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Formulation and Development of Two-Compartment HPMC Capsule for Concurrent Administration of Drugs

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The present study deals with the formulation of two-compartment capsule consisted of immediate release powder formulation of domperidone in the cap portion, polymer film fixed on the capsule body horizontally to create two compartments and omeprazole enteric pellets exhibiting a lag time, in the body portion. Domperidone and omeprazole, used in the treatment of gastro-esophageal reflux disease were selected as model drugs. Polymer film acted as dividing wall was made of HPMC and ethyl cellulose. It was assessed for uniformity of weight, thickness, folding endurance and tensile strength. Surface characteristic of film by scanning electron microscopy showed no cracks or pores. Evaluation tests of two-compartment capsule showed no transfer of drug in between two compartments through the polymer film. The results showed the capability of achieving two-compartment capsular system to handle varying release of solid-solid drugs in a single dosage form.

Keyword: Two compartment capsule, polymer film, HPMC capsule, enteric coated pellets.

1. Introduction

Growth in patient populations suffering from a multitude of ailments urges the need to lower the pill burden. But combining drugs with different chemistries and incompatibilities in single dosage form is difficult and unfeasible. Several recent research reports showed a constant quest for development of multi-compartment delivery device for the administration of multiple dosages to achieve patterned drug delivery by means of a plurality of individual drug delivery units.

Multi-compartment capsule has several significances such as combination of multiple release profiles like immediate, delayed, enteric, sustained and targeted dosage form, reduction of number of excipients as well as steps involved in formulation leading to consumption of less excipients. This system has many benefits to patients particularly for geriatric and pediatric populations; for handling and consumption of combined dosages than multiple capsules of actives, increase in compliance as fewer pills to be administered at all levels, decrease in the healthcare cost as the frequency of dosage consumption is reduced and administration of dosage form in correct sequence.

Gelatin, used as a material for hard capsules, is of animal origin, from either bovine bone or porcine skin [1]. Despite the fact that most of pharmaceutical capsules available in market are made of gelatin, several hydroxypropyl methyl cellulose (HPMC) capsules for powdered herbs and dietary supplements have been available in recent years. HPMC has been increasingly used for capsule manufacturing process [2]. HPMC capsules have several technical advantages over

gelatine capsules such as lower moisture content, chemical inertness and an ability to maintain mechanical integrity under very low moisture conditions [3].

Gastro-esophageal reflux disease (GERD) and non-ulcer dyspepsia (NUD) are overlapping disorders with common symptomatology with NUD. Erosive GERD is differentiated from functional dyspepsia, but there is a considerable overlap between functional dyspepsia and non-erosive reflux disease. There is a spectrum of disease with some patients having erosive esophagitis having common symptoms. The basic mechanisms underlying the spectrum are increased acid production, decreased tone of lower esophageal sphincter (LES) and disturbances in gut motility [4]. Domperidone is a dopamine antagonist with antiemetic properties, used in the treatment of nausea and vomiting. Domperidone acts by increasing lower esophageal sphincter tone and by enhancing upper gastrointestinal tract (GIT) motility and thus acts on one of the pathophysiological mechanisms of GERD [5]. Omeprazole, a proton pump inhibitor, is commonly indicated for the treatment of active duodenal ulcer (short term therapy or acute treatment), active benign gastric ulcer, gastroespohageal reflux disease (GERD), erosive esophagitis, and pathological hypersecretory conditions. Omeprazole seems to be well absorbed from the GIT. However, its oral bioavailability in humans is about 40 to 50%, suggesting a pronounced first-pass metabolism of drug before entering the systemic circulation [6]. The stability of omeprazole decreases with a corresponding decrease in the pH of the media with which it comes in contact. Therefore, exposure of omeprazole to the acidic contents of the stomach leads to significant degradation of the drug and hence reduces bioavailability [7]. To prevent acid degradation, omeprazole has been used in enteric coated dosage form. Combined therapy of omeprazole and domperidone is found to be effective in adult asthmatics with gastroesophageal reflux by reducing asthma symptoms, rescuing medication use and improving pulmonary function [8]. Combination of hydroxypropyl methylcellulose (HPMC E-15) and ethyl cellulose (Surelease® NG, E-7-1905) polymers was selected for formulating a polymeric film of two-compartment capsule [9]. Ethyl cellulose is odorless, tasteless and exhibits a high degree of stability not only under physiological conditions but also under normal storage conditions. Presence of plasticizer in polymeric solution increases free volume between the polymer chains by reducing the number of active centers available for rigid polymer-polymer contacts.

In the present research, two-compartment capsule system was engineered by inserting horizontally the dividing wall made up of polymer film in between cap and body of HPMC capsule shell. This polymer film acted as a barrier to cordon a line of separate compartments within a single encapsulating shell, covering the combination of powder formulation of domperidone and enteric coated pellets of omeprazole, used as model drugs in a single capsule.

