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Hydroxypropyl methylcellulose in drug delivery

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ABSTRACT

Hydroxy propyl methyl cellulose can be used in the development of different drug delivery technology. Nowadays it is a widely used polymer and different viscosity grade of this polymer is available. The hydrophilic and hydrophobic form (both variants) of this polymer is also available. This study includes a review of this polymer on use in different drug delivery system mosty focusing on more recent developments.

Keywords: Hydroxy propyl methyl cellulose, Drug delivery, Variants, Recent developments.

INTRODUCTION

Hydroxypropyl methylcellulose is an odorless and tasteless, white to slightly off-white, fibrous or granular, free-flowing powder that is a synthetic modification of the natural polymer, cellulose. Specifically, it is a modification of alkali cellulose, which is produced when purified wood pulp is treated with 18% sodium hydroxide solution. Methyl and hydroxypropyl ether groups are introduced into the molecule by reacting the alkali cellulose with methyl chloride and propylene oxide, respectively. The degree of substitution (DS) of commercial HPMC with these methoxy and hydroxypropoxy groups will vary depending on the commercial use and properties desired. These added groups confer on the molecule its unique properties of being cold-water soluble, while at the same time exhibiting reversible gelation when heated and recooled.

The reason for its widespread acceptance include (1) solubility characteristics of the polymer in gastrointestinal fluid, and in organic and aqueous solvent systems, (2) noninterference with tablet disintegration and drug availability, (3) flexibility, chip resistance and absence of taste and odor, (4) stability in the presence of heat, light, air or reasonable levels of moisture, (5) ability to incorporate color and other additives into the film without difficulty. The interaction of this polymer with colorants is rare. HPMC closely approaches the desired attributes of an ideal

polymer for film coating. When used alone, the polymer has the tendency to bridge or fill the debossed tablet surfaces. A mixture of HPMC with other polymers or plasticizers is used to eliminate bridging or filling problems. This polymer is also used considerably in glossing solutions.

HPMC are cellulose ethers which may be used as the basis for hydrophilic matrices for controlled release oral delivery. In tablet matrix systems the tablet is in the form of a compressed compact containing an active ingredient, lubricant, excipient, filler or binder. Controlled release by hydrophilic matrix remains a very versatile tool in the hands of the formulator and we can only look forward to greater formulation predicability as more and more fundamental studies become available. The matrix may be tabletted from wet-massed granule or direct compression.

The resulting products are commercially available in different viscosity grades. This polymer is a material of choice for air suspension and pan-spray coating systems.

HPMC finds use in the food, drug, and the dietary supplement industries. These uses are described in further detail below. The physical/chemical properties of HPMC described above make these materials useful in the food industry as stabilizers of emulsions and foams, as a replacement for fat and as a non-caloric bulking agent in foods, as a barrier to oil and in moisture retention, and as a binder. HPMC imparts little or no flavor to food.

The historical record in the literature is not entirely clear on when HPMC was first introduced into food or any other commercial use. However, references point to a US patent on its preparation having been issued in 1960 to the Dow Chemical Company, and also to safety data supported by Dow that date from the 1950s. Thus, it may reasonably be inferred that large-scale commercial use of HPMC began in the 1960s and 1970s.

It is used in the food industry as a multipurpose food ingredient. HPMC is approved by FDA as both a direct and an indirect food additive, and is approved for use as a food additive by the EU. JECFA has evaluated the food uses of HPMC and established an ADI of ‘not specified’ for such uses. HPMC has been shown generally to exhibit a very low order of toxicity in mammalian systems. Data show orally administered HPMC, and modified celluloses as a whole, to pass through the mammalian gastrointestinal tract largely unabsorbed and unchanged, behaving effectively as non-nutritive fiber. Rats have been exposed to HPMC of variable viscosity in dietary concentrations ranging up to 20–30% for durations of 90–120 days with little evidence of adverse effects other than growth retardation at the highest doses. Dogs exposed for 90 days to HPMC at 5% of their diet exhibited no adverse effects. Chronic data on HPMC, specifically, as well as on other modified celluloses, indicate that these materials do not possess mutagenic or carcinogenic potential; neither do they behave as developmental and/or reproductive toxicants. HPMC and modified celluloses have not been reported as irritants or sensitizers.

Exploration of use of HPMC:

Use of HPMC in ophthalmic treatment:

Phacoemulsification is a procedure of cataract surgery where high intensity ultrasound energy is used for the fragmentation and emulsification of the cataractous lens. This will cause high vibration in the tissue surrounding the anterior chamber of eye. To prevent this, Ophthalmic

viscosurgical device (OVD) is injected in the anterior chamber and in the capsular bag during phacoemulsification procedure. An OVD 1(Maar N., et al), 2 (Kiss B., et al) acts as a cushion between the instruments and the tissues. An OVD must acquire two special properties such as pseudoplastic behavior (low resistance to flow when applied at high shear rates and at the same time the formulations would not flow at rest or at low shear rates) and possess appropriate viscoelastic properties i.e. high elastic and viscous moduli. HPMC is a major component in many commercially available OVD (such as Ocucoat®). Maltese et al. 3 (Maltese A., et al) have made a comparison between commercially available OVD, named Viscoats and binary systems of HPMC with natural polysaccharides, a polyanionic one, hyaluronate (SH), or a polycationic one, chitosan glutamate (CG). HPMC at 0.8% and SH at 2.3% form the formulation of best mechanical performance with highest zero shear viscosity and entangled solution behavior. This combination has all the required properties as OVD in cataract surgery.

