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A Review on Hypromellose as Pharmaceutical Excipient for Oromucosal Drug Delivery

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Binisha K [*1], Remya S B [2], Prasobh G R [3], Jasbin Nisha S [1], Soorya S [1]

*[*1] B Pharm student, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.*

[1] B Pharm student, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

[2] Associate Professor, Department of Pharmaceutics, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

[3] Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

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ABSTRACT

Mucoadhesive nanoparticles represent a potential drug delivery strategy to enhance the therapeutic efficacy in oral therapy. Mucoadhesive buccal film is developed as a promising dosage form, which has prominent advantages because of drug delivery through buccal mucosa. Hypromellose, formerly known as hydroxy propyl methyl cellulose (HPMC), is by far the most commonly employed cellulose ether used in the fabrication of hydrophilic matrices. Hypromellose provides the release of a drug in a controlled manner, effectively increasing the duration of release of a drug to prolong its therapeutic effect. From this review, the use Hypromellose in the oral and Oro mucosal drug delivery is studied along with the advantage over other cellulose derivatives.

INTRODUCTION

Mucoadhesive drug delivery system may be defined as a drug delivery system which utilizes property of bio adhesion of certain water-soluble polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. A mucoadhesive drug delivery system provides various advantages by targeting and localizing the nanoparticles at a target site, by decreasing variation in drug level in the plasma, and by extending residence time at the confined target site of drug penetration, and thereby reducing side effects. [1]

Hypromellose, formerly known as hydroxypropyl methylcellulose (HPMC), is by far the most commonly employed cellulose ether used in the fabrication of hydrophilic matrices. Hypromellose provides the release of a drug in a controlled manner, effectively increasing the duration of release of a drug to prolong its therapeutic effect. Binders are typically used in solid dosage form manufacturing to promote adequate mechanical strength of granules or tablets. HPMC is a polymeric binder used in wet granulation. The effectiveness of HPMC can be influenced by its swelling and gelling properties which can delay drug dissolution or release or by the presence of other excipients types in a formulation. [2]

SITES FOR MUCOADHESIVE DRUG DELIVERY SYSTEM

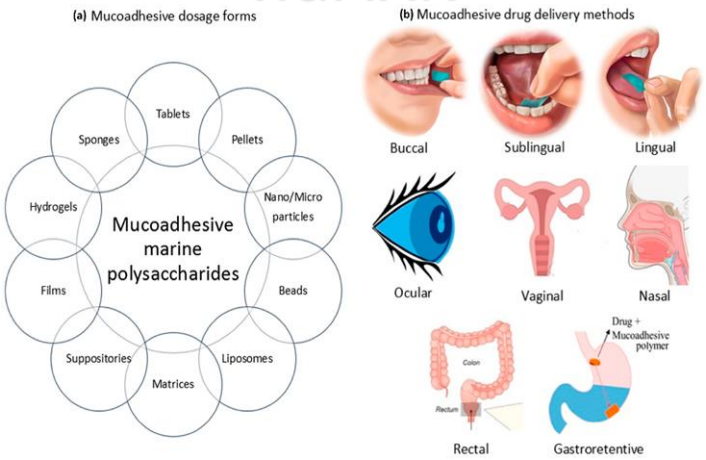


Fig. No. 1: Sites for Mucoadhesive Drug Delivery System

The common sites of application where mucoadhesive polymers have the ability to deliver pharmacologically active agents include oral cavity, eye conjunctiva, vagina, nasal cavity and GIT.

