

Review Article

HPMC AS CAPSULE SHELL MATERIAL: PHYSICOCHEMICAL, PHARMACEUTICAL AND BIOPHARMACEUTICAL PROPERTIES

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ABSTRACT

The most common instability problem of gelatin capsules arises from negative impact of extremes of temperature and especially atmospheric relative humidity on the mechanical integrity of the capsule shells with adverse effect extended even to the fill material. Moreover, choice of fill materials is highly restricted either due to their specific chemical structure, physical state or hygroscopicity. Additional reports of unpredictable disintegration and dissolution of filled hard gelatin capsules in experimental studies have prompted the search for a better alternative capsule shell material. The present review aims to provide an overview on the physicochemical, pharmaceutical and biopharmaceutical properties of hydroxypropyl methylcellulose (HPMC) as capsule shell material and perform comparative evaluation of HPMC and gelatin in terms of *in vitro/in vivo* performance and storage stability. HPMC capsule provides a highly flexible and widely acceptable platform capable of solving numerous challenges currently facing the pharmaceutical and nutraceutical industries and expands the possibilities for selection of different types of fill materials. The current topic introduces a new section on influence of various factors on *in vitro* dissolution of HPMC capsules. Delayed *in vitro* disintegration/dissolution of HPMC capsules in aqueous medium does not produce any negative effect *in vivo*. However, advancements in the processes of production and filling of HPMC capsule shells and detailed studies on effects of various parameters on their *in vitro/in vivo* dissolution would establish their supremacy over hard gelatin capsules in future.

Keywords: Gelatin, HPMC, Formaldehyde challenge test, *In vitro* dissolution, Stability study

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INTRODUCTION

Capsule, a versatile unit solid dosage form for oral administration is designed to enclose solid, liquid or semi-solid mixture of active pharmaceutical ingredient (API) and suitable excipients in hard gelatin shells or in soft shells of gelatin [1]. Capsule-based time controlled pulsatile drug delivery system has been designed and has ushered a new era in chronotherapeutics for synchronisation of drug delivery in management of diseases with circadian rhythm [2]. Capsules are capable of providing protection to encapsulated drug from deterioration induced by atmospheric oxygen, light, moisture etc. owing to the barrier effects of shell [3].

Gelatin is the most widely used capsule shell material because of its non-toxicity, solubility in biological fluids at body temperature, ability to undergo thermal gelation and form a strong, flexible and homogeneous film [4]. Gelatin is widely used for stabilisation of pharmaceutical suspensions and also in design of novel drug delivery systems such as wafers [5, 6]. However, few inherent characteristics of gelatin responsible for compromised *in vitro* stability of capsule and somewhat unpredictable disintegration and dissolution in experimental studies have given rise to the need for a better alternative for capsule shell material. Problems associated with selection and performance of gelatin are mentioned below.

Cross linking

Since, gelatin is a naturally occurring protein, it is susceptible to hydrolysis producing amino acids. Therefore, it can be reactive towards molecules of varying chemical structures mainly aldehydes or any formulation component possessing aldehydic functional group, reducing sugars, metal ions, plasticizers and preservatives. The amphoteric nature of gelatin may lead to incompatibility with anionic and cationic polymeric excipients as well as surfactants [7, 8]. Some of the commonly used excipients in preparation of various dosage forms such as fats, polyethylene glycol and its ethers, aliphatic alcohols or phenols, polysorbates and esters of unsaturated fatty acids can undergo auto-oxidation to form aldehydes. The aldehydic end-products of degradation can cross-link with gelatin resulting in

excipient-excipient interaction, formation of insoluble skin or pellicle on the gelatin shell and ultimately retarded dissolution [9]. A well known example of excipient-induced cross-linking of gelatin is that due to formaldehyde produced as a result of the decomposition of lactose. Environmental factors such as high humidity, high temperature and UV light can also induce cross-linking reactions [8].

Moisture content and stability problem

Water (13%w/w to 16%w/w) in the gelatin film acts as a plasticiser and enables the formation of a tough but flexible film. Change in relative humidity of the environment may either lead to brittle or soggy shells with sometimes a negative impact on the fill material [3, 4, 9, 10]. Sensitivity of gelatin to extremes of humidity is the major area of concern for use of capsules in too humid/dry climates.