Biomaterials 4 (Colthurst M. J., et al) are used extensively in the surgical treatment of posterior segment eye disease, especially in the repair of retinal detachment eye disease. Biomaterials will provide support 5 (Schepens - Acosta) that is required in retinal detachment surgery as a tamponade agent and will sustain drug release therapy 6 (Metrikin - Anand) in the management of infections of the posterior segment. Aqueous solutions of polymers will not act as tamponade agent. Solutions of viscoelastic polymers will not hold the retina in position so sealing of retinal break and retinal reattachment will not be obtained. But they are having greater biocompatibility than other available tamponade agents and proved themselves useful in front of the eye treatment 7 (Chan I. L., et al), 8 (Le Bourlais C. A., et al), 9 (Sintzel M. B., et al). For the reasons stated above, use of HPMC solution has been investigated and alone it is not suitable as a good tamponade agent. Its viscosity will fall very rapidly with dilution. Colthurst M. J., et al have investigated the intraocular behaviour of a 2.2% solution of HPMC. After 6 weeks, 70% of the polymer was in the vitreous cavity and after 10 weeks, the concentration was negligible. In spite of this, they have concluded that HPMC among the other biomaterials have an important role in an intraoperative tool and in combination with other biomaterial agent they must will act as an excellent tamponade agent.

Ocular drug delivery among the other drug delivery systems is still a most challenging task for most researchers. Drug can be administered in eye either by topical or systemic route. But topical formulations are easy to administer and also is of low cost. It is a common method of drug delivery to eye 10 (Lang J. C., et al). But it is mainly used to treat disorders affecting the anterior segment of the eye 11 (Leeand - Robinson). This is unsuitable for the disorder affecting posterior segment of eye. Only a subtherapeutic dose may penetrate to the cornea by passing through the anterior segment against the flow of aqueous humour, and diffusing throughout the vitreous. Systemic administration is often not feasible because only a small percentage of drugs can penetrate through the blood-retinal and blood-aqueous barriers which isolate the vitreous 12 (Cunha-Vaz J. G.,). Retinitis pigmentosa (RP) is an inherited retinal degeneration-associated blindness 13 (Shintani K., et al) which affects the pediatric and young adult population. Diabetic retinopathy, age-related macular degeneration (AMD) is the principle cause of blindness 14 (Klein B. E. K.,) 15 (Kaufman S. R.,) in middle-aged working adults. This will affect a large no of population. All these pathological condition is responsible for irreversible photoreceptor death or loss of function. These all will instigate for searching new useful therapy. Hydrogels based materials are investigated to develop new improved ocular delivery. Hydrogel systems are

formed by three-dimensional polymeric networks. In presence of water or biological fluid they will imbibe and will remain for a significant time in the vitreous cavity. Residence time can be enhanced. This residence time depends on pH, temperature and type of polymer. Poloxamers, HPMC are widely used polymer. But poloxamer is having lower mechanical strength, rapid erosion and non-biodegradability 16 (El-Kamel A. H.,). Oligomerization is a process for changing the critical gelling temperature of poloxamers. HPMC 17 (Ruel-Gariepy - Leroux) goes for gelation at higher temperature due to the interaction between hydrophobic components of the polymer. HPMC is also being diluted resulting lower mechanical strength. So research is going on to address this problem and changing in critical gelling temperature may be a solution to this problem.

Then targeted controlled delivery of drug with physical stable gel will be obtained. Gaudana et al. have shown use of HPMC in currently available different hydrogel based drug delivery system 18 (Gaudana R., et al) such as Hydrogel 1:Gatifloxacin is drug and Alginate, HPMC are used as polymer. Here Mechanism of gelation is ion depependent 19 (Liu Z., et al).

Hydrogel 2:Ofloxacin is drug and carbopol 940, HPMC are used as polymer. Here Mechanism of gelation is pH depependent 20 (Srividya B., et al).

Hydrogel 3: Puerarin is drug and carbopol, HPMC are used as polymer. Here Mechanism of gelation is pH depependent 21 (Wu C., et al).

Systemic Cyclosporine A (CsA) administration will avert graft rejection after organ transplantation. In the eye, CsA is also used for the treatment of autoimmune diseases, uveitis, Bechet's disease, keratoconjunctivis sicca, and corneal transplantation 22 (Mochizuki - DeSmet). Systemic effects of CsA can be avoided by using topical formulations and very less amount of this will penetrate to blood stream after topical administration. Different topical formulations an alpha-cyclodextrin vehicle 23 (Alba R. M., et al), vegetable oils 24 (BenEzra - Maftzir), liposomes 25 (Pleyer U., et al), collagen shields 26 (Kanpolat A., et al) micro- or nanospheres, and oil in-water emulsion are developed to improve ocular CsA penetration. Kuwano et al. 27 (Kuwano M., et al 2002) have formulated ophthalmic formulations containing hydroxypropyl Methylcellulose (HPMC, 65SH4000 grade) using polyoxyl 40 stearate as a solubilizer for CsA. They have concluded that topical instillation of the aqueous formulation was superior to that after instillation of an o/w emulsion and an oily formulation. An ocular pharmacokinetic study using 3H-CsA showed the distribution of CsA in ocular tissues, such as cornea, bulbar conjunctiva, and lacrimal gland, after. They have suggested that this aqueous CsA ophthalmic formulation will be clinically useful in the treatment of immune-mediated ophthalmic diseases. So HPMC is playing an effective role in aqueous solution formation for topical treatment of eye.

