PHARMA RESEARCH BULLETIN
Journal Home Page : www.eduspread.com

*Research Article*

ISSN: 2582-676X

# Formulation & Evaluation of Controlled Porosity Osmotic Pump of Mebeverine Hydrochloride for Colon Specific Drug Delivery

**Vishal Sapra*[1], Kumar Guarve[2], Sandeep Kumar[3], Priyanka Kriplani[2]**

*[1]Akorn Pharmaceuticals, Paonta Sahib-173025, Himachal Pradesh, India.*
*[2]Guru Gobind Singh College of Pharmacy, Yamuna Nagar-135001, Haryana, India.*
*[3]Department of Pharmaceutics, ASBASJS Memorial College of Pharmacy, Bela-140111, Ropar, Punjab.*

**Article History:**

Received: 17 April 2020
Revised: 18 May 2020
Accepted: 20 May 2020

**How to Cite:**

Sapra V, Guarve K, Kumar S, Kriplani P. Formulation & Evaluation of Controlled Porosity Osmotic Pump of Mebeverine Hydrochloride for Colon Specific Drug Delivery. PRB, 2020;2(1):20-36.

**Abstract:**

In the present paper, controlled release formulation of mebeverine hydrochloride was developed with an objective to achieve colon specific drug delivery with reduced frequency of dosing, to minimize gastric side effects and thus to increase patient compliance. The study includes a microbially triggered colon targeted controlled porosity osmotic pump, which was prepared in the form of a tablet containing drug and other excipients, spray coated with cellulose acetate solutions with varying amount of guar gum as pore former, the amount and nature of plasticizing agents. The coated core tablet was then further coated with enteric layer to protect the device from acidic environment of stomach. The effect of various formulation variables namely the level of solubility modifier in core, level of hydrophilic and hydrophobic plasticizers in semipermeable membrane, level of pore former in semipermeable membrane, concentration of cellulose acetate in semipermeable membrane coating layer have been studied. The drug release from the developed formulations was found inversely proportional to the level of solubility modulating agent in core compartment, hydrophobic plasticizers in semipermeable membrane and concentration of cellulose acetate in semipermeable membrane. As the proportion of guar gum was increased in coating solution, decrease in release rate of drug in small intestine and increase in release rate in colon was observed. The present results confirmed that the membrane controlling factors responsible for the drug release were the amount of pore former, the amount and nature plasticizers in the membrane.

**Keywords:** Guar gum, Colon targeting, Mebeverine hydrochloride, Solubility modifier, MAP-CT-OT.

## Introduction:

The expenses for developing new drugs are exorbitant. Thus in the present scenario, more stress is laid to develop newer drug delivery technologies which would ensure better patient compliance drug efficacy and extends the term of patents of the existing molecules. In this contemporary era, the pharmaceutical industry is facing several challenges due to worldwide cut through competition and growing demand for better products.

**Corresponding Author: Sapra V,** Akorn Pharmaceuticals, Paonta Sahib-173025, Himachal Pradesh, India.

In the area of targeted delivery, the colonic region of the GI tract is the one that has been accepted with enthusiasm by scientists and is being extensively investigated over the past two decades [1]. The colon specific diseases are often poorly and inefficiently managed by oral therapy because most orally administered drugs, including anti-inflammatory drugs, chemotherapeutic drugs and anti-cancer drugs, are absorbed before reaching to their colon target site. In addition the colon is considered to be a preferable site for the absorption of oral protein drugs, because the hydrolytic enzyme activity of the colon is lower than that of the small intestine [2]. The irritable bowel syndrome (IBS) is one of the most frequently encountered disorders of the GIT among young to middle age adults is often localized to specific sites in the gastrointestinal tract (GIT) [3]. As a result, this disorder can be treated with oral site-specific (targeted) drug delivery systems. Targeted delivery systems for treatment of IBS are designed to increase local tissue concentrations of drugs from lower doses compared with systemic administration.

IBS presents a challenging target for drug delivery, particularly by the oral route, as, contrary to most therapeutic regimens, minimal systemic absorption and maximal intestinal wall drug levels are desired [4]. Therefore, it appears that targeted drug delivery with an appropriate controlled-release pattern could be crucial in providing effective therapy for this colonic disease. Several delivery strategies are employed to achieve this goal, include time-controlled delivery systems, pH-dependent delivery systems, pressure controlled delivery systems, prodrugs and microflora-triggered delivery systems [5]. Polysaccharide-based delivery systems depend on the enzymatic degradation carried out by the inherent bacterial flora present in the colon, thereby resulting in drug release. The enzyme trigger mechanism in such delivery systems makes them highly site-specific [6].

