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HPMC a biomedical polymer in pharmaceutical dosage forms

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ABSTRACT

Hydroxy propyl methyl cellulose (HPMC)/hypromellose is widely used cellulose ether in the development of hydrophilic matrices for the development of various pharmaceutical dosage forms. HPMC is a polymer selected by most formulators as a hydrophilic matrix system probably due to the claim that it gives fast gel formation to control initial drug release. It is nontoxic, ease of compression and high drug loading capacity. It provides the release of drug in a controlled manner and giving maximum utilization of drug. This review gives idea about properties of HPMC, mechanism of drug release, factors affecting release from hypromellose and its application.

KEY WORDS: Hypromellose, hydrophilic matrices, nontoxic, application.

1. INTRODUCTION

Hydrophilic matrices are typically compressed (Hogan, 1989) powder mixtures of drug and excipients including one or more water swellable hydrophilic polymers which are generally regarded as safe (GRAS) excipients. Hydrophilic matrices use polymers with flexible chemistry that offers an opportunity to design controlled release dosage forms for wide range of drugs with varying solubility and doses. Swellable matrices can be administered in various routes such as oral, buccal, vaginal, rectal drug delivery system. There are many high molecular weight water soluble or water swell able polymers used in hydrophilic matrices such as HPMC, hydroxyl propyl cellulose, sodium carboxy methyl cellulose, sodium alginates, carbomer etc. HPMC is most popular polymer in matrix applications because of its ability to obtain desired release profiles for wide range of drugs, provides robust formulation, global availability, cost effective manufacture, broad regulatory acceptance etc. HPMC is typically used as primary polymer and other polymers which can modulate the drug release profile in controlled manner (Fallingborg, 1999). Solubility of drug determines the mechanism of drug release from HPMC hydrophilic matrices influencing the choice of polymer viscosity, chemistry and other excipients. Use of an appropriate viscosity grade will enable a formulation scientist to design matrices based on diffusion, erosion mechanism etc. Practically insoluble drugs dissolve slowly and have slow diffusion through gel layer of a hydrophilic matrix. The aim of this review is to give idea into hypromellose, mechanism of drug release, factors affecting release from hypromellose and its application.

Advantages of HPMC (Huichao, 2014**):**

Chemical inertness: HPMC is inert in nature. It is a nonionic cellulose ether which does not react with metal salt or ionic organics. Hence there is no interaction between it and other excipients during formulation of dosage forms.

Stability: It is stable in acid and alkali and provides good viscosity. It is stable between p^H 3-11 during long term storage. The aqueous solution of HPMC is enzyme resistant in nature.

Safety: It is a nontoxic and non-irritating material.

Viscosity can be regulatory: The different viscosity of HPMC grades make complex with each other according to different proportion. The viscosity may change according to certain rules and has linear relationship.

Metabolism: HPMC is metabolized in the body and does not produce heat.

Solubility: It is soluble in cold water, 70% ethanol, practically insoluble in hot water.

Properties of HPMC (Phadtare, 2014**):** Acidity/alkalinity - p^H 3.5-8.0 for a 1% w/w aqueous solution, Ash- 1.5-3%, Autoignition temperature - 360^0C, Density(bulk)- 0.341g/cm^3, Density(tapped) - 0.557g/cm^3, Density(true) – 1.326g/cm^3, Melting point -190^0C-200^0C (Brown), 225^0C-230^0C (Chars), 170-180^0C (Glass transition temperature), Specific heat Cp= 0.28 BTU/lb-F, Thermal conductivity k = 0.028 BTU/hr-ft-F, Surface tension- 42 to 56Mn/m, Specific gravity- 1.0012(1% Solution), 1.0117(5%Solution), 1.0245(10%Solution). LD_{50}(MouseIP):5g/kg, LD_{50}(RatIP):5.2g/kg

Stability and storage condition: Solutions are stable at p^H 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling respectively. The gel point is 50-90^0C depending upon the grade and concentration of material. Aqueous solutions are comparatively enzyme resistant providing good viscosity stability during long term storage. Hypromellose powder should be stored in a well closed container, in a cool and dry place.

Incompatibility: It is incompatible with oxidizing agent.

Refractive index: The refractive index of 2% aqueous solution at 20^0C is for all types nD_{20}=1.336.