Eye is an easily accessible organ but delivery of drug to the eye site is a very challenging task. Eye posses some self-protective mechanisms. The protective mechanisms are lacrimal secretion/drainage and blinking reflex and this protective action will reduce the drug concentration into the eye within the first 4–20 min after administration. As a result sub-therapeutic dose will be achieved and it is not so effective to treat the eye disorders. To get the desired activity, frequent instillation is needed. Several attempts have been made to overcome this problem. One of them is the prolongation of the contact time of the dosage form on the

ocular surface and thus it will reduce the amount of elimination of drug 28 (Bourlias C. L., et al), 29 (Ding S.,). Many researchers have developed different dosage forms such as inserts, collagen shields, temperature sensitive in situ-forming gel 16 (El-kamel A. H.,), liposome 30 (Nagarsenker M., et al) and microsphere and nanosphere 31 (Zimmer A., et al). Liu and Wang 32 (Liu - Wang) have worked on ophthalmic drug delivery vehicle. They have worked on some mucoadhesive polymers such as such as hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose (CMC), Carbopol, and alginate. They have considered these polymers taking into consideration of patients' compliance, manufacturing cost, dosage adherence, and blurring effect of other dosage form. In result, they have shown that HPMC and Carbopol 974P containing formulation indicated a relatively strong gel structure as well strong interaction evidence between polymer and mucin. So HPMC in combination with other mucoadhesive polymer is an effective alternative for drug delivery into eye.

The successful use of norfloxacin, ofloxacin, ciprofloxacin, gatifloxacin and levofloxacin for topical treatment of ocular infection as an eye drop has led to Cappello et al. 33 (Cappello B., et al) to check activity of rufloxacin as an alternataive eye drop for the same reason. Rufloxacin (RUF), a broad spectrum oral fluoroquinolone, is active against both gram-negative and gram-positive aerobic bacteria and also is used once-daily for treatment of urinary and respiratory tract infections. In present work Cappello et al. have developed topical formulations of RUF using hydroxypropyl methylcellulose 4000 as a base and also checked the effect of cyclodextrins (CDs) on the solubility and ocular bioavailability of RUF. Finally they have concluded that significant enhancement of RUF solubility will be achieved by associating the drug with CDs. Here particularly HP- β-CD will form the most soluble complex. They may have a stability problem than the other complexes which are formed by combining with parent CDs but free from the solubility limitations of the parent CD. Surprisingly it was observed that the addition of 0.25% HPMC to solutions containing HP-β-CD increased the solubilizing effect of this CD and help to solubilize more RUF. This will help to formulate a more solubilized complex with a reduction of the amount of CDs necessary for solubilization of RUF. 0.3% (w/v) RUF formulation containing 6.4% (w/v) HP-β-CD and 0.25% (w/v) HPMC is the most promisimg formula as an eye drop. So HPMC is also having a significant role in the development of RUF eye drop.

In situ gel-forming systems are nowadays used widely for ocular therapeutics. Gupta et al. 34 (Gupta H., et al) have shown the successful use of chitosan- and pluronic-F-127-based, pH and temperature triggered in situ gel for sustained ocular drug delivery and Nanjawade et al. 35 (Nanjawade B. K., et al) also have explored different types of in situ gel-forming systems by different mechanisms (temperature, pH, or ion activated) using different polymers and their successful use in ocular therapy. Other ocular delivery systems such as ointments, inserts are also available in the market but they are having certain disadvantages. Ointment will cause a blurred vision and insert is having a lack of patient compliance. So they have not got wide acceptance and these disadvantages have prompted Gupta et al., to investigate the efficiency of combination of chitosan and hydroxyl propyl methyl cellulose (HPMC) for the development of sustained ocular drug delivery system containing the drug timolol maleate radiolabeled with radioactive technetium (sodium pertechnetate; $^{99m}TcO4-$). Both polymers will form hydrogel. Chitosan is a bioadhesive, viscous nature polymer and also will act as penetration enhancer that increases transcorneal permeation of the drug. But at higher concentration they will not produce clear

solution and upon instillation into the eye, due to white precipitation of the polymer at pH 7–7.0, it will cause blurred vision. Chitosan is cationic in nature, it can cause ocular irritation. To get clear solution and to overcome irritation of eye, the concentration of chitosan has been reduced by adding HPMC, a viscosifying polymer. A higher permeation across goat cornea was observed with chitosan/HPMC-based formulation. Chitosan/HPMC-based formulation was also nonirritant also and will spread over the entire precorneal area. This formulation was found suitable for sustained topical drug delivery to eyes.