Temperature-dependent disintegration/dissolution

Temperature is a key parameter that should be strictly controlled during disintegration and dissolution testing of capsules. Problem arises when temperature falls below 37 °C, since gelatin solubility decreases. At temperature below 30 °C, the capsule shells are insoluble and simply absorb water, swell and distort. Because of this, compendia and Pharmacopoeia of different countries have set a limit of 37 °C±1 °C for carrying out these tests on capsules [3, 11].

Religious perspective

The animal source of gelatin is an area of concern for some sections of population such as vegetarians or vegans and people belonging to certain religious or ethnic groups who practice diets that forbid the use of animal products [12].

Special manufacturing conditions

Liquid and semi solid filling cannot be done in hard gelatin capsules. Although, soft gelatin capsules provide a better alternative for such fill materials, special manufacturing conditions and stringent environmental control of temperature and humidity are required for their production. During the process of capsulation, the temperature and humidity of the air are maintained at 57-59 °F and 20% RH.

Drying needs to be carried out in an environment corresponding to 25 °F. Typical environmental conditions for soft capsule manufacturing include 78 °F and 15% RH or 68 °F and 20% RH [13].

The above-mentioned shortcomings and pitfalls of gelatin as capsule shell have driven the development of alternative shell-forming materials. Extensive literature review results in few studies on capsule shells made of Hydroxypropyl methylcellulose (HPMC) and also provides names of suppliers of empty HPMC capsule shells in international market. No single study carried out till date can throw light on the various criteria that are fulfilled by HPMC as alternative capsule shell material and its comparison to gelatin. Although indications about the *in vitro* and *in vivo* performance of HPMC capsules could be found, studies on compatibility of HPMC with various excipients and fill materials, data on the effect of different parameters on dissolution of empty and filled HPMC capsules are lacking. The present review has been designed to bridge these existing gaps in comprehensive knowledge about HPMC as capsule shell material.

HPMC as an alternative capsule shell material

Selection of capsule shell material alternative to gelatine should start with a discussion on few essential criteria to be fulfilled by the material of choice. The alternative capsule shell material should be preferably of plant origin, should not undergo cross-linking reactions with various excipients, should be stable towards fluctuation of environmental temperature and humidity during production and storage, should not exhibit temperature-dependent disintegration/dissolution and should be able to contain any fill material. Commercial-scale manufacturing needs a capsule with gelatin-like performance that can run on existing filling equipment. Regulatory bodies will accept a polymer for capsule that has a proven safety record and wide regulatory acceptance. Clinicians ask for an alternative from which patient compliance is assured with comparative therapeutic efficacy as that of gelatin [14].

Recently, a research study has been reported with hard alginate capsule shell incorporating amoxicillin in the development of gastroretentive floating drug delivery system [15]. HPMC, also known as Hypromellose seems to fulfil the desirable criteria of an alternative shell material. It is produced by synthetic modification of the renewable, plant resource, cellulose obtained from either pine or poplar [12]. Chemically, it is a methyl and hydroxypropyl mixed ether of cellulose [16].

HPMC is available in different grades (E series, K series) with limits on methoxy and hydroxypropyl groups which influence the properties such as gelation temperature, viscosity, flexibility and hydration [14]. HPMC is very popular in fabrication of oral controlled release drug delivery systems, microsponges and in coating of conventional capsules for achieving sustained drug release profile [17-19].

Some of the physicochemical and pharmaceutical properties of HPMC that make it the most suitable and preferable alternative material to gelatin as material of construction for capsule shell are-

- a. It is semi-synthetic in nature, derived from plant cellulose,
- b. Cross-linking problem with the excipients is totally absent since, the polymer is free from amino acids,
- c. Can be used for a variety of fill materials containing aldehydic group,
- d. It readily dissolves in cold water giving a colloidal solution owing to the reversible thermal gelation property,
- e. Forms a flexible film of controlled dimensions,
- f. Water does not act as a plasticiser for HPMC. Hence, it has better stability at different temperature and moisture conditions, compared to gelatin. It has been reported that Quali-V® capsules from Shionogi Qualicaps with 4-6% moisture content are made from hypromellose and are stable at low humidity conditions during storage or when filled with hygroscopic formulations. They can be dried to <1% moisture content without being brittle. It has been seen that the rate at which water diffuses through Quali-V® capsule films