Mebeverine hydrochloride is the most prescribed product currently available for the treatment of irritable bowel syndrome (IBS). It acts as musculotropic antispasmodic agent with a direct action on the smooth muscle of gastrointestinal tract (GIT) especially of the colon, relieving spasm without effecting normal gut motility [7]. It is not a specific anticholinergic therefore it does not cause the unwanted effects such as dry mouth, blurred vision and difficulty with micturition typical of many other anticholinergic spasmolytic compounds [8]. The anti spasmodic drug mebeverine hydrochloride exerts a local anesthetic action by blocking voltage operated sodium channels, an action similar to lidocane. Although mebeverine hydrochloride has been used p.o. in the symptomatic treatment of bowel disturbances and intestinal discomfort related to irritable bowel syndrome. On the contrary to other local anesthetics mebeverine hydrochloride was reported to have nonsignificant central or peripheral side effects. Moreover, it has shown rapid and facile hydrolysis on reaching circulation. Little is known about its pathogenesis; meanwhile several studies have proved the efficacy of mebeverine hydrochloride in the treatment of IBS when taken at a dose of 135 mg three to four times daily. However, MB-HCl suffers from extensive first pass metabolism in the gut wall and liver. High plasma concentrations of veratric acid (one of the main inactive metabolites of MB-HCl) in addition to negligible amounts of the parent drug were observed in plasma 20-30 minutes after oral administration [3]. As pharmacokinetic profile of mebeverine hydrochloride indicates that the drug is completely and promptly absorbed after oral administration and not reaches to colon for local action. Its short biological half-life and thus frequent administration (usually thrice a day) and high water solubility makes it challenging candidate for controlled release preparation.

Conventional tablets are absorbed from the stomach, side effects like nausea, metallic taste, vomiting and headache are observed. Therefore targeting the drug specifically to the colon is advantageous in treatment of diseases such as amoebiasis, crohn's disease, ulcerative colitis and colorectal cancer. In the last decade, numerous clinical and animals studies have provided convincing evidence that pharmacokinetics and/or drug's effects-side effects can be modified by the circadian time and/or timing of the drug application within 24 hrs of a day [9]. Majority of per oral dosage form fall in the category of matrix and osmotic system. Matrix devices made with cellulose or acrylic acid derivatives, which release the homogeneously dispersed drug based on the penetration of water through the matrix, have gained steady popularity because of their simplicity in design. The drawback of matrix-type delivery systems is their first-order drug delivery mechanism caused by changing surface area and drug diffusion path length with time. This drawback has been addressed by osmotic delivery systems, which maintain a zero-order drug release irrespective of the pH and hydrodynamics of the GI tract [10]. Osmotic systems utilize the principle of osmotic pumping for the delivery of drugs. Various types of osmotic pumps and formulation aspects have been reviewed. Osmotic pump which was patented as OROS-CT has already been established to target the drug locally to the colon for local or systemic therapy. OROS-CT was designed with a 3–4 h post-gastric delay to prevent drug delivery in the small intestine.

Drug release begins when the unit reaches the colon. This system was essentially a time-controlled release system. Even through the transit time in small intestine is rather consistent, high variation of gastric retention time makes this system complicated in predicting the accurate location of drug release [11]. Keeping in view all these considerations, we planned to improve poor site-specificity by designing a novel device (MAP-CT-OT), combination of three approaches like pH-dependent, solubility modulation, microbially triggered osmotically controlled system. **Figure 1** shows schematic diagram of MAP-CT-OT, which consists of an osmotic core (containing drug and sodium bi carbonate with excipients), first semipermeable membrane layer on core tablet composed of the mixture of cellulose acetate and guar gum as natural polysaccharide and second layer consist of enteric polymer with S-100 base. During its transit through the GI tract, MAP-CT-OT remains intact in the stomach due to the presence of enteric-coating layer, but this layer will dissolve in the small intestine, where pH is above 7, and water is imbibed into the core. However, the drug is still not released in small intestine because the presence of solubility modifier (sodium bicarbonate) in core compartment and pore former (guar gum) in the semipermeable membrane is not degraded by aerobic bacteria of small intestine. When (MAP-CT-OT) reaches the colon, guar gum (pore former) in the semipermeable membrane is specifically degraded by microflora of the colon and thereby results in an in situ formation of a delivery pores. The solution of drug is delivered from these delivery pores at a relatively constant release rate for up to 24 h in the colon. The objective of the study was to develop controlled porosity osmotic pump of highly water soluble drug mebeverine hydrochloride for colon targeting using guar gum as a pore forming agent and sodium bicarbonate as solubility modifying agent.