Different physical or chemical agents, invasion of pathogens, ischemia, and excessive (hypersensitivity) or inappropriate (autoimmunity) operation of immune mechanisms will cause injury to the tissue. As soon as the as the injury is happened, manifestation of vascular and cellular response of the host tissue to injury occurs and this is known as inflammation. So inflammation can be regarded as self defense mechanism of body and it works by faciliating immune response and by subsequent removal of antigenic material and damaged tissue. Different chemical mediators like acidic lipids e.g. prostaglandins (PGs), thromboxanes, leukotrienes; vasoactive amines, cytokines etc. are produced from inflammatory cells during inflammation. Activation of cyclooxygenase pathway is responsible for the formation of PGs and thromboxanes and activation of the lipoxygenase pathway will produce eicosanoids. Non-steroidal anti-inflammatory drugs (NSAIDs) and Corticosteroids are considered as potential anti-inflammatory drugs and they act by by inhibiting the enzymes cyclooxygenase (COX 1 & COX 2) and by blocking the enzyme phospholipase A_2 respectively. Administration of these drugs to ocular inflammations is done by topical route as they provide higher localized drug concentration and avoids the systemic side effects which are associated with the oral administration. Indomethacin ophthalmic suspension buffered to pH 5.6 containing hydroxypropyl methylcellulose (HPMC) as viscolizer was observed to be physically and chemically stable 36 (Vulovic N., et al). HPMC based containing dicolfenac 37 (Sankar V., et al)provide better ocular tolerance and it can sustain in vitro drug release up to 9 h. The ocular inserts of ketorolac based on HPMC (4%) and ethyl cellulose (3%) were found to sustain ketorolac tromethamine release 38 (Jayaprakash P. S., et al)by zero order kinetics for 22 h.

Use of HPMC as a film, membrane and patch in transdermal and topical formations:

A number of effective antifungal drugs are available for topical and systemic therapy to eradicate Candida albicans. It is a normal commensal. It causes a common infection in people wearing dentures and can be severe for patients immunosuppressed or receiving anticancer radiotherapy 39 (Arendorf T. M., et al), 40 (Davies A. N., et al). Specially to treat oral candidosis, chlorhexidine is referred to be used as an adjunctive 41 (Ellepola - Samaranayake). Topical delivery of this drug in the oral cavity is generally accomplished by some traditional dosage forms, such as solutions and semisolid formulations. The short time of residence of the drugs due to their rapid dilution by saliva and the swallowing reflex will lead to a rapid decline in their concentration and as a result its use for the successful eradication of oral fungal infections has been limited 42 (Steinberg - Friedman). To encounter this problem, it is necessary to prolong the therapy and this can be only achieved by increasing the retention time of dosage form in oral cavity. Various bioadhesive dosage forms such as gels, tablets, and films forms have been recently formulated and have been reported to get the above stated advantages 43 (Mirth D. B., et al), Juliano et al., 44 (Juliano C., et al). in their research work have aimed to control the release of chlorhexidine diacetate drug from mono- and double-layered buccoadhesive films made of

alginate and/or hydroxypropylmethylcellulose and/or chitosan. From in vitro and in vivo evaluation they have concluded that polymeric films are the promising candidates for the sustained release of chlorhexidine diacetate in the oral cavity: When double layered films (prepared by sticking together a HPMC film and an alginate film) are applied to the oral mucosa with their mucoadhesive side, high chlorhexidine concentrations from HPMC layer and, subsequently, sustained release of drug from the alginate surface will be obtained. So HPMC is having an important role in forming buccoadhesive films.

To improve the activity, efficiency, convenience, and patient compliance, many drugs are nowadays delivered through transdermal route than the other conventional route. Transdermal system is aimed to deliver the drugs at a steady rate into bloodstream over an extended period of time. Avoidance of the 'first pass effect', termination of further administration if any side effects are observed, avoidance of degradation of drug moiety by gastric or intestinal fluids, can be obtained only via transdermal route. Patel et al 45 (Patel D. P., et al) have aimed to develop a transdermal film containing furosemide, a potent diuretic agent that induces a powerful diuresis, followed by the loss of sodium, potassium, and chloride into urine, by acting on thick ascending limb of the loop of henle 46 (Giebisch G.,). Lower molecular weight, good lipid solubility, lower elimination half-life, and lower melting make it an ideal candidate for transdermal formulation. In their work, they have developed a suitable matrix film for furosemide by employing ethyl cellulose (EC) and hydroxypropyl methylcellulose polymer and have studied the effect of EC and HPMC on the physicochemical properties of transdermal film. As the skin is a horny layer, penetration of drug through skin is very less. To improve the penetrability of drug, chemical enhancers are added. After completion of work it has been reported that incorporation of HPMC enhanced the flux of the drug and also was responsible for the swelling coupled diffusion controlled drug release. Propylene glycol will enhance the drug penetration through skin. Another work where the release from hydroxypropyl cellulose based gel containing furosemide was reported already 47 (Agyralides G. G., et al). So by using HPMC, films can be developed to deliver furosemide in blood.