is about half of the rate for Qualicaps® made of gelatin. This indicates that HPMC capsules are more suitable for moisture sensitive products. In a brochure on Embo Caps VG, it has been reported that their capsules are resistant to breakage during processing, transportation and are also more stable at moisture levels of 3-5% [20-22],

g. Its non-ionic nature makes it compatible with most of the commonly used excipients as well as APIs,

h. Does not require TSE(Transmissible Spongiform Encephalopathy) certification and hence time necessary for documentation and regulatory filings is reduced[16],

i. Adhesion property, optimum shell texture of HPMC film facilitates application of modified release uniform coating with excellent performance characteristics,

j. HPMC capsules are easy to swallow as gelatin based ones,

k. HPMC complies with USP/NF, EP and JP standards, and is permitted as a food additive for human consumption in accordance with 21 CFR 172.874 and Regulation (EC) No 1333/2008. It is included in the US FDA Inactive Ingredients Database, and is generally recognized as a non-toxic and non-irritant material. It is Kosher and Halal certified by Kosher and IFANCA respectively, approved for vegetarians by Vegetarian Society. It is globally available and accepted since it is manufactured in facilities which are ISO 9001 certified in compliance with IPEC's (International Pharmaceutical Excipient Council) Good Manufacturing Practice (GMP) Guide for Bulk Pharmaceutical Excipients [12,16, 23],

l. Non-GMO,

m. Preservative-free, allergen-free, starch-free and gluten-free,

n. Eligible for organic label language (EU), suitable for use with organic ingredients,

o. Different types of printing can be done such as axial, radial (spin), rectified axial and double-printing. Logo can be printed with approved inks, can be packaged in suitable materials and post-manufacturing treatments such as spraying of lubricants can be done. Laser technology can be used as anti-counterfeit strategy,

p. Can be coloured easily with globally approved iron pigments, titanium dioxide, caramel, riboflavin, carmine, sodium copper chlorophyllin [22] and

q. Dissolution performance is similar to gelatin capsule in terms of fast release of drug.

Special manufacturing conditions for production of empty HPMC capsule shells

The general manufacturing scheme for the production of HPMC empty capsule shells involves mixing of polymer with only water and approved colorants/opacifiers as needed, dipping of mould pins in temperature-controlled solution of the shell material, drying, positioning and stripping. After the formation of the cap and body of the capsule, the empty shell is available for filling of mixture of drug and excipients in suitable form and finally the filled capsules are to be polished and sealed. Coating and banding may be carried out depending on the bioavailability requirement or commercial purpose [24].

In the next section, special emphasis has been put on intermediate steps during manufacturing of HPMC capsule shells where they are either different from those of gelatin capsules in terms of processing conditions or where the need arises for an additional excipient to improve stability of HPMC capsule shell.

Gelation

Gelatin capsules are formed by sol-gel transformation at low temperature thereby producing a homogeneous film [10]. It is said to undergo cold-set gelation, where cooling results in enthalpically-stabilized inter-chain helix to form segments of individual chains leading to a three dimensional network. On the other hand, aqueous solution of methyl and hydroxypropyl methylcellulose are known to gel upon heating i.e., heat-set gelation [25]. These gels are

completely reversible in that they are formed upon heating yet will liquefy upon cooling. The precipitation temperature, gelation temperature, and gel strength of these methylcellulose solutions were determined as a function of molecular weight, degree of methyl and hydroxypropyl substitution, concentration, and presence of additives. The precipitation temperature of these polymer solutions decreases initially with increasing concentration until a critical concentration is reached above which the precipitation temperature is little affected by concentration changes. The incipient gelation temperature decreases linearly with concentration. The strength of these gels is time dependent, increases with increasing molecular weight, decreases with increasing hydroxypropyl substitution, and depends on the nature of additives.

