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The application of biomedical polymer material hydroxy propyl methyl cellulose(HPMC) in pharmaceutical preparations

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ABSTRACT

Introduced the latest application of biomedical polymer material Hydroxypropyl methyl cellulose (HPMC) in pharmaceutical preparations. An extensive search was performed within PubMed, MEDLINE, CNKI, Vipand Wan-Fang up to March 2014.Based on the analysis and induction, and elaborated it in the application of solid preparation, liquid pharmaceutical, sustained-controlled preparation, capsule formulations, gel preparation and bio-adhesion preparation. HPMC can be widely used and will play a greater role in the field of pharmaceutical preparations.

Keywords: Hydroxy propyl methyl cellulose(HPMC), Pharmaceutical preparation, Biomedical polymer material.

INTRODUCTION

HPMC as a hydrophilic gel matrix material and bio-adhesion materials is widely used in pharmaceutical preparation. HPMC is an excipient 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 and that the formation of its strong viscous gel controls further release[1]. Its popularity can be attributed to its nontoxic nature, ease of compression, and capability to accommodate a high level of drug loading [2,3].Base on the difference of molecular weight and viscosity, it is equipped with characteristics and application of emulsification, bonding, thickening and adhesion, suspension, gelation and film-forming. This article mainly reviews the hydroxylpropyl methyl cellulose (HPMC) application in pharmaceutical preparation in recent years.

1. Fundamental Properties of HPMC[4,5,6]

Hydroxypropyl methylcellulose, empirical formula is $C_8H_{15}O_8$-$(C_{10}H_{18}O_6)$n-$C_8H_{15}O_8$, and molecular weight is about 86000. In the material of this product is a semisynthetic part of methyl cellulose and hydroxypropyl ether. Produced in two ways: One way is an appropriate level of methyl cellulose treated with NaOH, reaction with epoxy propane under high temperature and high pressure again; Another is treated with caustic soda cotton or wood pulp fiber, methane chloride and propylene oxide and its reaction to obtain, through further refined, crushing, become fine powder or particles evenly.

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.

Due to the different contents of methoxyl and hydroxypropyl in the structure of HPMC, there are various types of products. In certain concentration, various types of products with specific viscosity and thermal gelation temperature, so it is of different nature, and can get different application. Pharmacopeial Specifications for models and expression all countries are different: In PhEur 2002, it is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa·s, of a 2%

w/w aqueous solution at 20℃. Hypromellose defined in the USP 32 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g. hypromellose 2906. 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, that is, E, F series and K series, each series has a variety of models of products to choose from. E series for thin film coatings, coating for tablets, closed core; E, and F series for adhesion promoter and release resistance of eye ophthalmic preparation, suspending agent and thickener of liquid preparation and adhesive of tablet and granule; K series for release resistance and hydrophilic gel matrix of sustained-controlled preparation.

2. Advantages of HPMC[7,8,9]

Currently, HPMC, which has become one of the largest pharmaceutical excipients in dosages, is because the HPMC possesses the advantages of other complementary makings don't have.

2.1. Chemical inertness

HPMC is a kind of non-ionic cellulose ether, whose solution doesn't take ionic charge and don't react with metal salt or ionic organics. So there is no reaction between it and other materials during the preparation.

2.2. Stability

it is relatively stable in acid and alkali, and providing good viscosity stability between pH3 ~ 11 during long-term storage. Aqueous solutions are comparatively enzyme-resistant. Preparation materials using HPMC, its quality and stability is better than the traditional materials (dextrin, starch, etc.).

2.3. Safety

HPMC is generally regarded as a nontoxic and non-irritating material, The WHO has not specified an acceptable daily intake for HPMC since the levels consumed were not considered to represent a hazard to health.

2.4. Viscosity can be regulatory

The derivatives of different viscosity of HPMC can complex with each other according to the different proportion. Its viscosity can be change according to certain rules, and has a good linear relationship, so it can be chosen according to requirements in terms of proportion.