Female sexual dysfunction (FSD) is an age-related complex medical problem. It was reported to affect nearly 30–50% of women globally 48 (Laumann E. O., et al), 49 (Spector - Carey) and is severe for atherosclerosis or diabetes mellitus suffered women 50 (Doruk H., et al), 51 (Enzlin P., et al). In this case, diminished vaginal blood flow with reduced vaginal lubrication is responsible for female sexual arousal disorder. Any strategy with enhancement of the vaginal blood perfusion is a way to treat FSD. Many researchers have attempted to develop vaginal mucoadhesive film that is preferred over other vaginal delivery systems such as such as gels and creams. These delivery systems suffer from leakage, messiness and low residence time. But bioadhesive films are over this disadvantages improving patient compliance. Yoo et al., 52 (Yoo J., et al) have developed and evaluated Nitric oxide (NO)-releasing vaginal films and have shown it to be a potential advanced treatment option for female sexual arousal disorder (FSAD). Here also, use of HPMC has been proved to be essential to formulate vaginal mucoadhesive film with controlled release of S-nitrosoglutathione.

Mouth was is generally available in liquid form to get instant local action. But use of liquid form is limited by several disadvantages like problems of handling, inconvenience of use during traveling, stability aspects and inconspicuous nature 53 (Dinge - Nagarsenker). Solid dosage

form is over these advantages. But it will release drug in a very slow way and instant action of drug will not be achieved. To encounter this sole problem, many research works are aimed to develop fast dissolving tablets that it will allow rapid release of drug and also will be inconspicuous in nature with easy handling. Fast dissolving film is an excellent alternative of fast dissolving tablet 54 (Liang - Chen). When it is placed in the oral cavity, it quickly gets hydrated and adheres onto the site of application with quick release of drug due to rapid disintegration of film. Dinge et al in their research work have tried to develop a fast dissolving film for the delivery of Triclosan (TC). Triclosan (TC), a broad spectrum antimicrobial agent, is active against a wide range of gram-negative and gram positive bacteria, molds, yeast and even against parasites that are responsible for malaria and toxoplasmosis. Its broad spectrum activity make it useful for several personal care products such as toothpaste, mouthwashes, body washes, antimicrobial creams, lotions and hand soaps 55 (Nissen - Ochs), 56 (Regos - Hitz), 57 (Surolia - Surolia). HPMC is a good film former 58 (Peh - Wong). Here, the fast dissolving films have been formulated with polymer HPMC. In vitro and in vivo evaluation of the HPMC and xanthum gum based films with the help of solubilizers such as HPBCD and poloxamer 407 was investigated and it confirmed their potential as an innovative dosage form to improve delivery of TC.

Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged ill health and early death 59 (Arunachalam - Gunasekaran). It is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency and it is often combined with insulin resistance. Glibenclamide and glipizide are an oral blood-glucose-lowering drug of the sulfonylurea class. They have been used extensively to treat NIDDM and acts by increasing the release of endogenous insulin as well as its peripheral effectiveness. It has been associated with severe and sometimes fatal hypoglycemia and gastric disturbances like nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy. Since these drugs are usually intended to be taken for a long period, patient compliance is also very important. Transdermal delivery has many advantages over oral route of drug administration; it avoids hepatic first pass metabolism, termination of further administration, long term duration, potentially decreases side effects and improves patient compliance. So an attempt was made to formulate transdermal patches 60 (Bennette N., et al), 61, 62, 63, 64, 65 (Mutalik - Udupa) which will reduce frequency of dosing and some of the complications of higher dose oral therapy. Mishra et al. 66 (Mishra M. K., et al) have developed transdermal patches (TDP), microcapsules (MC) loaded with an identical dose of glibenclamide (GL) and compared the hypoglycemic activity of GL from the two formulations. GL-loaded transdermal patches formulations were prepared by solvent casting method using HPMC as polymer. It has been observed that patches contain comparatively higher GL content than MC and transdermal system of GL produced significantly higher hypoglycemic response compared to oral microcapsule after 12 h. So HPMC based patches have been proved to be excellent.

Pranoprofen, a potent non steroidal anti-inflammatory drug (NSAID) is widely used for the treatment of the acute and long-term management of rheumatoid arthritis and osteoarthritis. Although it is a best tolerated NSAID, gastropathy occurs following oral administration. So it is suggested that topically applied NSAIDs are safer. The topical application will provide a higher local concentration of the drug at the site of initiation of the pain. Due to lower or negligible systemic drug levels, there are fewer or no adverse drug effects. Topical drug delivery offers 67

(Ganesh S., et al) many important advantages. It is easy to apply and painless. It protects the active compound from gastric enzymes and it minimizes the problems associated with liver metabolism. Sustained and controlled delivery of drug also can be targeted. Shin et al. 68 (Shin - Cho) have tried to develop the new topical formulations of pranoprofen that have suitable bioadhesion. The formulation with suitable bioadhesion confirms good applicability, localization of formulation and it can be removed very easily. For bioadhesion, they have chosen hydroxypropyl methylcellulose (HPMC), a non toxic polymer with Poloxamer 407 as copolymer. HPMC has been considered here because of its good swelling property, its control over the drug release. After their study, they have selected 2% HPMC based bioadhesive polymer gels containing the 20% poloxamer 407 as suitable base with proper bioadhesion property and finally they have concluded the enhanced transdermal delivery of pranoprofen from the HPMC-poloxamer gels containing penetration enhancer can be developed. So HPMC in combination with poloxamer can be used for transdermal delivery development to deliver pranoprofen.