MECHANISMS OF MUCOADHESION

The mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage. The first stage is characterized by the contact between the mucoadhesive and the mucus membrane, with spreading and swelling of the formulation, initiating its decontact with the mucus layer. [6]

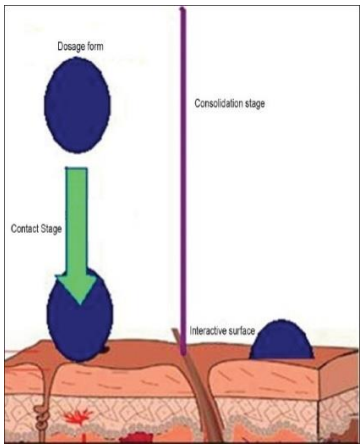


Fig. No. 2: mechanism of mucoadhesion

ANATOMY OF ORAL MUCOSA

EPITHELIUM

This is a highly organized, a vascular, and semipermeable tissue whose thickness and degree of keratinization varies according to the location in the oral cavity and the area's functional and mechanical requirements.

Prickle cell layer: Above the basal layer round or ovoid cells form a layer several cells thick called the prickle cell layer. These cells show the first stages of maturation, being larger and rounder than those in the basal layer.

Granular layer: The cells are larger and flatter but, most significantly, now contain large numbers of small granules, 0.5–1.0 μm in length, called keratohyaline granules These contain profilaggrin, the precursor to the protein filaggrin that eventually binds the keratin filaments together into a stable network.

Keratinised layer: The cells of the keratinised layer become filled entirely with closely-packed to no filaments surrounded by the matrix protein filaggrin. This mixture of proteins is

called keratin, is also strongly cross-linked by disulphide bonds, contributing to the mechanical and chemical resistance of the layer.

LAMINA PROPRIA

The lamina propria provides mechanical support for the epithelium as well as nutrition. Its nerves have a sensory function, while its blood cells and salivary glands have important defensive roles. The connective tissues having two layers: a superficial, papillary layer between the epithelial ridges, in which the collagen fibres are thin and loosely arranged; and, beneath this, a deep, reticular layer dominated by thick, parallel bundles of collagen fibres.

LINING EPITHELIUM

In lining epithelium, the cells are nonkeratinized at the surface like the cells in keratinised epithelia, those in lining epithelium enlarge and flatten as they shift towards the surface lining epithelium generally lacks filaggrin and loricrin, but contains involucrin.

SUBMUCOSA

It is a connective tissue of variable thickness and serves primarily attachment for lamina propria to the underlaying bone or muscle. It contains glands adipose tissues vascular and neural components. [3]

ORO MUCOSAL DRUG DELIVERY

The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40µm to 300µm. Though the sublingual glands and minor salivary glands contribute only about 10% of all saliva, together they produce the majority of mucus and are critical in maintaining the mucin layer over the oral mucosa. It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems. A thorough understanding of the glycoprotein mucin component is very important with regard to understanding the properties of mucus. [4]

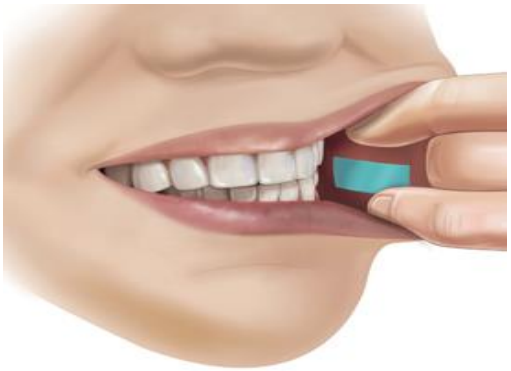


Fig. No. 3: Oro Mucosal Drug Delivery

HYPROMELLOSE

It is a methyl and hydroxy propyl mixed ether of cellulose and is a natural polysaccharide found in all plant parts mainly wood. It is slightly of white powder or granules and is a semisynthetic, inert polymer. It is insoluble in hot water, acetone and chloroform. It is soluble in cold water giving a colloidal solution.