Safety: It is widely used as an excipient in oral and topical pharmaceutical formulations. It is extensively used in cosmetics and food products. It is used as controlled release polymer for various dosage forms. Hypromellose is generally regarded as a nontoxic and nonirritant material. The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.

Handling precautions: Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

Viscosity: Hypromellose chains swell faster with an increase in polymer viscosity (Wan, 1991). The pores of high-viscosity hypromellose block up quickly and inhibit further liquid uptake. This leads to the formation of a turbid gel, which resists dilution and erosion, subsequently resulting in slower drug diffusion (Kim, 1997) and release rates. If a good gel layer is formed, the rate of drug release is reduced and becomes dependent on the rate at which the drug molecules diffuse through the gel, as well as the rate at which the barrier layer is mechanically removed by attrition and disentanglement of the matrix. Three characteristics of swelling were observed from MRI images (Tritt-Goc, 2002) the growth of the gel layer with time, a reduction in the size of the dry core of the polymer as more of the polymer becomes hydrated and, finally, an increase in the diameter of the matrix with time. Commercial desingnations of hypromellose products are based on viscosity values determined in water at 20^0C with a concentration of 2% hypromellose.

Table.1.Hypromellose Commercial grade with respective viscosity (Phadtare, 2014**)**

USP Designation	Hypromellose Commercial grade	Viscosity (cP)
2910	E 3 Premium LV	3
2910	E 5 Premium LV	5
2910	E 6 Premium LV	6
2910	E 15 Premium LV	15
2910	E 50 Premium LV	50
2910	E 4M Premium	4000
2910	E 4M Premium CR	4000
2910	E 10M Premium CR	10000
2906	F 4M Premium	4000
2208	K 3 Premium LV	3
2208	K 100 Premium LV	100
2208	K 100 Premium LV CR	100
2208	K 100 Premium LV LH	100
2208	K 100 Premium LV LH CR	100
2208	K 4M Premium	4000
2208	K 4M Premium CR	4000
2208	K 15M Premium	15000
2208	K 15M Premium CR	15000
2208	K 100M Premium	100000
2208	K 100M Premium CR	100000

CR – Controlled Release Grades, LV-Low viscosity

LH - Product with lower Hydroxypropyl content specification 7%-9%

Specification: Hypromellose has a polymeric backbone of cellulose and is produced by processing pulp cellulose with caustic soda, then reacting with methyl chloride and propylene oxide, leading to hydroxypropyl substitution on the anhydroglucose units. The fibrous reaction product is purified and ground to a fine, uniform powder (Chan, 2003). HPMC is an odorless and tasteless, white or creamy-white fibrous or granular powder. It can be dissolved in water, and formed a transparent to milky white and has a certain viscosity colloidal solution. Hypromellose defines in USP 32 that the substitution type by appearing a four digit number to the nonproprietary name. The first two digits refer to the approximate percentage content of the methoxy group(OCH_3).The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$) calculated on a dried basis. Calocan of hydroxypropyl methyl cellulose products called methocel there are series i.e.E, F and K series (Dow Commercial Company, 2002).E series is used for thin film coatings. F series is used for adhesion promoter, suspending agent and thickening agent in liquid formulation. K series is used for release resistance and hydrophilic gel matrix of sustained release formulation. Hypromellose contains varying ratios of hydroxypropyl and methyl substitution which determines the organic solubility as well as thermal gelation temperature of aqueous solution. The extent of substitution is desingnated by weight percentage of substituent group attached to the ring known as degree of substitution. A lower degree of substitution (D.S.) results in lower solubility and only soluble in caustic solution.

Table.2.Degree of substitution for different grades of hypromellose

Grade	Methoxyl D.S	Methoxyl (%)	Hydroxypropyl molar substitution	Hydroxypropyl (%)
E	1.9	29	0.23	8.5
K	1.4	22	0.21	8.1
F	1.8	28	0.13	5
J	1.3	18	0.82	27

Thermal properties: The hydration of hypromellose depends upon temperature which has significant effects on the characterstics of its gels. Increasing the gel temperature influences loss of water that causes to decrease in relative velocity and continuous loss leads polymer polymer interactions of the methoxy substituents and this is known as gel point (Mitchell, 1990).Also increasing temperature causes hypromellose gel precipitation. The incipient temperature can be recorded that corresponds to the commencement of visual precipitation of polymer molecules. Light transmittance uses to identify incipient precipitation which is normally defined by 97.5% transmittance. The value when the transmittance reaches 50% is known as the cloud point (Sarkar, 1979).The cloud point depends on the concentration of hypromellose. High concentration gives gel before turbidity occurs, but low concentration appears turbid solution before gelatin occurs.