2. Materials and Methods

Omeprazole and domperidone drugs were provided by Natco Pharma Ltd., India. Omeprazole pellets and ethyl cellulose (Surelease® NG, E-7-1905) was kindly supplied by Aashi Industrial Ltd., Mumbai, India and Colorcon Asia Pvt. Ltd., Goa, India, respectively. Hydroxypropyl methylcellulose capsule shells were gifted by Associated Capsules Group, Mumbai, India.

2.1 Preparation of dispersion of polymer film

An aqueous dispersion of Surelease® was diluted to 15% w/v with distilled water. Similarly, 5% aqueous solution of HPMC E15 was prepared by dispersing the powder in preheated water (80-90 ºC) and then diluting it with additional cold water. Both the solutions were blended in the ratio of 8:2 adding triethyl citrate as plasticizer. Dispersion was stirred continuously for 5 h and was poured into levelled flat-faced teflon plates (casting area =10x10cm). To slow down the solvent evaporation, the teflon plate was covered with a funnel. Upon evaporation of the solvent at room temperature, overnight, the film produced was peeled off from the plate and carefully cut

into film strips. Film strips were stored in desiccators at room temperature for further study.

2.2 Physical tests of polymeric film

2.2.1 Film weight and thickness

For evaluation of film weight, three films of 30mm diameter were weighed individually on a digital balance. The average weight was calculated. Similarly, thickness of the film strips was measured at five different points using a micrometer screw gauge and the mean thickness was calculated [10].

2.2.2 Folding endurance

Film of size (2x2) cm was cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times the film could be folded at the same place without breaking resulted in the value of folding endurance [11]. Test was performed in triplicate.

2.2.3 Tensile strength

Tensile strength of the film was the total weight required to break or rupture the film. This was determined by a device having rectangular frame with two plates made up of plexiglass. The one of the plate in the front was the movable part of the device and pulled by loading weights on the string, which was further connected to the second stationary plate. Polymer film of size (1x2) cm^2 was fixed between the stationary and movable plate. The force needed to fracture the film was determined by measuring the total weight loaded in the string. The weight required to break the film was taken as tensile strength of the film [12].

2.2.4 Surface topography by Scanning Electron Microscopy

To characterize the surface property of film, the scanning electron microscopy (JEOL JSM-6360A, Tokyo, Japan) was used and micrograph was taken at 1000x.

2.3 Formulation of capsule

2.3.1 Formulation of powder formulation

Weighed quantities of drug domperidone (10 mg) and the magnesium stearate (0.14 mg) were blended together to get powder formulation.

2.3.2 Characterization of powder formulation

Bulk density, Hausner ratio, Carr's index and angle of repose of powder formulation were determined to study the flow property.

2.4 Characterization of enteric coated pellets

Enteric coated pellets of omeprazole as received were characterized as follows:

2.4.1 Size distribution of pellets

Size of the enteric coated pellets was determined by sieve shaker analysis. Sieves of different sizes # 20(840 µm), #18(1000 µm) and #16(1190 µm) and #14(1410 µm) were placed on mechanical shaker for 20 min. Particles retained on all sieves were collected and average pellets size was determined.

2.4.2 Assessment of acid uptake and disintegration test of pellets

Acid uptake evaluation provides an indication of the ability of the enteric coating to protect the active from the effects of gastric fluid. For acid uptake test, the weighed quantity of enteric coated omeprazole pellets (n=3) were placed in disintegration apparatus (Electrolab ED 2L) in 900 ml of 0.1N HCl at 37±0.5 °C, and acetate buffer (pH 4.5). The amount of media taken up by the coated pellet was determined by calculating the percent difference between pellet weight before and after exposure to media for 2h.

Percent acid uptake (%) = [(Tf – Ti)/Ti] x 100

Tf: Final weight (mg) Ti: Initial weight (mg)

2.4.3 Drug content

Enteric omeprazole pellets (400 mg) were triturated to form powder. Accurately weighed quantity of the powdered pellets equivalent to

50 mg of omeprazole, was put in 70 ml of 0.1M sodium hydroxide and mixed in ultrasonic bath for about 5 min. After suitable dilution, resulting solution was analysed at 305 nm by UV spectrophotometer (UV-1601, Shimadzu, Japan).

2.4.4 Flow property

Bulk density, Hausner ratio, Carr's index and angle of repose were determined to study the flow property of pellets. All the properties were performed in triplicate.

2.5 Formation of two-compartments, filling and sealing of HPMC capsule

Size '0' HPMC capsule was separated into cap and body. Enteric omeprazole pellets were filled in the capsule's body (lower compartment). Polymeric film was cut circular with slightly greater circumference of the capsule body. The film was kept horizontally on the body of the capsule and slightly pressed inside body portion. The edge of the polymer film was fixed to the circumference of capsule body by applying paraffin wax. Immediate release domperidone powder was filled in the capsule's cap (upper compartment). The cap was placed on the body taking care not to lose any of the material in the cap or to disrupt the film on the capsule body.