**Uncoated tablet** **First coating layer** **Second coating layer**

**Figure 1: Formulation of MAP-CT-OT**

## Materials & Methods:

### Drugs and Chemicals:

Materials used included mebeverine hydrochloride (MB-HCL), which was kindly provided as a gift sample by Rantus Pharmaceuticals Pvt. Ltd. (Hyderabad). Following excipients and chemicals were purchased from commercial sources and used as such: guar gum and sodium bicarbonate was obtained from S.D fine chemicals Ltd. (Mumbai, India), cellulose acetate 39.8% acetylation from G.M Chemicals (Mumbai, India), Acetone from Qualigens fine Chemical (Mumbai, India), Iso propyl alcohol from Alliancz Poly Chem. and Overseas Ltd, Galactomannanase and Pancreatin from Niche Marketing (Delhi, India), Pepsin from Biocon Limited (Banglore, India) Methylene dichloride from Gujrat Alkalies and Chem. Ltd (Baroda, India), talc and magnesium stearate from Central Drug House Pvt. Ltd. (Mumbai, India), Starch from Bharat Starch Industries (Yamuna Nagar, India), Lactose from R.M.A Chemical (Faridabad, India), PVP K-30 from CDH (Delhi, India) polyethylene glycol (PEG-400) N.B. Pharma Pvt. Ltd. (Yamuna Nagar, India ) and Di butyl phthalate was obtained from Merck Chemicals (Mumbai, India). All other chemicals were of analytical grade.

### Drug excipients interaction study:

Before initiating formulation development, compatibility of mebeverine hydrochloride with different excipients was tested by using the techniques such as FT-IR (Perkin Elmer 1600) and DSC (Shimadzu Japan).

**i) Fourier transforms Infrared spectroscopy:**

The Fourier transform infra-red analysis was conducted for the structural characterization. FTIR of pure drug, polymers, and their physical mixtures were recorded. Samples were taken in a KBr pellet using FTIR instrument.

**ii) Differential scanning calorimetry:**

In this technique, the difference in energy inputs into a substance and reference material is measured as a function of temperature as the specimens are subjected to controlled temperature program. Samples were heated in an open aluminum pans at a rate of 10 °C $min^{-1}$ in a 0 °C to 350 °C temperature range under a nitrogen flow of 40 ml/min.

**Determination of solubility of mebeverine HCl with sodium bicarbonate:**

100 mg of mebeverine hydrochloride was added to 10 ml of water in conical flask containing different concentration of sodium bicarbonate (0-200 mg). Then the suspensions were shaken at 37° C. After equilibrium is attained, the supernatant liquid was withdrawn filtered through 0.45 µm membrane filter, appropriately diluted and analyzed for mebeverine hydrochloride.

**Formulation and Characterization of blends:**

All the ingredients like drug, solubility modifier and excipients were co-grounded in mortar & pestle (except talc and magnesium stereate) and after wet granulation by solvent methylene dichloride, the dried mass were passed through mesh no. 40. Finally talc and magnesium stearate were added and mixed for 10 min. The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. The characterization of mixed blend was performed for the evaluation of flow properties of powder that are hausner's ratio, compressibility index and angle of repose as standard values shown in **Table 1** [12].

**Table 1.** Standard values of angle of repose, carr's index and hausner's ratio as an indication of powder flow properties.

| Carr's index | Hausner's ratio | Angle of repose | Type of flow |
|---|---|---|---|
| 15-21 | - | <20 | Excellent |
| 12-16 | <1.25 | 20-30 | Good |
| 18-21 | - | 30-40 | Fair to passable |
| 23-35 | >1.25 | - | Poor |
| 33-38 | 1.25-1.5 | - | Very poor |
| >40 | - | >40 | Extremely poor |

## Preparation of core tablets:

**Granulation and punching:**

The core tablet of mebeverine hydrochloride was prepared by wet granulation technique. The drug, solubility modifier and diluents were weighed accurately and mixed properly. This mass was granulated by wet granulation method using methylene dichloride as granulating solvent and PVP K-30 (25% *w/w* of drug) was used as a binder. The wet mass was passed through 14 mesh sieve and dried to evaporate the solvent. Dried mass was passed through 16 mesh sieve. Sufficient concentration of magnesium stearate and talcum of I.P grade were added as lubricant and glidant respectively. Compression was done on a single punch tablet machine (Dhiman, India) using 9.0 mm standard concave punches [13].