Hydration: When the dosage form contacts with aqueous fluid there is rapid uptake of water. Water penetrates into the spaces of the polymer causes hydration, chains gradually uncoil and extend but does not form linear coils. These causes cleavage of polymer hydrogen bonds making sites available for further hydrogen bonding (Gao, 1995) with additional water molecules and leading to mass of polymer entanglement. When the water content increases the polymer becomes hydrated and the layer forms gel. Gel layer thickness depends on water penetration,polymer swelling, drug dissolution, drug diffusion and matrix erosion. Controlled release matrix requires quick hydration to form protective gelatinous layer.

Mechanism of drug release: The drug release from gel layer (Tahara, 1996) of HPMC matrices is controlled by diffusion and erosion. The drug present on the surface of the matrix by burst effect. This is followed by expansion of the gel layer due to water permeation into the tablet. If a good gel layer is formed (Talukdar, 1996) the rate of drug release is reduced and becomes dependent on the rate at which the drug molecules diffuse through the gel, as well as the rate at which the barrier layer is mechanically removed by attrition and disentanglement of the matrix. The hypromellose is regarded as glassy because water has yet to fully penetrate the matrix. The mobility (Kiil, 2003) of macromolecules is hence very low, which leads to low diffusion rates of water. The erosion front is the boundary between the matrix and the dissolution medium. The mobility of the polymer chains is increased, leading to higher rates of diffusion. The diffusion front is the boundary in the gel layer itself between solid and dissolved drug. Drug dissolution (Siepmann, 1999) occurs at this diffusion front. When the diffusion front is formed, the thickness of the dissolved drug–gel layer (i.e. the distance between the diffusion and the erosion front) is the main drive for drug release, not the whole gel layer thickness (i.e. the distance between the swelling and erosion fronts).Movement of the erosion front determines drug-release kinetics. If the polymer in the diffusion front is diluted to such an extent that the gel has no structural integrity, it dissolves and erodes away. A water-soluble drug is released by diffusion and erosion of the gel layer. If a drug is highly insoluble then the mechanism is predominantly erosion.

Polymer factors affecting release from hypromellose matrices (Maderuelo, 2011**):**

Influence of compression speed: The tensile strength of hypromellose tablet is affected by compression speed. The tensile strength of hypromellose matrices is decreased by increase in compression speed.The better quality matrices is produced by low compression speed.

Hypromellose polymer level: A Strong gel is formed by high polymer content,but a low polymer level does not form gel quickly.The increase in hypromellose content causes gelatinous diffusion layer more stronger and more resistant(Xu, 1995) to diffusion and erosion.The particular level of polymer concentration the effects such as viscosity,burst effect and particle size are less.The drug to polymer ratio has effect on drug release rate.Drug release rate deviates from linearity after 70% of drug release.Attrition causes drug depletion from the matrix.

Substitution type effect on matrix: Drug release rates depend on substitution type in polymer if the polymer level is less then the polymer content does not overriding factor controlling drug release rate.The hydrophobic methoxy groups decrease hydrogen bonding within and between particles of close proximity in particular in the dry regions closest to the tablet core where the level of water is lowest.This causes retardation of the drug release rate and is confirmed with NMR imaging when different substitution levels gave rise to different water mobilities leading to differing drug release characterstics.The quantity of water that attaches to the polymer and the amount of tightly bound water depends on the degree of substitution (Mc Crystal, 1999).

Hypromellose particle size: Hypromellose particle size and size distribution have significant effects on the hydration rate of the polymer and play an important role in moderating drug release from hypromellose matrices. Particles of increased size require increased time for hydration to take place. Swelling hypromellose particles

cannot effectively bind with adjacent ones so the polymer characteristics tend to lead to disintegration (Campos-Aldrete et.al.1997).The polymer particles tended to dissolve slowly and failed to provide adequate controlled release. From a purely physical standpoint, decreasing particle size may achieve a matrix that has a higher tensile strength, since smaller particles allow greater packing density and contact points between particles, which allow better interparticle bonding.