2.6 Evaluation of two-compartment capsule

2.6.1 Partition film strength test

Partition film strength test of two-compartment capsule concerned the strength of the film fixed between the cap and body portion of the capsule to retain its integrity during packing, transport and storage. For this, capsules were placed in the Roche friabilator and rotated 100 times. Capsules were removed from the drum and opened carefully to check the presence of intact film. Also, both the compartments (cap and body) were analyzed to check any transfer of drug, intermittently. The upper and lower compartments were analyzed for the contents of domperidone or omeprazole, respectively using simultaneous estimation of the drugs. Mixed standards of domperidone or omeprazole were scanned using sampling points at 286nm and 305 nm. Overlain spectra of the five mixed standards were used to determine the concentration of two drugs in either compartments of capsule [13]. From the concentrations, the amount of drug was calculated.

2.6.2 *In vitro* release study

Drug release of two-compartment capsule was assessed by *in vitro* dissolution test under the following conditions: USP type II dissolution apparatus at 50 rpm in 900 ml of 0.1 N HCl (pH 1.2) for first 2h followed by 900 ml of phosphate buffer (pH 6.8) maintained at 37±0.5 ºC. Aliquots equivalent to 5 ml of the sample was withdrawn at regular intervals and replaced with the same volume of prewarmed (37±0.5 °C) fresh dissolution medium. Drug content in powder formulation and enteric coated pellets was analyzed for domperidone and omeprazole after suitable dilution at 286 nm and 305 nm, respectively, using a UV spectrophotometer.

2.7 Stability testing

Accelerated stability study of two-compartment capsule was performed at the 40±2 °C and 75±5% RH (Stability Chamber 200 L, Thermolab Scientific Equipments, India) for 6month as per the ICH guidelines. The sampling intervals were zero day, 15 days, one month, two month, three month and six month to evaluate physical appearance, drug content, transfer of drug through the film and *in vitro* release.

3. Results and Discussion

3.1 Physical tests of polymeric film

The film weight and thickness was found to be uniform. In folding endurance test, film did not develop any cracks or breaks, thus showing good folding ability required for fixing in between cap and body of the capsule. Tensile strength is the maximum stress applied to a point at which the film breaks. The risk of cracking of a film enhances increases with low tensile strength. The film was found to have good tensile strength to retain its integrity during handling to keep both the compartments intact in the capsule (Table 1). The films prepared were transparent. The finding of good folding endurance was also supported by scanning electron microscopy. It showed the

irregular surface of the film without any pores or cracks on it. This prevented the transfer of drug formulation from one compartment to other (Figure 1).

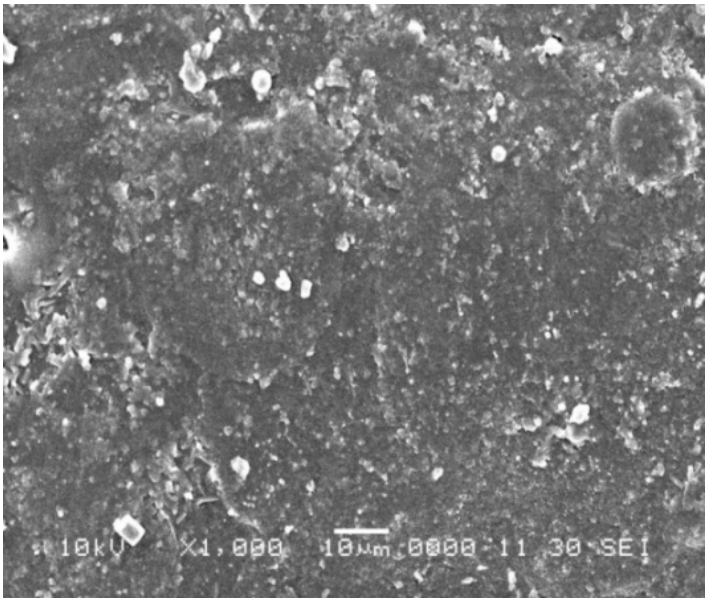

Fig 1: Scanning Electron Microscopy of polymer Film

Table 1: Physical tests of polymeric film

S. N	Physical Parameters	Observation
1.	Film weight (mg)	40.0±1.8 to 56.0±0.7
2.	Film thickness (mm)	0.24±0.02 to 0.28±0.03
3.	Tensile strength (g/cm^2)	113.6±1.3 to 116.8±1.7
4.	Folding endurance	181.3±4.2 to 184.8±3.6

Mean ± SD, n=3

3.2 Characterization of powder formulation and pellets

Size distribution of enteric coated pellets was found to be 850-1100 nm. Drug content of enteric coated omeprazole pellets was found to be 8.5±0.2%. Bulk density, Hausner ratio, Carr's index and angle of repose of domperidone powder formulation and omeprazole enteric coated pellets indicated good flow properties (Table 2).