**Formulations and preparation of first semipermeable membrane layer:**

Cellulose acetate in acetone and isopropyl alcohol (solvent mixture) containing different levels of pore forming agent (guar gum) was used as coating formulation as shown in **Table 2**. The weight gains of micro-porous semipermeable membrane were 3 % and 5 % respectively. PEG 400 and DBT were acted as hydrophilic and hydrophobic plasticizers respectively. They were used to enhance the physical-mechanical property of CA membrane. The coating was performed in Stainless steel pan of 20 cm diameter with 3 baffles. Continuous stirring was performed throughout coating process to avoid sedimentation of guar gum in solution.

**Table 2.** Composition of semipermeable membrane coating solution with different level of pore former

| Ingredients | Coating Solutions | | | | |
|---|---|---|---|---|---|
| | **A** | **B** | **C** | **D** | **E** |
| Cellulose acetate (*w/v*) | 3% | 3% | 5% | 5% | 5% |
| Solvent system (Acetone/IPA) | 90/10 | 90/10 | 90/10 | 90/10 | 90/10 |
| PEG-400 (*w/w* of CA) | 10% | - | - | - | - |
| DBT (*w/w* of CA) | - | 10% | 15% | 15% | 15% |
| Guar gum (*w/w* of CA) | 20% | 20% | 20% | 30% | 40% |

**Coating conditions:**

i) Rotation rate of the pan was kept at 20 rpm.
ii) Spray rate 4-5 ml/min.
iii) Spray pressure was kept at 2 bars.
iv) Air inlet temperature was kept at 38-42 °C.

After coating the tablets were dried for 10 h at 50 °C before further evaluation.

**Formulation and preparation of enteric coating layer:**

Pan-coating system was adopted to apply the enteric coat layer. The enteric layer was applied to the core already encased by the semipermeable membrane by using the suitable conventional air spray pan coating system. The enteric coat material comprised 8 % by the weight of total core. The enteric coating composition was formulated with plasticizer PEG-400 (15% *w/w* of polymer concentration) acted as hydrophilic polymer and also utilized to enhance the mechanical strength of layer. Appropriate concentration of talcum was added to provide smooth flow of solution from nozzle of spray gun. The tablet mass was kept at 40 °C for 10 minutes while the pan rotated at 10 rpm. The rotating speed was then increased to 15 rpm and coating solution was sprayed at a rate of approximately 5 grams/minute. The composition of enteric coating solution is shown in **Table 3**.

**Table 3.** Composition of enteric coating solution

| **Ingredients** | **EC1** |
|---|---|
| Colon coat S-100 | 8% |
| Solvents (IPA: Acetone in *w/w*) | 60:40 |
| PEG-400 (*w/w* of polymer ) | 15% |
| Talc (*w/w* of polymer) | 20% |
| Titanium di oxide | 2% |
| Sun set yellow (lake) | 1% |

**Spraying parameters:**

i) Inlet air pressure was adjusted to 2-3 bar.
ii) Bed temperature was kept at 30 °C - 40 °C.
iii) Inlet air temperature was maintained at 50 °C to 60 °C respectively.

The process was continued until the whole solution was sprayed on to the tablets and sufficient layer was formed. It was checked manually to break the tablet and observe the formed layer. Thereafter the tablets were dried at 40 °C for one hour to remove the residual solvent. The continuous stirring was performed throughout the coating process. The composition of osmotic tablets of mebeverine hydrochloride is shown in **Table 4**.

**Table 4.** Composition of osmotic tablets of mebeverine hydrochloride

| Ingredients | Formulation codes | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **S1** | **S2** | **S3** | **S4** | **S5** | **S6F1** | **S7F2** | **S8F3** | **S9F4** |
| MB-HCL | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| $NaHCO_3$ | 0 | 0 | 0 | 0 | 0 | 25 | 50 | 75 | 100 |
| Starch | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 50 | 25 |
| Lactose | 129 | 129 | 129 | 129 | 129 | 104 | 104 | 104 | 104 |
| Talcum | 14 | 14 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| Mag. Stearate | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| SPM coating | A | B | C | D | E | E | E | E | E |
| Enteric coating | EC1 | EC1 | EC1 | EC1 | EC1 | EC1 | EC1 | EC1 | EC1 |

**Preparation of *in-vitro* dissolution fluids:**
**i) Preparation of simulated gastric fluid:**

Dissolved 2 gm of sodium chloride and 3.2 gm purified pepsin i.e. derived from porcine stomach mucosa with an activity of 800 to 2500 unit/mg of protein in 7 ml of hydrochloric acid and sufficient quantity of water to make 1000ml. This test solution was adjusted to pH of about 1.2 [6].