Lidocaine, procaine, and tetracaine all are the local anesthetics and they have been extensively used by parenteral route. They have short life after parenteral injection and sustained analgesic effects of drugs can not be achieved 69 (Ben-David B., et al). To encounter these problems, other route should be considered. Transdermal and topical drug delivery of drugs may be the alternative for parenteral route. For the purpose, a thorough research has been carried out on this. For local action, this route will allow higher localized concentration of the drug at the site of application but lower or negligible systemic drug levels may reach resulting fewer or not adverse drug effects 70 (Boinpally R. R., et al). If local anesthetics are applied through this route, it can penetrate the stratum corneum and will desensitize the underlying pain receptors within skin 71 (Hou - Yu). Jin et al. 72 (Jin - Shin) have tried to develop a locally active anesthetic formulation with the enhanced efficacy and suitable bioadhesive property. For suitable bioadhesiveness, hydroxypropyl methylcellulose K 100 and poloxomar are used in this formulation. Suitable bioadhesion will allow keeping the formulation in the application site for a longer time and sustained effect of drug can be obtained. A vasoconstrictor was used in formulation. Vasoconstrictor will impair the flow and as a result drug entry from epidermal layer to dermis to systemic circulation will be hampered and drug will be on the skin layer for long time. They have pointed out that as the concentration of HPMC-K100M is increased, the bioadhesiveness will also increase and also concluded that local anesthetic gels with enhanced activity containing an enhancer could be obtained using the bioadhesive polymer gels based on HPMC and poloxamer. So HPMC with the combination of poloxamer will act as good bioadhesive agent and sustain the activity.

Ampicillin is a potent antibiotic and is used against a broad range of bacterial infections 73 (Ahren I. L., et al). When it is administered through parenteral route, it will be quickly available to the systemic circulation and bioavailability will reach to maximum. It can distribute rapidly to a wide area of the body including bile. After reaching to the bile 74 (Acred P., et al), it will be excreted to the gut very quickly and as result normal intestinal microflora will be destructed. This is the main disadvantage and other disadvantage is that it will increase the probability of the presence of yeast as well as inducing a high risk of Clostridium difficile colitis 75 (Harmoinen J., et al). To get improved antibiotic activity and to reduce the allergic and toxic reactions to ampicillin, topical formulations are mainly used to deliver the drug 76 (Fontana G., et al),

Bagyalakshmi 77 (Bagyalakshmi J., et al) have aimed to check the performance of a membrane-moderated transdermal patch with a hydrophilic membrane.

Membranes were prepared by using hydroxypropylmethylcellulose (HPMC) 4000 cps polymer and other hydrophilic polymer. They have performed different in vitro and in vivo tests and finally concluded that in this developed transdermal patch, hydrophilic sodium alginate (SA) polymer will act as the reservoir and HPMC will be the rate-controlling membrane. So they proved membrane prepared with HPMC to be an alternative to an IV dosage form without causing skin irritation and improving patience compliance.

Both oil-in-water and water-in-oil emulsions are topical formulations and they can be used for therapeutic purpose. Different drugs have been delivered to the skin by using this emulsion as a vehicle. Emulgel is also an alternative excellent topical formulation. To prpepare emulgel, one gelling agent has to be added in emulsion. This will have both emulsion and gel properties. Emulsions may be oil-in-water or water in-oil type. Some reaserchers have shown their successful use 78 (Abd El-Bary A., et. al), 79 (Zhang X. L., et al), 80 (Hamza Y. E., et al) as a topical formulation. In the present work, Mohamed 81 (Mohamed M. I.,) have tried to develop an emulgel containing chlorphensin. chlorphenesin (CHL) is an antifungal agent. It is having antibacterial property also. It can be applied on the skin in mild uncomplicated dermatophyte and other cutaneous infections. Carbopol and HPMC were used as gelling agents. It has been shown that Carbopol 934 or HPMC will provide acceptable physical properties, drug release, and antifungal activity and will remain stable for 3 months without any change upon storage. He has come to a conclusion that the HPMC-based emulgel with the liquid paraffin in its low level and the emulsifying agent in its high level has been proved to be the formula of choice, since it showed the highest drug release and antifungal activity. So HPMC is again proved to be useful in therapy.

3-O-Methylquercetin (5,7,3′,4′-tetrahydroxyflavone) is a natural 3-methoxyflavone. It is used as antiviral drug with moderate anti-inflammatory and antioxidant properties 82 (Middleton E., et al). Topical application of 3-MQ is having more enhanced therapeutic activity, especially for the treatment of Herpes Simplex Virus infections. It has low water solubility and to overcome this solubility, solubility enhancers such as cyclodextrins is considered by Schwinge et al. 83 (Schwinge L., et al). Incorporation of the drug:cyclodextrin complex is done in topical dosage form and this dosage form is made by hydrophilic polymer HPMC. Surprisingly it has been observed that when inserted in the hydrophilic matrix, flux and total permeation of 3-MQ is higher. So it has been confirmed that HPMC is having permeation effect probably due to the favorable partition between hydrogel and stratum corneum, and this effect will allow the passage of 3-MQ to the skin.

Growth factors, such as basic and acidic fibroblast growth factors (FGF), epidermal growth factor 84 (Cho Lee A. R., et al), rhVEGF 85 (Gu et al. 2004;), insulin-like growth factor 86 (Nauman J. V., et al), and transforming growth factor-β 87 (Puolakkainen P., et al) are applied on wound by topical formulations and they perform very well for wound healing.