Gel promoter

Comparatively lower mechanical strength of the cellulosic film necessitates the creation of a proper gelling system during manufacture of empty HPMC capsule shell. Different natural polymers have been investigated as gelling agents till date. Marine polysaccharide, carrageenan, mainly kappa and iota varieties, has been shown to induce gelation of HPMC at room temperature, in presence of potassium chloride. This occurs due to ionotropic gelation of carrageenan in presence of potassium ion, where carrageenan and potassium chloride act as network former and gelling agent/gel promoter [26]. This particular gelling system enables the use of existing conventional gelatin capsule manufacturing equipments for HPMC capsules [7, 10]. This particular variety of HPMC capsule dissolves in gastric fluid (pH 1.2). Similar results have been obtained with another gelling system consisting of gellan gum as the gelling agent and either ethylene diamine tetra acetic acid (EDTA) or sodium citrate as a gel promoter (sequestering agents) [7, 21].

Temperature control

In the manufacturing of hard gelatin capsules, the temperature of the dipping pins or moulds should be 22 °C and the gelatin solution should be maintained between 45 °C to 55 °C. For manufacturing of hard HPMC capsules, the temperature of HPMC gelling solution must be at least 70 °C in order to form a film. The temperature of the pins is controlled post-dip to avoid liquefaction of the films formed on the pins, by using induction heating system for the mould pins. Temperature should be kept unaltered till drying out of the films in order to retain the shape of the capsule [27]. It is noteworthy to mention that moisture control is not an essential criterion for HPMC capsule shell production.

Sealing and banding

Sealing of the capsule parts provides protection against leakage of the liquid fill material, makes the product tamper-resistant, reduces oxygen permeation through the shell, increases stability of the fill material and also retains any strong odours generated by the product within the shell itself [20]. Banding is a process applied for both gelatin and HPMC capsules, where the junction between the two parts of the capsule are sealed with the help of a sealing liquid and/or by applying a coating on the said junction with a layered solid material. Banding of HPMC capsules is done by dissolving HPMC powder in binary solvent mixture of ethanol and water at room temperature, with > 50% w/w of ethanol. Although high ethanol percentage facilitates faster drying, it may cause flammability and may precipitate toxic effects due to residual vapors. Sealing of patented HPMC capsules has been done with ethanol at 50 °C on commercial gelatin capsule shell sealing machine with good results where the band did not peel off after 1 w storage [28]. However, in order to improve the performance of HPMC capsule on high speed filling machine, the capsules are treated with a gliding agent on the external surface. This may lead to irregularity of the sealing/banding edge [29]. Ethanol-free banding is done with HPMC water solution containing small percentage of gelling agent. Incorporation of gelling agent increases the band strength, reduces tendency for band shrinkage, minimises air bubble formation and significantly reduces leakage rate.

The capsules are available in sizes ranging from 00E to 4 and size 9 for early trials with rodents up to size 00, the largest used in human

medicine [27]. Thus, the empty capsules are being manufactured in compliance with GMP and ISO 9002 regulations, without the addition of ethylene oxide or sulfites at any stage and they have been provided FDA "GRAS" status [12].

The resulting HPMC capsules were found to be of reproducible qualities in terms of flawless, shiny appearance, weight uniformity, dimensional specifications and exhibited robust performance on high speed and semi-automatic filling machines with high output rates, low rates of rejection (with fewer than 0.01% defects) and blister packaging equipments. All these factors shortened dosage form development time and thus economically acceptable for any commercial scale production. Moreover, tight and reliable sealing was also obtained with liquid-filled modified HPMC capsules leading to hermetically sealed one-piece capsules [16].

Effect of fill materials on HPMC capsule shell stability

HPMC capsules can be filled with hygroscopic fill materials without affecting their mechanical strength or stability [10].

HPMC capsule becomes standard choice for dry powder inhalers (DPI) for two reasons. Since, in this type of formulation the fill amount is very less, adverse effects of moisture-sensitivity of APIs and equilibrium water content of the capsule shell on the dosage form can be significant. Secondly, build-up of static charge (triboelectrification) can increase the affinity between dry API and interior of shell leading to incomplete delivery of the dose. This problem occurs less with HPMC capsules. For a capsule-based DPI, an essential requirement is that the capsule should be punctured easily without being broken into fragments which could have been inhaled. Since, HPMC can tolerate extreme deviations in environmental humidity, it is resistant to breakage and clean puncture is produced by the inhaler device without fragmentation and also does not shrink when kept at low humidity environment [30-32]. In order to have favourable drug delivery from device, the HPMC capsule for inhalation usually contains slightly higher percentage of moisture. Residual amount of drug in capsule and inhaler device after actuation and particulate drug dispersion profile in the pulmonary region depend on the level of surface lubricant applied to the mould pins during capsule manufacture as well as moisture level [16, 26].