**ii) Preparation of simulated intestinal fluid:**

Dissolved 6.8 gm of monobasic potassium phosphate in 250 ml of distilled water, mixed and added 77 ml of 0.2N sodium hydroxide and 500 ml of distilled water. Added 10 gm of pancreatin and mixed and adjusted resulting solution with either 0.2 N sodium hydroxide or 0.2N hydrochloric acid to a pH of 7.4 ± and diluted it with distilled water to 1000 ml [6].

**iii) Preparation of simulated colonic fluid with rat caecal medium:**

To assess the suceptibility of guar gum being acted upon by the colonic bacteria, drug release studies were carried out in the presence of rat caecal contents because of the similarity with human intestinal microflora. In order to induce enzymes specifically acting on guar gum in the caecum, healthy albino rats (Wistar strain) of either sex or weighing between 150 and 200 g and maintained on normal diet were incubated with teflon tubing and 1 ml of 2% *w/v* dispersion of guar gum in water was administered directly into the stomach. The tubing was removed and this treatment was continued for 7 days. Thirty minutes before the commencement of drug release studies, three rats were killed by spinal traction. The abdomen were opened, the caecai were isolated, ligated at both ends, cut loose and immediately transferred into pH 6.8 phosphate buffer saline previously bubbled with $CO_2$. The caecal bags were opened the contents were weighed, pooled and then suspended in phosphate buffer saline pH 6.8 to gave a final caecal dilution of 4% w/v, which was used as simulated colonic fluid. As the caecum is naturally anaerobic all these operations were carried out under $CO_2$ [14]. The animals were procured from National Institute of Pharmaceutical Education and Research (NIPER, Mohali, India) and housed in the Central animal house at ASBASJSM College of Pharmacy, Bela. Specific and environmental conditions were strictly monitored. The

research protocol of the animal experimentation was approved by the Institutional Animal Ethics Committee of CPCSEA, India.

***In vitro* drug release study:**

The developed formulations of mebeverine hydrochloride were subjected to *in-vitro* drug release studies. These studies were carried out using a USP XXIV dissolution rate test apparatus (Apparatus 1, 50 rpm, 37 °C) (Lab India USP). The tablets were tested for drug release for 2 h in simulated gastric fluid (SGF) (pH 1.2, 900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with simulated intestinal fluid (SIF) (phosphate buffer pH 7.4, 900 ml) and tested for drug release for 4 h as the average small intestinal transit time is about 4 h. Then the dissolution medium was further replaced with 100 ml only of (SCF) simulated colonic fluid (pH 6.8 phosphate buffer saline containing 4% *w/v* of rat caecal contents) contained in 200 ml beaker and immersed in water maintained in 900 ml vessel, which in turn was in the water bath of the apparatus [15]. The experiment was carried out with continuous $CO_2$ supply into the beaker. Dissolution in the caecal content media was carried out till completion of 24 h. At various time intervals, 5 ml of the dissolution sample was withdrawn without a pre-filter. The samples were centrifuged and the supernatant filtered through a 0.45-mm membrane filter and the filtrate was analyzed for MB-HCL at 263nm by using a double beam UV spectrophotometer.

**Comparative drug release studies:**

For simplifying the *in-vitro* drug release procedure, it was preferred to use the enzyme produced by colonic bacterial microflora which is responsible for degradation of polysaccharides. For that purpose, the pH was adjusted at 6.8 and galactomannanase, which is an enzyme produced by bacteria present in the colon, was added at a concentration of 0.1% in the last 2 h. Three ml samples were withdrawn every 1h and replaced by fresh aliquots of the medium. The MB-HCl concentration in each sample was determined using UV-spectrophotometer at λ max 263nm. A comparative drug release studies was also performed for conventional market product (Sugar coated tablet of mebeverine hydrochloride) with that of MAP-CT-OT (S9F4) tablet.

**Kinetics of drug release:**

*In-vitro* drug release data were fitted to various release kinetic models viz. Zero-order, First-order and Higuchi matrix model employing the following set of equations [16].

| | | |
|---|---|---|
| a) Zero order | % R = Kt | Eq. 7 |
| b) First order | Log % unreleased = Kt/ 2.303 | Eq. 8 |
| c) (Higuchi matrix) | % R = Kt 0.5 | Eq. 9 |

**Stability studies:**

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

As per ICH Q1AR2 guideline, a drug substance in general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and if applicable its sensitivity to moisture. Selected formulation of MAP-CT-OT (S9F4) tablets were stored in amber-colored glass bottles and subjected to accelerated stability studies at 40 °C ± 2 °C and 75% ± 5% RH for four weeks in a stability chamber (Stability Oven, Nirmal Instruments, Delhi, India) [17]. Release profiles were compared using model independent pair wise approach, which include the calculation of 'difference factor' f1 and 'similarity factor' f2. The two release profiles were considered to be similar if f1 value was lower than 15 (between 0 to 15) and f2 value was more than 50 (between 50 to 100). Difference factor f1 can be calculated as:

$$f_1 = \frac{\sum_{j=1}^{n}[Rj - Tj]}{\sum_{j=1}^{n}(Rj + Tj)/2} \times 100 \qquad Eq.10$$

Where n is the sampling number, Rj and Tj are the percent dissolved of the reference and test products at each time point j. The percent error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles.