Table 2: Characterization of formulations

Parameters	Powder formulation	Enteric pellets
Bulk density (g/ml)	0.67±0.02	0.53±0.03
Hausner ratio	1.06	1.17
Carr's index (%)	21.0±1.1	16.0±0.5
Angle of repose (°)	27.0±0.1	29.0±0.4

Mean ± SD, n=3

3.3 Assessment of acid uptake and disintegration test of pellets

The higher acid uptake attributes to rapid solubility of the enteric polymer. Low acid uptake at higher enteric coating thickness can be explained by the longer time required to dissolve a thicker film. Acid uptake of enteric coated omeprazole pellets was found to be 8% with disintegration time of 26 min.

3.4 Evaluation of two-compartment capsule

3.4.1 Partition film strength test

The polymer film was fixed horizontally on body of the capsule. Polymer film was not fractured or cracked when tumbled in the friabilator confirming the intact two separate compartments in the capsule. Simultaneous estimation of both the drugs in either compartment showed no drug transfer through the film or along the circumference in between the two compartments (Table 3). This confirmed the strength and leak test of the film.

Table 3: Simultaneous estimation of drugs in capsule compartments

Compartment of capsule	Amount of drug in (mg)	
	Omeprazole	Domperidone
Capsule's body (Enteric pellets)	9.98 ± 0.11	0.0
Capsule's cap (Powder formulation)	0.0	9.91 ± 0.21

Mean ± SD, n=3

3.4.2 *In vitro* dissolution study

In vitro dissolution study of two-compartment capsule formulation in 0.1N HCl released the domperidone powder formulation present in the cap of the capsule, simultaneously releasing the enteric pellets from the body of the capsule. Polymeric film present on the body of the capsule also got separated from the capsule portion. Results of the dissolution test showed more than 90% domperidone release in 40 min. While, the enteric coated pellets released very less amount of omeprazole (less than 3%) showing lag time in first two hours in acidic media followed by 90% of drug release at the intestinal pH 6.8 within next 25 min (Figure 2).

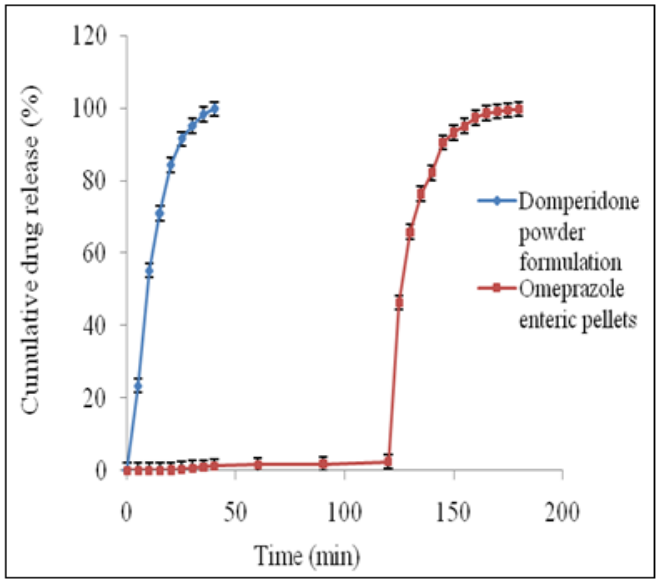

Fig 2: *In vitro* drug release profiles of two-compartment capsule. Mean (n=3)

3.5 Stability study

Physical appearance of two-compartment capsule did not change after subjecting to the accelerated stability conditions for six months. No drug was transferred through the film in between the two compartments confirming the strength and leak test of the film. The samples did not show much difference in dissolution of drug release profiles indicated by the unchanged release pattern. All these parameters reflected the stability of two-compartment capsule.

4. Conclusion

The current study successfully attained the development of two-compartment capsule in a single capsule to overcome the problem of gastric damage (GERD) by immediate release powder formulation of domperidone and enteric coated pellets of omeprazole. The two-compartment capsular system by virtue of its design and composition provided a robust formulation to handle solid-solid drugs in a single dosage form. Appropriate selection of drugs in hydroxypropyl methyl cellulose capsule can be used to develop two-compartment capsule via a simple, efficient, and economical unit operation for benefits of patients especially for geriatric and pediatric populations, ultimately reducing the health care cost. Thus, a hydroxypropyl methyl cellulose capsule based two-compartment drug delivery system has been a suitable choice for different release rates of drugs such as immediate release powder and enteric release of pellets.

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