PROPERTIES OF HYPROMELLOSE

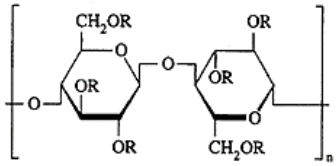
- **Molecular weight**: 86000 g/mol
- **Acidity/alkalinity**: pH = 5.5–8.0 for a 1% w/w aqueous solution.
- **Ash**: 1.5–3.0%, depending upon the grade and viscosity.
- **Autoignition temperature**: 360°C
- **Density (bulk)**: 0.341 g/cm^3
- **Density (tapped)**: 0.557 g/cm^3
- **Density (true)**: 1.326 g/cm^3
- **Melting point**: browns at 190–200°C; chars at 225–230°C
- **Glass transition temperature** is 170–180°C.
- **Moisture content**: Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

➢ **Solubility**: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

➢ **Specific gravity**: 1.26

➢ **Viscosity (dynamic)**: Hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared Hypromellose 347 using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions.

STRUCTURE OF HYPROMELLOSE



Where R is H, CH_3, or $CH_3CH(OH)CH_2$

Fig. No. 4: Structure of Hypromellose

Hydroxypropyl methylcellulose (HPMC or hypromellose) is a partly O-methylated and O-(2-hydroxypropylated) cellulose ether derivative. Molecular weights ranges from 80,000 to 1,200,000 Da.

HYPROMELLOSE AS EXCIPIENT IN OROMUCOSAL DRUG DELIVERY

Hypromellose, formerly known as hydroxypropyl methylcellulose (HPMC), is by far the most common cellulose ether used to form swellable-soluble matrices. It is a water-soluble hydrophilic, non-ionic cellulose ether that gels, is stable over the pH range 3.0–11.0 and is enzyme resistant. HPMC is used to provide the release of a drug in a controlled manner. It is hydrophilic with rapid swelling due to its ability to absorb water, and considered a first generation mucoadhesive polymer (adheres to the mucus non-specifically) that is non-toxic, biocompatible, and biodegradable. It acts as a drug-dispersing and viscosity-modifying agent and is a controlled delivery component in oral formulations.

HPMC is a popular hydrophilic polymer that is widely used in many pharmaceutical applications due to its ease of use, flexibility, good film-forming properties, biocompatibility, and biodegradability. HPMC demonstrates rapid swelling due to its ability to absorb water and has moderate mucoadhesive properties. Many studies have shown that mucoadhesive blend films demonstrate appropriate adhesion and adhesive times on buccal membranes and display drug release within the required time. However, a crucial restriction of buccal drug delivery is low drug permeability through the membrane that causes low bioavailability.

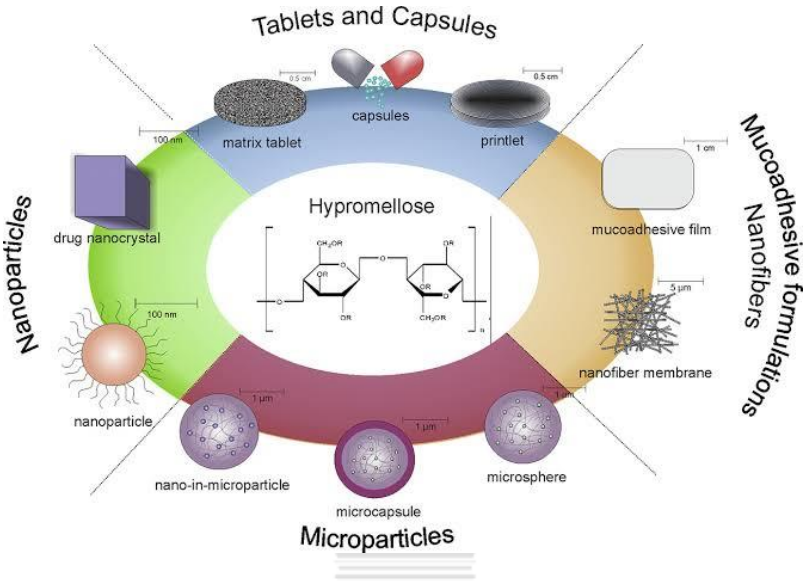


Fig. No. 5: Application of Hypromellose

ADVANTAGES OF HPMC

- **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.

- **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.).

- **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.

- **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.

- **Metabolism inertia**

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

- **Soluble in cold water**

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

- **Adaptability**

HPMC is very versatile and thus it can be used in products that need to be clear or it can be used to add opacity.