The similarity factor (f 2) is a logarithmic transformation of the sum-squared error of differences between the test Tj and reference products Rj over all time points [18].

$$f_2 = 50 \times \log\left\{\left[1+(1/n)\sum_{j=1}^{n} wj\,(Rj-Tj)^2\right]^{-0.5} \times 100\right\} \qquad Eq.11$$

Where Wj is an optional weight factor.

## Results and Discussion:

**Drug excipients interaction study**:

**i) Fourier transforms Infrared spectroscopy:**

The characteristic peaks of mebeverine hydrochloride as reported in Clark's analysis of drugs and poisons were observed in the spectrum at 1718.16 $cm^{-1}$, 1560.26 $cm^{-1}$, 1132.84 $cm^{-1}$, 1291.94 $cm^{-1}$ and 1221.23 $cm^{-1}$ in sample spectra corresponding to the functional groups C=O, COOH, C-C and C-O. The peaks observed in FTIR of physical mixture of mebeverine hydrochloride and sodium bicarbonate were 1718.62 $cm^{-1}$, 1514.79 $cm^{-1}$, 1132.90 $cm^{-1}$ and 1269.79$cm^{-1}$ respectively for the above mentioned functional group.

The peaks observed in FTIR of physical mixture of mebeverine hydrochloride and guar gum were 1718.21 $cm^{-1}$, 1560.29 $cm^{-1}$, 1132.78 $cm^{-1}$ 1264.56 $cm^{-1}$ and 1220.74$cm^{-1}$ respectively. From the above interpretation, it was understood that there was no major shifting in the frequencies of mebeverine hydrochloride which indicated that there is no chemical interaction between mebeverine hydrochloride and polymers which were used in the formulations.

**ii) Differential scanning calorimetry:**

DSC provides information about the physical properties of the sample as crystalline or amorphous nature and demonstrates a possible interaction between drug and polymers in formulations. According to the thermograms, mebeverine hydrochloride presented a sharp endothermic peak at 132.32 ºC corresponding to the melting point of the drug in the crystalline form. While the thermogram of physical mixture of mebeverine hydrochloride with polymers sodium bicarbonate and guar gum was 128.54 ºC and 131.57 ºC. Thus the thermograms of physical mixture showed that drug was in its crystalline form and also there is no interaction between the mebeverine hydrochloride and the polymers.

**Scanning electron microscopy:**

The SEM photographs of MAP-CT-OT (S9F4) were taken to show the thickness of both layers of MAP-CT-OT as shown in **Figure 2** and **3** by scanning electron microscope (JSM 6100, JEOL, Japan) with 10-k V accelerating voltage.