2.5. Metabolism inertia

HPMC is not absorbed and metabolized in the body, and cannot give heat, so it is a safe medicinal preparation material.

2.6. Soluble in cold water

Soluble in cold water under 40 ℃ or 70% ethanol, practically insoluble in hot water but gelation.

3. The Application of HPMC in Pharmaceutical Preparation

3.1. As Binder and Disintegrant

Lower-viscosity grades 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.

Li Houtao[10] to screen the binder of the Tinidazole tablet. The tablets were produced by binder, including 8% polyvinylpyrrolidone (PVP-K30), 10% starch, 40% sirup and 2.0hydroxy propyl methyl cellulose ($HPMC_{K4}$) in 50% alcohol. The appearance of the tablets was observed, and the changes of the appearance after coating were also observed. The hardness, fragility, disintegration time and dissolution rate were measured. The appearance, hardness, fragility, disintegration time and dissolution rate of the tablets produced by using HPMC were better than other binders. Guan Shihai[11] to optimize the prescription and technology of Fuganning tablets, and to screen the binder, including 50% alcohol, 15% starch paste, 15% PVP, 10% alcohol solution, 5% CMC - Na and 15% HPMC solution (5 mPa•s) in pressure, smooth finish, brittle broken degree as evaluation index. The tablet prepared with 15% HPMC solution (5 mPa•s), surface bright and clean, crisp fragile degree qualified, pressure can be good; can satisfy the requirements of coating. Thus HPMC (5 mPa•s) was selected as adhesive.

3.2. As Film-coating and Film-forming Material

Using HPMC as film coating materials, the table has no significant advantages compare with the traditional tables in hiding the taste, appearance, etc. But its degree of hardness, friability, hygroscopicity, disintegration, coating weight gain has a better quality indicator. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets.

Zhang Jixing[12]optimize the preparation of a premixed film coating powders by the central composite design-response surface methodology (RSM plus CCD). In the preparation design, independent variables were the amount of the film coating powders HPMC, PVA and plasticizer PEG, and viscosity of the premixed film coating solution, permeability and tensile stress of the film coating as indexes were dependent variables, and mathematic models were used to estimate the relationship between them. Its amount of film-former $HPMC_{E5}$ 11.88 g, PVA 24.12 g, plasticizer PEG 13.00 g, and coating suspension liquid viscosity is 20 mPa•s, respectively. The membrane permeability and tensile strength reached the best effect.Zhang Yuan[13] improve the preparation technology, using HPMC as adhesive instead of starch slurry by changing Jiahua table into film coated one, and improve its hygroscopicity, easy film color, loose pieces, segment, the stability of the tablets and so on. The orthogonal test method was used for prescription optimization that is 2% HPMC (70% ethyl alocohol).Liang Meiyi[14] and Lu Xiaohui[15] use HPMC as film-forming materials to prepare respectively fibrauretine colon targeting tablet and sophora colonic localization tablet, respectively, which are bright, tenacity, good isolation effect, and no significant influence on drug release. Huang Yunran[16] prepared Longxuejie colon-target tablet, 5% HPMC was used in swelling coating layer. Thus, HPMC can be widely applied in the colonic drug release system. HPMC is not only excellent thin film coating material, also can be used as film forming materials. Wang Tongshun[17] optimize the prescription of compound licorzinc and Amlexanox oral complex pellicle. Softness, uniformity, smoothness, and transparency of the pellicle were regarded as parameters. The optimal preparation of film-forming materials was PVA: 6.5g, HPMC: 0.1g, propylene glycol: 6.0g, Preparation of the above prescription can be excellent oral complex pellicle to meet the requirements of slow release and safety.