DISADVANTAGES

- Hypromellose is incompatible with some oxidizing agents. Since, it is non-ionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.
- Some surfactants and other ingredients make HPMC incompatible with others.
- HPMC is quite expensive.

APPLICATIONS OF HPMC IN PHARMACEUTICAL PREPARATIONS

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.

As Film-coating and Film-forming Material

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

As Retardant, Controlled release agent and Channel agent

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 includes the spread and corrosion of the gel layer.

As Biological Adhesive

Recently it is 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.

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%.

As Capsule Wall Material

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. Theophylline used 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.

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 are 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.

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. 2% HPMC appeared to be a satisfying suspending agent by evaluating the sedimentation rate and the redispersion.

As Inhibitor of SMEDDS

Self-micro emulsifying 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. 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. 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 surfactants 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.

PREPARATION

PREPARATIONOF HYPROMELLOSE

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

PREPARATION OF HPMC FROM α-CELLULOSE BETUNG BAMBOO

The preparation of hpmc from α-cellulose betung bamboo involves 3 stages.

- Extraction of fine bamboo powder.
- Isolation of α-cellulose betung bamboo.
- Preparation of hpmc from α-cellulose betung bamboo.

EXTRACTION OF FINE BAMBOO POWDER

- Coarse bamboo was dried in a oven at 106℃ for 6 hrs.
- Ground to a fine powder and sieved with 80 mesh sieve.
- The powder was washed repeatedly with water and dried at 60℃ for 24 hrs.
- About 300 gm of fine bamboo powder was macerated with 3 litre of n hexane: ethanol (2:1) for 24 hrs and stirred every 8 hr.
- The pulp was filtered and dried at room temperature.

ISOLATION OF α-CELLULOSE BETUNG BAMBOO

- 150 gm of fine bamboo powder was mixed with 2 litre of nitric acid and heated in a water bath at 90℃ for 2 hr.
- The insoluble part was separated by vacuum filter and the residual obtained was washed with distilled water.
- The residue was immersed into 1.5 litre of a mixed solution containing sodium sulphate and sodium hydroxide at 50℃ for 1 hr followed by filtration and washing with distilled water.
- The residue obtained was bleached with sodium hypochlorite and distilled water and heated for 10 minutes and repeat the process.
- Then the residue was mixed with NaOH and heated at 80℃ for 30 min followed by washing and drying at 60 ℃, the powder obtained is α-cellulose.

PREPARATION OF HPMC FROM α-CELLULOSE BETUNG BAMBOO

- 5g of α - cellulose was mixed with 100 ml of isopropyl alcohol and alkalised with 20 ml 0f NaOH then stirred with magnetic stirrer for 1 hr at room temperature.
- Furthermore, dimethyl sulphate was added for methylation reaction followed by addition of 6 ml propylene oxide for hydroxypropylation reaction.
- Beaker was tightly closed with aluminium foil and heated at 43.2℃, 50℃, 60℃ etc… for 3 hrs with stirring. Then it is cooled and neutralised with acetic acid and filtered with vacuum filter. The precipitate obtained is HPMC.

PREPARATION OF BUCCAL FILMS USING HYPROMELLOSE

Method (Solvent casting method)

The solvent system used was 50:50 ratios of ethanol and chloroform. The drug was then dispersed uniformly in the viscous solution with continuous stirring on magnetic stirrer. In order to avoid entrapment of the air bubble inside the film, the entire drug-polymer-solvent system was subjected to sonication with ultrasonic bath sonicator. The solution was poured into moulds for casting and dried at (room temperature) for a period of 24 hrs. After drying

the medicated patches of 2 × 2 cm2 area were cut using a sterilized stainless-steel scalpel, each film containing 5.0 mg of drug.

EVALUATION OF BUCCAL FILM

1. Weight variation test

From each formulation, five films of similar specifications have been chosen and subjected to weight variation test as per the IP procedure using Shimadzu digital balance. The average weight of five buccal films was subtracted from individual film weight. The mean ± SD values were calculated for all the formulations.