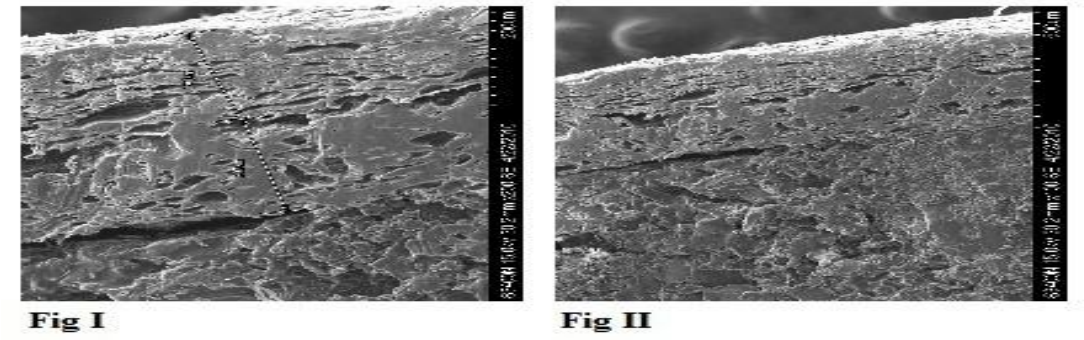


**Figure 2: SEM micrograph showing membrane thickness of both coating layers**

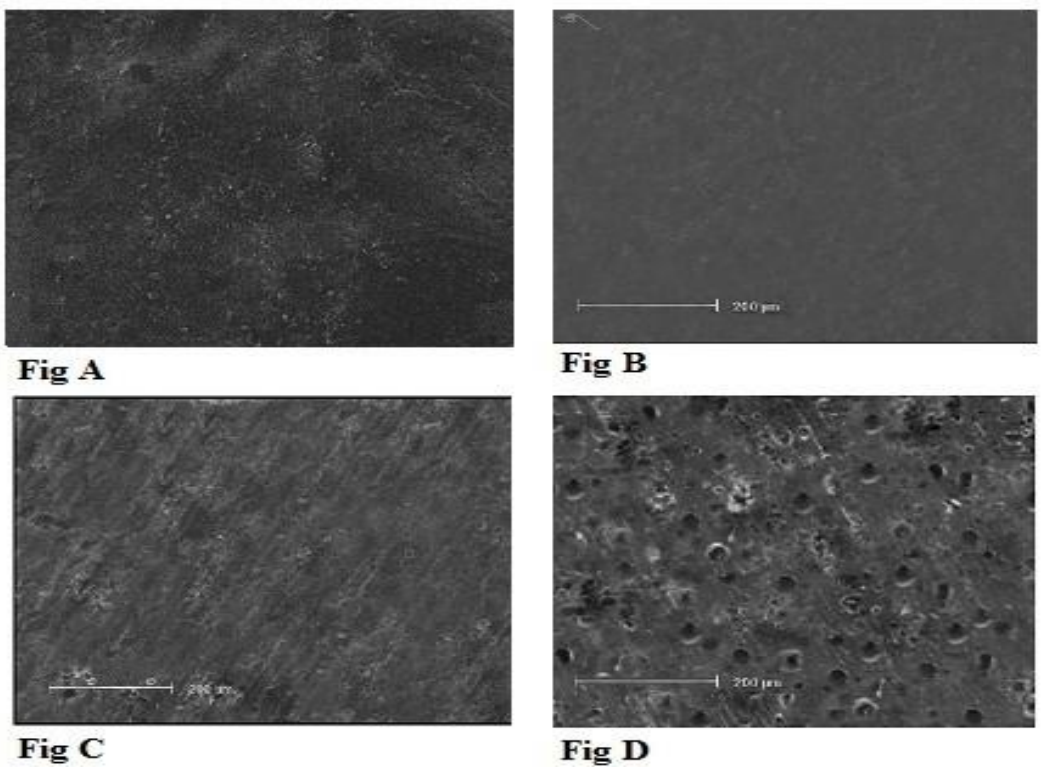


**Figure 3: SEM micrographs showing the membrane structure of formulation S9F4 (A) before dissolution study (B) after SGF dissolution (C) after SIF dissolution and (D) after SCF dissolution respectively.**

**Solubility profile of mebeverine HCl in sodium bicarbonate:**

The solubility profile of mebeverine hydrochloride is shown in **Table 5**.

**Table 5.** Solubility studies of mebeverine hydrochloride with $NaHCO_3$

| Sr. No. | Amount of $NaHCO_3$ added (mg) | Concentration (µg/ml) |
|---|---|---|
| 1 | 0 | 19.92 |
| 2 | 25 | 19.67 |
| 3 | 50 | 17.66 |
| 4 | 75 | 10.29 |
| 5 | 100 | 7.85 |
| 6 | 125 | 7.33 |
| 7 | 150 | 7.11 |
| 8 | 200 | 7.02 |

The characterization of mixed blend was performed for determination of mass volume relationship parameters. The evaluated parameters are bulk density, tapped density, hausner's ratio, compressibility index and angle of repose are given in **Table 6**.

**Table 6.** Characterization of blend

| Formulation code | Bulk density ($gm/cm^3$) | Tapped density ($gm/cm^3$) | Hausner's ratio | Carr's index (%) | Angle of repose (°) |
|---|---|---|---|---|---|
| **S5** | 0.572 ± 0.013 | 0.645 ± 0.005 | 1.117 ± 0.017 | 10.42 ± 0.004 | 24.228 ± 0.725 |

| | | | | | |
|---|---|---|---|---|---|
| **S6F1** | 0.663 ± 0.021 | 0.756 ± 0.018 | 1.142 ± 0.019 | 12.28 ± 0.015 | 24.986 ± 0.716 |
| **S7F2** | 0.612 ± 0.039 | 0.684 ± 0.052 | 1.112 ± 0.024 | 10.52 ± 0.006 | 24.218 ± 1.026 |
| **S8F3** | 0.598 ± 0.014 | 0.682 ± 0.020 | 1.132 ± 0.016 | 12.31 ± 0.018 | 21.538 ± 0.894 |
| **S9F4** | 0.586 ± 0.023 | 0.668 ± 0.040 | 1.130 ± 0.026 | 12.20 ± 0.012 | 23.295 ± 0896 |