Moreover, it is challenging to fill in liquids inside hard gelatin capsules, due to the potential for product-shell interactions [20]. The liquid ingredient should be non-solvent for gelatin [4]. But HPMC capsule can be filled with liquid fill material without compromising stability. HPMC capsule provides a very flexible vehicle for the formulator to solve many of the challenges currently facing the pharmaceutical and nutraceutical industries and expands the possibilities [20].

Oils and lipids or drug solution in lipid phase can be filled in HPMC capsules with ease, if they are in liquid state below 35 °C. On the other hand, if lipid phase is in solid state at 35 °C, they are transformed into semi-solid matrices which are thermo softening mixtures or are converted into tixotropic mixtures. Semi-solid formulations up to 80 °C can be filled in HPMC capsules [20].

Gelatin capsules turned brown when filled with ascorbic acid. This problem did not occur with HPMC capsules containing ascorbic acid, even when stored at 40 °C and 75% RH for 2 mo [33].

When salicylic acid was used as a fill material for capsules, maximum of 2% degradation was observed with HPMC capsules when stored at 25 °C/ 60% RH for 18 mo. Percentage of salicylic acid decomposition was higher for gelatin capsules stored under identical conditions [30].

Visual inspection and brittleness test were carried out on both gelatin and HPMC capsules filled with a wide range of liquid and semi-solid excipients after being stored at 45 °C for 1 mo. The excipients included in the study were propylene glycol, Polyethylene glycol (PEG) 400, labrasol, triacetin, triethyl citrate, medium chain triglycerides (MCT), cottonseed oil, soybean oil, sesame oil, squalene, PEG 400-water-MCT emulsion and gelucire 44/14. Among all the excipients studied, only propylene glycol caused softening of both gelatin and HPMC capsules. Gelatin capsules were found to break for most of the liquid and semi-solid excipients except

labrasol, triacetin, triethyl citrate, squalene and gelucire. Labrasol caused deformation and sweating was observed in HPMC capsules filled with PEG 400. HPMC capsules passed the brittleness test with all of them except with PEG 400 [33].

In another investigation, stability study was carried out on both gelatin and HPMC capsules with commonly used solvents,

surfactants and co-surfactants for liquid preparations. Study was carried out at 45 °C and 75% RH for 7 w and the capsules were visually inspected for shrinkage or swelling as well as leakage of fill materials [7]. Comparative effects of various excipients on stability of gelatin and HPMC capsules are presented in table 1. Surfactants may cause denaturation of gelatin resulting in swelling or shrinkage followed by leakage from the enlarged pore size.

Table 1: Excipient compatibility with capsule shell

Excipient	Function	Compatibility with gelatin capsule shell	Compatibility with HPMC capsule shell
Polyethylene Glycol 400	Solvent	For 7 w	For 3 w; shrinkage occurs after that
Caprylic/capric triglyceride	Solvent	For 3 w; leakage occurs after that	For 7 w
Propylene glycol monocaprylate 90% (Type II)	Co-surfactant	For 4 w; leakage occurs after that	Not Compatible; leakage occurs in 1 st week
Propylene glycol monolaurate (Type II)	Co-surfactant	For 3 w; leakage occurs after that	For 7 w
Mono-and di-glycerides (Imwitor 742®)	Co-surfactant	For 4 w; swelling occurs after that	Not Compatible; leakage occurs in 1 st week
Mono-and di-glycerides (Capmul MCM®)	Co-surfactant	For 3 w; swelling occurs after that	For 4 w; leakage occurs after that
Caprylocaproyl Polyoxylglycerides	Surfactant	For 4 w; swelling occurs after that	For 7 w
Lecithin in caprylic/capric triglycerides/alcohol	Solvent	For 7 w	For 7 w
Polysorbate 80	Surfactant	For 4 w; shrinkage occurs after that	For 7 w
Polyoxyl 35 Castor Oil	Surfactant	For 3 w; leakage and shrinkage occur after that	For 7 w