3.3. As Retardant, Controlled release agent and Channel agent

High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Low-viscosity grades as the channel agents used in sustained and controlled release preparations, the therapeutic effect of this kind of tablet for initial dose can be reached quickly and drug sustained or controlled release, thus effective blood concentrations are maintained in the body. HPMC under water after hydration gel layer formation, the release mechanism of drugs from the skeleton mainly include the spread and corrosion of the gel layer. Jung Bo Shim[18] used HPMC as sustained-release material for preparation of carvedilol sustained-release tablet. Currently, HPMC sustained-release skeleton is a large number of applications in traditional Chinese medicine, especially in Chinese medicine effective component, effective parts and single preparations. Liu Wen[19] use 15% HPMC as sustained-release material, 1% lactose and 5% microcrystalline cellulose as filler to prepared Hetaochengqitang into oral framework sustained-release tablets. Tang Guanguang[20] adopt astragaloside as model medicine to prepare HPMC framework tablet, and discuss the factors of affecting Chinese medicine effective parts of drug release. With increase content of HPMC and the release of astragalus saponin is reduced, there is a linear relationship between the release centigrade of the drug and corrosion degree of skeleton, so as the hydrophilicity chemical monomer. HPMC is not only to the hydrophilic compounds, and is suitable for the hydrophilic of material.Liu Guihua[21,22] adopt 17% $HPMC_{K15M}$ as sustained-release framework to prepare Saussurea involucrate Gel sustained-release matrix tablets. The release of chlorogenic acid and rutin was conformed to Higuchi equation and could be well described in vitro. HPMC is not only applied to traditional Chinese medicine effective constituents and effective parts of slow-release matrix tablets, and more and more application in the traditional Chinese medicine compound preparations. Wu Huichao[23,24] prepare Yizhi hydrogel matrix tablets with hydroxylpropylmethylcellulose (HPMC) as the main carrier by direct powder compression can sustained release in 12 h, displaying constant release effect, and the release curve smooth. Gardenin, Panax Notoginseng Saponins R_1, ginsenoside Rg_1, and ginsenoside Rb_1 were used to investigate the influence of factors in vitro releasing. And the release mechanism of Gardenin was non-Fick diffusion, while Panax Notoginseng Saponins R_1, ginsenoside Rg_1, and ginsenoside Rb_1 were coupled diffusion and erosion modal.

3.4. As Biological Adhesive

Bioadhensive technology, application of 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. Now widely used in areas such as the treatment of gastrointestinal tract, vagina, oral mucosa diseases. Gastrointestinal biological adhesion technology, is a new kind of drug delivery system developed in recent years, it not only prolongs the retention time of pharmaceutical preparations in the gastrointestinal tract, but also makes drugs and absorption site contact performance of the membrane

increase, change of cell membrane fluidity, make the drug penetration enhancement of intestinal epithelial cells, so as to improve the bioavailability of drugs. The preparation of NCaEBT pellet was optimized by central composite-design/response surface methodology with the independent variables of the amount of $HPMC_{K4M}$ and CP940, and-with the dependent variables of the dissolution of Ca^{2+} at 1.4 hand adhesive property of pellet. Optimizedpreparation-nofpelletofNCaEBTconsistedof15mg$HPMC_{K4M}$and27. 5mgCP940. Show that biological adhesion materials (e.g., HPMC) can obviously increase the adhesion between preparation and tissue.[25]

Oral biology adhesive preparation is also a new drug delivery system in recent years, oral biology adhesive preparation can adhere to injured part, not only extend the retention period of drug on the oral mucosa, but also play a role in the protection of oral cavity mucous membrane, achieve a good therapeutic effect, improve the bioavailability of drugs. Xue Xiaoyan[26] prepare formulations using CS, AP, CP, HPMC, CMC-Na and SA as adhesive excipient. Double-layer insulin buccal adhesive tablets were prepared by lyopyilization. The tablets have sponge-like porous structures, which might promote the release of insulin. The impermeable layer ensured directional release of insulin and attenuated drug loss. The Qing Huang Zhu Buccal bioadhesive tablets were prepared by using bletilla hyacinthine gum, HPMC and carbomer(Carbopol 974P) as adhensive excipients.[27]

In vaginal drug delivery system, the biological adhesive technology is also widely used. Zhu Yuting[28] use CP and HPMC as adhesion and sustained-release matrix material to prepare different prescriptions of clotrimazole Biological adhesive vaginal tablet. Adhesive force, adhesion time and swelling percentage were measured under the artificial vaginal fluid environment; screen out the suitable prescription for CP: HPMC is 1:1, the adhesion performance of preparation is good, and preparation technology is simple and feasible.