2. Thickness variation test

From each formulation, five films were chosen, and thickness was measured at different places with the help of screw gauge. The average film thickness and standard deviation were computed.

3. Surface pH study

The surface pH of the patch was determined in order to investigate the possibility of any side effects, *in vivo.* A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.6 ± 0.2) for 15 min at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 min.

4. Content uniformity of film

To ensure uniform distribution of Ivabradine in film, a content uniformity test was performed. The film was added to 100 ml of phosphate buffer pH 6.6 contained in a 250 ml beaker, which was placed on temperature controlled magnetic stirrer maintained at 37°C. The medium was stirred at 300 rpm with a Teflon coated magnetic bead for 3 hrs. Then, the solution was filtered through 0.45 µm membrane filter, and the filtrate was examined for the drug content at 286.0 nm using UV Spectrophotometer.

5. Percentage moisture absorption and loss

The percentage moisture absorption test was carried out to ensure physical stability or integrity of buccal films. Buccal films were weighed and placed in a desiccator containing 100ml of saturated solution of aluminum chloride, and 75 ± 5% RH was maintained. After

three days, the buccal films were taken out and reweighed. The percentage moisture absorption was calculated using the formula specified below. Buccal films were weighed and kept in a desiccator containing anhydrous calcium chloride. After three days, the patches were taken out and reweighed. The percentage moisture loss was calculated using the formula.

$$\%\text{Moisture absorption} = (\text{final weight-initial weight})/ (\text{initial weight}) \times 100$$

$$\%\ \text{Moisture loss} = (\text{initial weight-final weight})/ (\text{initial weight}) \times 100$$

6. Swelling study

The purpose of measuring swelling index is to determine the ability of hydrophilic polymers used in formulation to take up water upon hydration. The hydration and swelling behavior of the polymer was reported to be crucial for its bioadhesive character, because the former is necessary to initiate intimate contact of the film with the mucosal surface. The adhesion increases with the degree of hydration until a point where over hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer tissue interface. The rate and the extent of film hydration and swelling also affect the film adhesion and consequently, the drug release from the film. The rate of swelling affects the duration of adhesion with faster swelling, resulting in adhesion of shorter duration. The present study revealed that excessive hydration (HPMC patches) can lead to a weakening of the adhesive bond due to dilution of functional groups responsible for the adhesive interaction between the bioadhesive film and mucosa.

7. Folding endurance

Films did not show any cracks even after folding for more than 300 times. Hence, it was taken as the endpoint. Folding endurance did not vary when the comparison was made between plain films and drug loaded films. Folding endurance of the film was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good film properties.

8. *In vitro* drug release studies

The patches containing Ivabradine were evaluated for *in vitro* release. As there was no official method prescribed for *in vitro* drug release study for buccal patches, a simple in house laboratory assembly was utilized simulating the conditions of oral cavity. A buccal

strip of 2 × 2 cm2 (containing 5 mg of drug) affixed with the membrane was held at the center of a microscope slide by means of cyno acrylate adhesive. The slide was placed at an angle of 45º in a 150 ml beaker containing 100 ml of pH 6.6 buffer preheated to 37ºC. The beaker was kept in water bath at 37ºC. A non agitated system was selected to eliminate any effect of turbulence on the release rate to assure that no disruption of strip occurred. Periodically samples were withdrawn and assayed for drug content by spectrophotometrically at 286 nm.

CONCLUSION

HPMC have been used and experimented as thickening agent, in controlled release systems and as a coating polymer. In addition to the listed excipient categories, HPMC polymer is now used as shell material for capsules. Two important areas where improvements have to be achieved in order to qualify the HPMC capsules ahead of gelatin capsules are in their machine ability and in the *in vitro* and *in vivo* disintegration/dissolution performances. The main area where HPMC capsules can have better prospect compared to gelatin capsules is in wider patients' preferences and the dietary sensitivities in certain markets.

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