Non-polymer factors affecting release from hypromellose matrices:

Drug factors: Drug solubility: High solubility drugs dissolve by diffusing through the gel matrices and give the pathway for drug release.The other pathway is by erosion of gel.Highly soluble drugs act as pore formers with the formation of microcavities and make the gel more porous and weaker.Poorly soluble drugs (Bettini, 2001) release drug predominantly by erosion from the gel matrix.

Drug particle size: The increase in drug loading (Kim, 1999) increases drug release due to greater channel formation in the swollen matrix.The channel size depends on drug size and leads to promotion of complete drug release.Particle size affects drug release for poorly soluble compounds because erosion is the predominant release mechanism.The effect of drug particle size on drug release from hypromellose matrix is minimum and lower hypromellose levels in matrix has low tortuosity and high porosity characteristics (Velasco, 1999).

Chirality: Hypromellose exhibits stereo selective release of the R and S isomers of some drugs e.g.propanolol.The interaction is observed in gels rather than tablets that there is no enantiomeric (Solinis, 2002a) reaction.

Lubricants: Lubricants may affect tensile strength,friability and drug release rates. It depends on the type of lubricant used, its quantity, the method of addition, the type of blender and the blending time.

Tablet shape and modifications: The release rate of the drug is affected by surface area to volume ratio from hypromellose matrix. The drug release profile is chacterized by optimum tablet shape, size and drug levels. There are many tablet shapes are available for modifying drug release rate such as geomatrix tablets, smatrix tablets, bilayer caplets etc.

Core in cup: Core in cup technology (Danckwerts, 1994) involves an insoluble cup and soluble core to allow varying drug release rates controlled by matrix. The two parts are compressed together to form one unit.

Geomatrix: Geomatrix tablet technology (Conte, 1996) is developed by Sky pharma. It uses multilayer tablet design.The unit is effectively a two or three layer tablet that a layer contains drug. The release of drug is controlled by the hydrophilic polymer matrix.

Bilayer caplets: These are used to deliver an immediate (Maggi, 1999) dose followed by a prolonged release of drug.

Salting in and out: The ions of inorganic salts have greater affinity for water which can remove water of hydration from a polymer. Hence dehydrating and salting out (Lapidus, 1968) of polymer will occur. Low ionic strength of the gel is unaffected, but intermediate ionic strength leads to loss of gel integrity and disintegration of the matrix.

Matrices containing drug-release modifiers:

Soluble and insoluble components: The drug release rate is increased by the addition of super disintegrants e.g.explotab, ac-di-sol. The gel matrix uptake water quickly followed by swelling (Zulger, 2002) and wicking. As a result of which the matrix is porous and disintegrates quickly.

P^H: Hypromellose is stable at p^H range (Streubel, 2000) of 3-11.The gel matrix does not preserve neutral environment inside the matrix and p^H is less than with buffer ions in the surrounding media. There is a p^H gradient across the gel with the outermost layer having a higher p^H than the layer closer to the tablet core. If an acidic drug is buffered to a p^H above its p^{Ka} then the drug is ionized and the drug has greater solubility results faster drug release rates.Acidification of the matrix core stabilizes the gel p^H microenvironment such that a particular p^H is maintained within the matrix core.It stabilizes the drug release profiles of drugs of p^H dependent solubility.

Surfactants: The surfactants enhance the drug release rate by controlling wettability. Propranolol hydrochloride interacts with sodium dodecyl sulphate (Ford, 1991) forming propranolol dodecyl sulphate within hypromellose matrix.This complex is poorly soluble and reduces drug dissolution rate comparing with cetrimide.

Combination of different HPMC polymers: HPMC is a nonionic water soluble polymer may have possibility of chemical interaction or complexation with other formulation components is greatly reduced and the hydration and gel formation of its matrices are P^H independent. Drug solubility and dose are the most important factors to consider the design of HPMC controlled release matrices. In general controlled release for calculating the viscosity of the blend product(Tiwari, 2009).

$$\eta_B^{1/8} = X_1 \eta_1^{1/8} + X_2 \eta_2^{1/8}$$

Where η_B, η_1 and η_2 are the solution viscosity(cp) for polymer blend,polymer one and polymer two respectively and X_1 and X_2 are the weight fractions of polymer one and two respectively.