Topical formulations of these growth factors are prepared from various materials such as alginate, gelatin, fibrin, polyethylene glycol diacrylate etc. Hydrogel formulations, prepared from

different water cellulose ethers are also very effective excipients in wound healing preparations. Ji et al. 88 (Ji J. A., et al) have tried to develop topical formulations of rhVEGF gel and for preparation, different cellulose derivatives such as HPMC, MC, HEC and CMC were considered. Pseudo plasticity is a characteristic feature of topical formulation and the rheological behavior of HPMC gel containing rhVEGF is pseudoplastic and due to the interaction of positively charged protein patches with the negatively charged carboxyl groups of CMC, the release from CMC gel was much slower than that from the HPMC. In this report they have shown that as for rhVEGF, or other proteins of similar properties, when formulated with HPMC gels, may not require a tight viscosity specification to ensure a particular release rate of drug. So HPMC in topical formulations of growth factor also can be considered for enhanced therapeutic activity.

Buspirone hydrochloride (BH) is an orally administered anxiolytic drug that is used for children in attention deficit hyperactivity disorder and for adolescents with anxiety disorders 89 (Balon R.,). It undergoes extensive first-pass metabolism and the average elimination half-life of single doses is about 2 to 3 hours. So frequent dosing is needed and higher amount of dose is needed. To improve patient compliance, delivery of this drug through skin would be effective. Al-Khalili M et al., 90 (Al-Khalili M., et al) in their research work, they have prepared gels using hydroxypropyl methylcellulose (HPMC: viscosity of 2% aqueous solution at 20°C: 80-120 cps) and carboxymethylcellulose (CMC) (medium viscosity, viscosity of 2% aqueous solution at 20°C: 400-800 cps) to investigates whether there is any improvement of penetration of ionic drug through skin using terpene chemical enhancers (menthol, cineole and terpineol) with the combination of iontophoresis. Menthol with the combination of iontophoresis delivered more BH from HPMC gel than carboxy methyl cellulose at proximate viscosity. It may be possible that counter ion (Na^+) of CMC will interfere with iontophoresis because of the competition of ion with buspirone and also its anionic nature will hamper mobility of cationic drug through gel system. So HPMC would be an effective base for topical or transdermal delivery of drugs through skin.

Use of HPMC in other dosage form:

Itraconazole is an excellent antifungal drug. Some researchers 91 (De Beule – Van Geste) 92 (Willems L., et al) have shown that itraconazole is effective in oral route in terms of its safety aspects and wide distribution in the body. It is known that it is poorly water soluble drug and for poorly water soluble drug, dissolution will be the rate limiting step. As a consequence effect, less amount of drug will be absorbed through gastrointestinal tract and bioavailability of the drug will be lower. So for itraconazole, enhancement of its solubility and bioavailability is a challenging issue. Micronization, formation of solvates, adsorbates, complexes, microspheres, or more often, solid dispersions of itraconazole are the different methods used for the above stated purpose. Lee et al. 93 (Lee S., et al) have worked on aerosol solvent extraction system (ASES). They have modified this system to spray drug/polymer solution with carbon dioxide through a nozzle into SC-CO_2. But the solid dispersions of itraconazole with hydrophilic polymer such as hydroxypropylmethylcellulose (HPMC 2910, Pharmacoat 606) were prepared to improve drug solubility and bioavailability by ASES. So HPMC also play a potential role in ASES technique to improve the solubility of low water soluble drug.

Microencapsulation is a standard process to prepare controlled drug delivery systems. For development of this dosage form, different polymers have been explored and successful results have been obtained. These systems are mainly useful for the drugs owing short biological half life. By controlling drug relaese, minimization of frequency of dosing as well as more patience compliance will be obtained. Mucoadhesive drug delivery systems are another approach. These are obtained in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, and topical routes. Mucoadhesiveness will increase the contact time or residence time with the target site and will improve the bioavailability of drug 94 (Ikeda K., et al), 95 (Nagai T., et al), 96 (Illum L., et al). Some researchers have combined both approaches (microencapsulation and mucoadhesiveness) and have proved them to be an excellent drug delivery systems 97 (Sakagami M., et al), 98 (Takishima J., et al), 99 (Lim S. T., et al), 100 (Cuna M., et al). Chowdary et al. 101 (Chowdary K. P. R., et al) in their work have developed, characterized, and evaluated mucoadhesive microcapsules of glipizide employing various mucoadhesive polymers for prolonged gastrointestinal absorption. Hydroxypropyl methylcellulose (HPMC, having a viscosity of 50 cps in a 2% by wt/vol aqueous solution at 20°C) as a mucoadhesive polymer was used to prepare microcapsules containing glipizide employing sodium alginate in combination. Microcapsules with a coat consisting of alginate and mucoadhesive polymer HPMC exhibited large spherical microcapsules with good mucoadhesive properties and slow-extented drug release profile for a longer period of time.