3.5. As Thickening Agent and Protective Colloid

HPMC used as a thickening agent for concentration of 0.45% ~ 1.0%. HPMC can also increase the stability of hydrophobic adhesive. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments, the commonly used concentration of 0.5%~1.5%.Wang Zhen[29] determine the best technique for medicinal charcoal clysma preparation. The best preparation was using 0.5% CMC-Na and2.0%HPMC (Methoxy 23.0%, hydroxypropyl 11.6%) as thickener. The optimized technic is credible, andcanbe used to promote the stability of medicinal charcoal clysma. Zhang Zhiqiang[30] developed the pH-triggered level of loxacin hydrochloride in-situ forming eye gel. The gel was formed carpool as gel base and hydroxylpropylmethylcellulose (HPMC) as thickening agents. The optimized formulation was made by dissolving levofloxacinhydrochloride 0.1g, $HPMCE_{50LV}$ 2.0g, carbopol(9400) 0.3g, Na_2HPO_4 0.35g, NaH_2PO_4 0.45g, NaCl 0.50g, and ethyl paraben 0.03g in 100ml water. In the study, the HPMC(K_{4M}, E_{4M}, E_{15LV}, E_{50LV}) of Calocanin different concentrations were screened, and HPMC E_{50LV} was selected.

3.6. As Capsule Wall Material

Usually, capsule wall material of capsule is given priority to Gelatin. The processing of Gelatin is simple, but there are series problems and phenomenon, such as the protection of wet oxygen sensitive drug is poor, drug dissolution reduced, capsule shells disintegrating delay in the storage. HPMC used as the substitute of Gelatin for capsule preparation, which improve the moldability and usage results, and has been widely spread in the world. Podczeck[31] used theophylline as controlled drugs and found that dissolution rate of the capsule prepared in HPMC is increased compared with Gelatin. Analysis the reason for the disintegrating of the HPMC is the capsule shells disintegrated at the same time, but the disintegrating of the Gelatin capsule shell is disintegrated in the mesh structure first, then the whole. Chiwele[32] got the similar conclusions, and compared the dissolution of gelatin, gelatin/polyethylene glycol and HPMC, and found that HPMC capsules shell dissolution were soon under different PH conditions, while gelatin shell is greatly influenced by different pH conditions. Tang Yue[33]screened a new type of capsule shell to be used for dry powder inhalants. By studying the difference of capsule shell stability, the behavior of powder inside capsule shell, and the percentage of fragmentation of capsule shell between HPMC capsules and gelatin were investigated. The stability of HPMC capsule shell is better than that of gelatin capsule shell. The percentage of fragmentation of HPMC capsule shells was lower than that of gelatin capsule shells. HPMC capsule shell can protect the powder better. HPMC capsule shells are more suitable for used as dry powder inhalants.

3.7. As Topical Gels

Gels as a kind of adhesive preparation, has a series of advantages, such as safety, beautiful, easy to clean, low cost, simple preparation technology, and good compatibility with drugs, thus become the development direction of skin, eye and other external preparation. For instance, percutaneous drug delivery gels is a new dosage forms being studied in recent years, it not only avoids drugs be destroyed in the gastrointestinal tract, but also has become the one of Effective drug release systems to overcome the drug side effects. [34] Zhu Jingjie[35] investigate the effect of different matrixes on the in vitro release of scutellarinethosomes gel and select the suitable matrixes from Carbopol(980NF) and $HPMC_{K15M}$. The suitable matrixes for scutellarinethosomes are 1.0%Carbopo, l.5%Carbopo, l.0%