HPMC and ionic hydrophilic polymers: The combination of HPMC and polymethacrylates mostly anionic polymers (Eudragit L100) in hydrophilic matrices develops p^H independent release profiles for weakly basic drugs (Tatavarti, 2006).The incorporation of anionic polymer in the matrix influences drug release in basic media by

lowering the micro environmental p^H and retards the drug release in acidic media by forming an insoluble mass which acts as a barrier to drug diffusion. The enteric polymers have high molecular weights and the residence time within matrix gel layer is long and facilitate their p^H modulation effect to last longer compare to smaller molecular weight acids e.g.citric acids. Anionic polymers may change the gel strength and erosion rate of the matrix to control the micro environmental p^H. Incorporation of cationic polymethacrylate polymers in HPMC matrices develop p^H independent controlled release matrices for basic drugs.

HPMC and fatty acids, alcohols or waxes: Low melting lipophilic materials blended at low concentrations with HPMC have potential in achieving controlled release for metformin. The combination of HPMC with lipophilic materials at higher concentrations produce mixed results (Hossain, 2004).

HPMC and nonionic hydrophilic polymers: HPMC and poly ethylene oxide (PEO) are used for modulating drug release and to prevent the burst release of highly soluble drugs. The high swelling capacity (Gusler, 2001) of PEO is used in HPMC matrices to achieve expanded swelling resulting in enhanced gastro retention of the dosage form. Combination of HPMC and HPC in the matrix system is used to provide retardation in the drug release profiles compared to single polymer system.

The Application of HPMC in Pharmaceutical Preparation (Huichao, 2014**):**

As binder and disintegrant: Lower viscosity grades of HPMC are used as binder and disintegrant in tablet, pill, granulation. While higher viscosity grades are used as binder only. Concentrations between 2% and 5% W/W may be used as a binder in either wet or dry granulation processes according to different types and requirements.

As film coating material: HPMC is used as film coating material which may change degree of hardness, friability, hygroscopicity, disintegration, weight gain of tablets. Lower viscosity grades of HPMC polymers are used in aqueous film coating solutions, while higher viscosity grades are used in organic solvents. Generally 2-20%w/w concentrations of HPMC are used film forming solutions for film coated tablets.

As controlled release polymer: High viscosity grades are used to retard the release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules. Low-viscosity grades are used as the channel agents used in sustained and controlled release preparation.

As biological adhesive: Bioadhensive technology uses polymer materials with biological adhesion, through adhesion in biological membranes, enhance contact with the mucous membrane of continuity and compactness, slow drug release and absorbed by the mucous membrane reach the purpose of treatment. It is used for the treatment of gastrointestinal tract, vagina, and oral mucosa diseases.

As capsule wall material: Gelatin is used for the formation of capsule wall material, but it has lot of problems such as sensitive to oxygen sensitive drugs, less drug dissolution, disintegration in storage delay. Hence HPMC is the substitute for gelatin capsule preparation.

As suspending agent: Higher-viscosity grades are used as suspending agent in suspension type liquid formulations at level of 0.5-1.5% w/w, the suspension effect is good, easy to spread out, not stick wall, flocculation grain is fine and smooth.

As inhibitor of self microemulsifying drug delivery system: Self-microemulsifying drug delivery system (SMEDDS) uses the drug, oil phase, emulsifier and auxiliary emulsifier of uniform which is stable and transparent mixture. But for the insoluble drugs, water-soluble fiber polymer materials often added, such as HPMC, PVP, Make free drugs and drugs in the microemulsion reach to supersaturated solution in the gastrointestinal tract, to increase the solubility and enhance bioavailability.

2. CONCLUSION

HPMC is widely used in various dosage form design due to its physical, chemical and biological properties. But HPMC may cause dose dumping in preparation. Hence researchers are doing lots of work for HPMC could do better in preparation and with the depending of the research on its properties and preparation technology improvement. HPMC are used in the study of new preparations, new drug delivery system and promote the continuous development of various dosage forms.

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