabetes in treated hypertensive subjects. Hypertension. 2004; 43:963–9.
6. American Association of Clinical Endocrinologists, American College of Endocrinology. Medical guidelines for the management of diabetes mellitus. Endocr Pract. 2002; 8:40–82.
7. Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: The Systolic Hypertension in the Elderly Program. SHEP Cooperative Research Group. Arch Intern Med. 1998; 158:741–51
8. Samuelsson, O .et al. Diabetes mellitus in treated hypertension: Incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial Goteborg, Sweden. J Hum Hypertens. 1994; 8:257–63.
9. Lundgren, H.et al. Diabetes in patients with hypertension receiving hydrochlorothiazide pharmacological treatment. BMJ. 1988; 297:1512.

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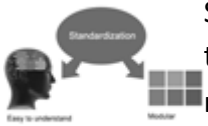

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2. Ethical Guidelines,

3. Submission of Manuscripts,

4. Manuscript's Category,

5. Structure and Format of Manuscript,

6. After Acceptance.

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Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript--must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Yet, use comprehensive sentences and do not let go readability for briefness. You can maintain it succinct by phrasing sentences so that they provide more than lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to maintain the initial two items to no more than one ruling each.

- Reason of the study - theory, overall issue, purpose
- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

Introduction:

The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.

- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
- Shape the theory/purpose specifically - do not take a broad view.
- As always, give awareness to spelling, simplicity and correctness of sentences and phrases.

Procedures (Methods and Materials):

This part is supposed to be the easiest to carve if you have good skills. A sound written Procedures segment allows a capable scientist to replacement your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt for the least amount of information that would permit another capable scientist to spare your outcome but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section. When a technique is used that has been well described in another object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text all particular resources and broad procedures, so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step by step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures
- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

What to keep away from

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.

Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
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- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to your results, and put the whole thing in a reasonable order.
- Put figures and tables, appropriately numbered, in order at the end of the report
- If you desire, you may place your figures and tables properly within the text of your results part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
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- In spite of position, each table must be titled, numbered one after the other and complete with heading
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- Make a decision if each premise is supported, discarded, or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
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- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
- Submit to work done by specific persons (including you) in past tense.
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Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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ISSN 9755896