Carbopol+1. 0% HPMC, and 1.5% Carbopol + 1.0% HPMC. In the study, HPMC can change carbomer gel matrix mode of drug release, and 1.0% HPMC can improve early drug release rate of 1.0% and 1.5% carbomermatrix.. Reason may be that HPMC for faster expansion, rapid inflation at the early stage of the experiment, make carbomer gel material molecular gap get bigger, so as to accelerate the drug release rate.Carbopol-934 and HPMC as matrix were used to make norfloxacin ophthalmic gel, the preparation process of norfloxacin ophthalmic gel is simple and feasible, and the quality of gel were satisfied the quality requirements of ophthalmic gel in "Pharmacopoeia of the People's Republic of China"(2010 editon).[36]

3.8. 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. Song Tian[37] use hydrophilic polymers (HPMC, CMC-Na, PVPK90, Xanthan gum and MC) as suspending agent to prepare racecadotril suspension. The stability of suspension was studied by detecting the rheology property, suspension viscosity, and microscopic morphology and the stability of particle morphology under accelerated experiment of drugs was also detected. 2% HPMC appeared to be a satisfying suspending agent by evaluating the sedimentation rate and the redispersion of racecadotri. The suspension meets the requirements of suspension preparation with stable quality.

Compared with the methyl cellulose, HPMC has the characteristics of more transparent form solution, there is only very little dispersion of fiber synthesis, so HPMC is also often used as suspending agent in ophthalmologic preparations. Liu Jie[38] used HPC, Carbomer 940, PEG, HPMC, hyaluronic acid(HA) and the combination of HA and HPMC (HA/HPMC) as suspending agents, respectively, to prepare acyclovir ophthalmic suspensions. The sedimentation volume ratio, particle size and redispersibility were used as indexes for the screening of optimal suspending agent. The effects of temperature and light on the suspension were also investigated. The combination of 0.05 % HA and 0.05 % HPMC may be the optimal suspending agent for acyclovir ophthalmic suspension, and temperature has a significant effect on the stability of the suspension.

3.9. As Inhibitor of SMEDDS

Self-microemulsifying drug delivery system(SMEDDS) is a new drug delivery system, by the drug, oil phase, emulsifier and auxiliary emulsifier of uniform, which is stable and transparent mixture, and the prescription composition is simple, security and stability.[39]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.[40] Peng Xuan[41] prepare the supersaturation self-emulsifying drug delivery system (S-SEDDS) containing silymarin. The optimum silymarin S-SEDDS was composed of medium chain triglycerides (MCT)40%, Cremophor RH40 (ethoxylated hydrogenated castor oil) 48%, Labrasol 12%, the adding amount of hydroxypropyl methylcellulose (HPMC) was 50mg/g. HPMC is added in the S-SEDDS, which effectively sustained a metastable supersaturated state, and prevent silymarin precipitate out. Compared with the traditional self-microemulsion prescription usually add a lot of surfactant in order to prevent incomplete drug package, the addition of HPMC can keep the silymarin solubility in the dissolution medium is relatively constant, reduces the dosage of emulsifier in the self-microemulsion prescription.

CONCLUSION

Thus, hydroxypropyl methyl cellulose (HPMC) due to its physical, chemical and biological properties is widely used in the preparation. But HPMC in preparation has many deficiencies, such as dose dumping, Studies[42] have found that by adding a new hydroxypropylcellulose-methyl methacrylate could ameliorate. At the same time, the researchers[43] through the preparation of Carbamazepine Sustained-release Tablets and Verapamil Hydrochloride Sustained-release Tablets to investigate penetration theory in the application of HPMC, in order to further study its release mechanism. In a word, more and more researchers are doing lots of work for HPMC could do better in preparation, and with the deepening of the research on its properties and preparation technology improvement, HPMC will be applied in larger amounts in the study of new preparations, new drug delivery system, and promote the continuous development of preparation.

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