Quality control tests on HPMC capsule shell

The use of HPMC as an alternative to gelatin as capsule shell material can only be confirmed by analysing and comparing the quality control parameters of the empty and filled HPMC capsules versus hard gelatin capsules. The evaluation of the capsules includes physico-mechanical parameters such as mechanical strength, gas permeability, physicochemical parameters like formaldehyde challenge test, biopharmaceutical studies including *in vitro* and *in vivo* disintegration and dissolution tests, oesophageal sticking tendency test, animal studies and human bioavailability studies, and finally development of *in vitro-in vivo* correlation. Stability studies on HPMC capsules under different conditions of temperature and humidity form an integral part of quality control tests.

Parameters mentioned above have been studied by various manufacturing companies as well as research laboratories. Only those parameters where results for the two types of capsules have been found to be significantly different are discussed in the following section.

Physico-mechanical and physicochemical parameters

Mechanical strength

As a part of mechanical strength estimation, the burst test or breaking-force test is employed for determining % brittleness as a function of relative humidity for capsules stored under different conditions. Brittleness is directly related to quality, stability, consistency and resiliency of capsules and more so for liquid-filled hard capsules. During the test, no broken or otherwise compromised HPMC capsules were found at 2.5%-50% RH. With gelatin capsules, 100% of the samples were found to be brittle at 2.5% with no breakage at 50% RH [7, 20, 30, 34].

Gas permeability studies

Hard gelatin capsules have demonstrated excellent protection against oxygen permeability (3.14cc/m²/day) while HPMC capsules offer less protection against oxygen transmission (166 cc/m²/day) which is attributed to looser structure of HPMC film as observed in SEM studies of film cross-sections [10, 30]. Protection against oxidation of sensitive APIs or excipients in HPMC capsules can be achieved by including an anti-oxidant in the formulation or by packaging in blister package with aluminum foil [33]. HPMC capsules offered better protection against moisture-induced deterioration of the fill material as demonstrated from moisture uptake studies by dynamic vapor sorption method when compared

against gelatin capsules at all relative humidity percentages up to 40% at 25 °C [35]. Similar results were obtained when the films were stored in close proximity to calcium chloride in an environment of 92% RH and 25 °C. Water vapor transmission rates were found to be 446 and 263 g/m²/24hr, respectively for gelatin and HPMC films [30].

Formaldehyde challenge test

Capsules are first filled with lactose spiked with formaldehyde at 25 ppm and stored in HDPE bottles at room temperature for 1 w, emptied and filled with Acetaminophen USP at a fill weight 380 mg (± 10 mg). After 1 w storage at room temperature, release of Acetaminophen from capsule is observed as per the USP monograph for Acetaminophen Capsules. The test concludes that the dissolution of Acetaminophen from HPMC capsules shell is unchanged while gelatin capsule shell retarded drug release due to cross-linking reaction induced by formaldehyde [7].

Biopharmaceutical parameters

In vitro disintegration test

Carrageenan, gel promoter in HPMC capsules caused a delay in initial burst of the capsules in aqueous medium at body temperature. But, once the capsule has ruptured, comparable release profile was obtained as with gelatin capsules. This happened due to slow hydration of carrageenan [10]. In the disintegration test, HPMC capsules without gelling agent have demonstrated disintegration times of less than 10 min, as observed with gelatin capsules [16]. The disintegration times of green tea extract loaded HPMC capsules, without gelling agent, were tested in acetate buffer and demineralised water and were found to be <30 min, satisfying the USP limits for herbal formulations. Cations in acetate buffer did not have any negative impact on HPMC shell material. However, gelatin capsules disintegrated comparatively faster [36]. Disintegration time of spiranomycin loaded HPMC capsules in acidic medium (pH 1.2) was not altered, even after storage at 60 °C and 75% RH for 10 d. However, disintegration time was delayed with spiranomycin encapsulated in gelatin capsules [33].