Nystatin is used in oral cavity to treat oral candidosis 102 (Millns -Martin). It will not remain in the oral cavity for a longer period of time if given in tablet form and sustained action of the drug can not be obtained to treat oral candidosis. Bucoadhesive drug delivery systems may be the alternative of this tablet form as this form will increase the retention time in oral cavity. Drug from this bucoadhesive system will be removed in a sustained way. To form buccoadhesive system, polymers with suitable physicochemical properties such as polyacrylic acid (carbomer [CB]) and cellulose derivatives; hydroxypropyl methylcellulose 103 (Bottemberg P., et al), 104 (Ponchel G., et al) are recommended to use. Lablot et al. 105 (Llabot J. M., et al) have planned to design a double-layered buccoadhesive tablet of nystatin containing CB:HPMC mixtures as mucoadhesive polymers. The water uptake, the swelling process and rate of drug release through this system was determined. The most working polymer ratio was fixed by them by measuring in vitro mucoadhesion time. CB: HPMC in the ratio of 9:1 has been proved to be the most suitable mixture. As the polymers are hydrophilic in nature, they can easily swell in water due to relaxation of structure and drug will be released from this swollen polymers. So mucoadhesion and amount of drug release both can be modulated from this system. This combination of HPMC and CB has fulfilled their attempt of designing bucoadhesive tablet.

Approximately 1% of all female population worldwide is affected by human papilloma virus (HPV) infection which causes cervical cancer 106 (Lacey C. J. N.,), 107 (Rose P. G.,). It is reported that cervical cancer is the most common cause of death for women under the age of 50 years 108 (Gross G.,). Antiprophylactic agents such as Podophyllin/podophyllotoxin 109 (Lacey C. J. N., et al), cidofovir 110 (Snoeck et al. 2001;) or 5-fluorouracil (5-FU) 111 (Mansell P. W. A., et al) in the form of gels, creams or pessaries are marketed in the form of topical or intralesional injection for management of HPV-related diseases. Vaginal drug delivery systems are developed to apply the drug at HPV-infection site, the vagina and the genital tract. It is comprised of creams, gels, tablets, foams, pessaries and irrigations. But it suffers from lower

residence time at application site. They will be washed rapidly from the application site by the self-cleansing action of the vaginal tract 112 (Deshpande A. A., et al). Bilensoy et al. 113 (Bilensoy E., et al) have tried to develop mucoadhesive, thermosensitive vaginal gel formulation containing 5-FU for longer residence at HPV-infection site. Hydroxypropyl methylcellulose (HPMC; Metolose 90SH) USP was used as mucoadhesive polymer. HPMC has affected gelling properties and rheological behavior of gels. It is able to provide more favorable thermosensitive properties. After completion of their work, they have concluded that new developed formulation with highly soluble cyclodextrins including β-CD, HP- β-CD and HPMC is having higher anticancer efficacy with much lower doses avoiding unwanted side effects of the drug with controlled release and prolonged residence time in administration site.

It is a very challenging task to deliver the drug at esophagus. Drugs are generally given to cure local diseases of the esophagus. Batchelor et al., 114 (Batchelor H.,) has described different types of local diseases. Achalasia, a local disease is caused due to insufficient lower esophageal sphincter (LES) relaxation and ineffective peristalsis resulting difficulty in swallowing the food material from the easophagus. It has been reported to be an uncommon ailment 115 (Woltman B. K., et al). Sometimes LES can be in relaxed state and it will allow the stomach's acidic contents to reflux back into the esophagus. This is known as Gastroesophageal Reflux Disease (GERD). Heartburn is a symptom of this. Infections of the esophagus are seen to the patient associated with immunocompromised hosts, including patients undergoing cancer chemotherapy or those with HIV 116 (Nandurkar – Talley). Solid dosage form can not be used always to treat, because the injuries can be caused due to lodging of tablets and capsules within the esophagus. Liquid formulations may be the alternative for this disease. As an example, some drugs in HPMC liquid solution with proper adhesion may be used to treat local infection.

High solubility, short half-life, and therapeutic use of verapamil in chronic diseases have prompted the researcher to think it as an ideal drug candidate for the design of oral controlled release dosage forms. Controlled release form is generally formed form different polymers. HPMC is one of them, widely used in designing controlled dosage form. Any dosage system prepared from polymers is generally of low cost. But they may have certain disadvantages. Polymer made matrix will swell in presence of media and due to burst of matrix, maximum amount of drug will be released and sustained release of dosage form may not be obtained. To encounter this disadvantage, various matrix geometries have been designed in an attempt to control release of the drug with time 117 (Conte U., et al), 118 (Narasimhan - Langer). Multi-layer matrix devices consist of core and coat. The matrix core contains the drug or any other active solute and the coat is surrounded by one or more modulating layers that act as rate-controlling barriers 119 (Lee E. S.,), 120 (Bodmeier – Paeratakul), 121(Krishnaiah Y. S., et al). Siahi et al. 122 (Siahi M. R., et al) in their present research work, have tried to develop 3-layer tablet containing water-soluble drug, verapamil hydrochloride from tragacanth, acacia and HPMC polymer to sustain the release of drug. Acacia when used single, is not able to enough prolong effect. But when combined with HPMC may prolong effect. HPMC gel has greater rigidity and more viscosity, it will act as a barrier for penetration of dissolution medium into HPMC gel and diffusion of drug out of that layer will be delayed. They have carried out in vitro release study from tablet containing the polymers of different combination and finally concluded that higher gelling ability polymer i.e. HPMC have the potential for sustaining and/or controlling the release of water soluble drug, verapamil hydrochloride.

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