In vitro dissolution test

To assess the effect of HPMC on release of drugs belonging to different BCS (Biopharmaceutical Classification System) classes, release of BCS Class II (ibuprofen) and Class III (acetaminophen) drugs were studied in phosphate buffer with potassium or sodium ions. Results obtained were compared with data from gelatin

capsules collected under similar conditions. In neutral potassium phosphate buffer medium, ibuprofen release was incomplete and highly variable from HPMC capsules compared with the gelatin capsules which was attributed to the presence of potassium ions (K⁺) in the dissolution medium. In neutral tribasic sodium phosphate buffer (pH 7.2) medium, both HPMC and gelatin capsules showed complete and less variable drug release. In neutral tribasic sodium phosphate buffer (pH 7.2) medium, lag time in releasing acetaminophen was less when sodium ions were present instead of potassium ions in phosphate buffer. Gelatin capsules rupture fastest. Faster disruption is observed as sodium ions do not efficiently bind as potassium ions [36]. Various factors affecting dissolution of HPMC capsules are discussed below.

Interaction effect of gelling agent in HPMC capsules and dissolution medium components on release profile

Change in ionic composition of the dissolution buffer medium by using potassium salt instead of sodium salt, resulted in significant delay in release of caffeine from HPMC capsules with carrageenan as gelling agent, when studied in acidic medium. Increase in potassium ion concentration produced further retardation in drug release, leading to non-compliance with acceptable limits of USP. However, HPMC capsules developed without gelling agent exhibited drug release profile independent of pH of dissolution medium, medium components, interaction due to shell material or dietary components [16, 37]. HPMC capsules developed with carrageenan as gelling agent dissolved in gastric fluid (pH 1.2), whether taken before or after meals, due to solubility of carrageenan at pH<4 [21]. Dissolution study of green tea extract loaded HPMC capsules was carried out in acidic medium (pH 1.2), acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) (FaSSiF and FeSSiF). Results from study in pH 1.2 revealed that release of catechin was significantly delayed and impaired from the capsules with gellan as gelling agent due to interaction of the polyphenolic compound with the shell material. Acidic pH of the dissolution medium lowered the solubility of gellan, preventing complete rupture of the capsule shell and release of the entrapped extract powder inside. Penetration of the medium and wetting occurred without any problem. Disintegration study also corroborated the observation where large portion of intact shell material remained on the mesh, even after 30 min.

Effect of capsule shell-food interaction on release profile

Effect of food interaction was evident during dissolution study from both types of HPMC capsules in FeSSiF. There was no indication of effect of capsule shell material or food material on catechin release from gelatin capsules in any of the buffers or FaSSiF and FeSSiF medium used for the study. It is advisable to administer HPMC capsules on an empty stomach. Addition of digestive enzymes in the dissolution medium did not alter drug release profile for either gelatin or HPMC capsules in mixed phosphate buffer (pH 6.8), in comparison to data observed in simulated medium without enzymes [36].

Effect of fill materials on dissolution profile

Gelatin and HPMC capsules filled with acetaminophen and pyridoxine hydrochloride were stored in three different conditions: 30 °C and RH 60% for 1yr, 40 °C and RH 75% for 6 mo, and 60 °C for 1 w. Dissolution study was carried out in JP 1st fluid (pH 1.2), acetate buffer (pH 4), JP 2nd fluid (pH 6.8) and water for a period of 30 min. There was no adverse effect on release of either of the drugs from HPMC capsules in any dissolution medium. However, drug release from gelatin capsules was delayed in all cases except those stored at 30 °C and RH 60% [33].

Effect of temperature of dissolution medium

An investigation was carried out to ascertain the effect of temperature variation of dissolution medium from 10-55 °C, on dissolution of gelatin and HPMC capsule shell. It was observed that temperature increase did not induce any change in drug release profile from HPMC capsule shells as long as the pH of the medium was less than or equal to 5.8. On the other hand, in simulated intestinal fluid maintained at temperatures varying from 10-55 °C, shell dissolution was found to be rapid up to 30 °C, increased above body temperature and did not occur till 2 h, beyond 55 °C. Impaired

dissolution was attributed to uptake of moisture, hydration of HPMC shell, resulting in comparatively slower penetration of dissolution medium. However, gelatin capsule shells failed to dissolve below 30 °C. Thus, in order to ensure therapeutic efficacy, gelatin capsules should preferably be ingested with warm drinks and HPMC capsules can be administered with cold or warm drinks [38].

Effect of size of capsule

Statistically significant differences in dissolution times were observed for HPMC capsules of size 0 and 3 [38]. In another study, no difference in drug release profile could be seen in HPMC capsules of different sizes, prepared without gelling agent [16].

Oesophageal sticking tendency

As HPMC is a bio adhesive material, it is expected that an increase in the oesophageal residence time would occur before reaching the stomach. No prolonged oesophageal hold up or sticking tendency was observed for both HPMC as well as gelatin capsules, when tested in healthy male volunteers. But, to avoid oesophageal entrapment of solid dosage forms, it was suggested that they should be taken in upright body position with at least 50 ml of water to minimise entrapment [27].

In vivo disintegration and dissolution test

Studies with prolonged release radio-labelled formulations containing different viscosity grades of HPMC powder in healthy human volunteers found HPMC capsules to dissolve in 9 min as compared to 7 min for gelatin capsules. Therefore it is observed that slow disintegration/dissolution of HPMC capsules *in vitro* in water or phosphate buffer (pH 6.8 or 7.2) does not produce negative effect on *in vivo* disintegration or dissolution. Thus, HPMC capsules can be considered as a good alternative to gelatin capsules [27].

Bioavailability studies

From analysis of plasma data of male dogs where single dose capsules have been given under both fasted and fed conditions, it was observed that HPMC capsules produced a rapid T_{max} for immediate release formulations, indicating that the dissolution of the capsule shell was not rate-limiting for absorption. Bioavailability studies in healthy human volunteers revealed median T_{max} of about 1 hour in fasted state which reflected the rapid disintegration of the HPMC capsule shell. Therefore, HPMC capsules yield a quick *in vivo* plasma profile for humans [7].

In vitro-in vivo correlation

HPMC capsules may demonstrate low correlation between the *in vitro* dissolution/disintegration and the *in vivo* performance due to observed *in vitro* interaction between the medium and the HPMC capsule gelling systems, which is not seen in *in vivo* studies in animals or human volunteers. To achieve better correlation, dissolution/disintegration testing specifications should be different from that of hard gelatin capsules. For hard gelatin capsules, 2-tier dissolution testing should be adopted and similar such modifications should also be employed during dissolution study from HPMC capsules [39].

Stability studies

HPMC capsules (200 capsules) were filled into glass bottles and heated at different temperatures (up to 90 °C) for 24 h in an oven. The glass bottles were kept at room temperature for at least 5 h before opening and the capsules were visually inspected and evaluated for mechanical strength and disintegration-dissolution performance. No change in visual appearance could be observed for HPMC capsules stored at 40 °C although deformation occurred at 70 °C. Mechanical strength and disintegration-dissolution performance remained unaffected even at 90 °C. However, the maximum tolerable temperature for gelatin capsules was found to be 60 °C when changes were reflected in all the parameters studied [7]. Similar results were obtained in another study when tested under identical conditions as also when exposed to temperatures ranging from 4 °C to-18 °C. Long-term stability studies at 40 °C and 75% relative humidity (RH) for 6 mo and at both 25 °C and 65% RH or 30 °C and 70% RH for 2 y did not reveal any alteration in disintegration and dissolution characteristics [37].

CONCLUSION

In spite of gelatin being the most widely used capsule shell material, it has several demerits. The key challenges put forward by gelatin capsules with respect to the phenomenon of cross-linking, variable mechanical strength under altered conditions of processing or storage temperature and relative humidity, preferential compatibility with only certain types of fill materials and excipients have been successfully overcome by hydroxypropylmethyl cellulose, a semi-synthetic alternative exhibiting better physicochemical, pharmaceutical and biopharmaceutical properties as also comparable performance. Studies conducted by various manufacturing companies and research laboratories have reported HPMC capsules to be superior to hard gelatin capsules in terms of mechanical strength and compatibility with a wide range of drugs and excipients possessing reactive functional groups and varying degrees of hygroscopicity. It exhibits better short term stability at high temperature and maintains flexibility even at low relative humidities. HPMC capsules have demonstrated better commercial prospect due to their wider patients' acceptance attributed to its plant origin. However, processing steps for HPMC capsules need to be improved in terms of their machineability and necessary modifications in the dissolution study protocol should be done to ensure establishment of high level of *in vitro-in vivo* correlation.

CONFLICT OF INTERESTS

Declared none

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