The bulk density of mixed blend varied between 0.572 ± 0.013 to 0.663 ± 0.021 gm/cm$^3$. The tapped density was found in the range of 0.645 ± 0.005 to 0.756 ± 0.018 gm/cm$^3$. By using these two density data hausner's ratio and compressibility index was calculated. The powder blends of all formulations had hausner's ratio of 1.142 ± 0.019 or less indicating the good flowablity. The compressibility index was found to be between 10.42 ± 0.004 to 12.31 ± 0.018. The compressibility-flowability correlation data indicating a good flowability of the powder blend. The flowability of the powder was also evidenced by the angle of repose. The angle of repose is below than 30$^o$ reflecting good to excellent flow properties of powder.

After coating, the tablets were evaluated for their organoleptic (colour and taste), physical (size, shape and texture) and in-process quality control parameters (weight uniformity, thickness, hardness and friability). The surface of prepared tablet after first coating was found rough because of presence of guar gum in first coating layer. The colour of outer enteric coat layer was found sunset yellow with excellent exterior. Bitterness of un-coated tablet was also masked by coating membranes. The thickness of the tablet was found 3.18 ± 0.13 to 3.21 ± 0.16 mm. The average weight of the prepared tablet was found 374.57 ± 0.64 to 378.21 ± 0.87 mg. So it was predicted that all the tablets exhibited uniform weight with low standard deviation values within the acceptable variation as per Indian Pharmacopoeia (I.P. Vol 1. 2007). The friability of all the formulations was found to be less than 1.0%, which indicates the tablets ability to withstand abrasion in handling, packaging and shipment. The hardness of tablets varied from 5.1 ± 0.28 to 5.5 ± 0.14 kg/cm$^2$, which indicated satisfactory strength to withstand applied mechanical shocks. The drug content was found to be within the pharmacopoeial limits. The results for physical properties of all formulations are given in **Table 7**.

**Table 7.** Evaluation parameters of Tablets

| Formulation code | Weight uniformity (mg) | Thickness in (mm) | Hardness (kg/cm$^2$) | Friability (%) |
|---|---|---|---|---|
| **S5** | 377.33 ± 0.61 | 3.19 ± 0.16 | 5.3 ± 0.32 | 0.01 ± 0.01 |
| **S6F1** | 375.39 ± 0.81 | 3.20 ± 0.18 | 5.1 ± 0.28 | 0.02 ± 0.01 |
| **S7F2** | 374.57 ± 0.64 | 3.18 ± 0.13 | 5.2 ± 0.22 | 0.01 ± 0.01 |
| **S8F3** | 376.52 ± 0.82 | 3.20 ± 0.15 | 5.4 ± 0.16 | 0.02 ± 0.01 |
| **S9F4** | 378.21 ± 0.87 | 3.21 ± 0.16 | 5.5 ± 0.14 | 0.01 ± 0.01 |

The release of MB-HCl from coated (MBH-T), modified MAP-CT-OT and uncoated tablets in simulated gastric, intestinal and colonic media was investigated. **Figure 4** reveals that the release of MB-HCl from uncoated tablet was very fast about 97.84% of the drug was liberated in 1 h. This indicates that the drug is completely released in the stomach but as the drug acts selectively on the smooth muscles of the colon. It would be beneficial to formulate the drug in a colon-specific drug delivery system. The release characteristics of the coated systems revealed that the enteric coating (Colon coat S-100) prevented the drug release in simulated gastric conditions (pH1.2) in the first 2 h. In simulated intestinal fluid at (pH 7.4) high liberation of the drug was observed from S1-A as shown in **Figure 4**. At that pH 7.4, the S-100 base of enteric coat polymer was completely dissolved and the first semipermeable membrane becomes permeable. However there was a significant difference in the percent of drug released from the five initial coating formulations (A, B, C, D and E) on core tablet of mebeverine hydrochloride. As **Figure 4** shows that release rate was decreased significantly in small intestine, when changes were made in coating compositions of first semipermeable membrane of cellulose acetate as shown in **Table 8**.

**Table 8.** Drug contents in coated MB-HCL tablets and modified (MAP-CT-OT)

| Formulation code | Drug content (%) |
|---|---|
| S5 | 99.51 ± 0.0721 |
| S6F1 | 98.85 ± 0.0664 |
| S7F2 | 98.14 ± 0.0264 |
| S8F3 | 97.60 ± 0.0321 |
| S9F4 | 98.51 ± 0.0421 |

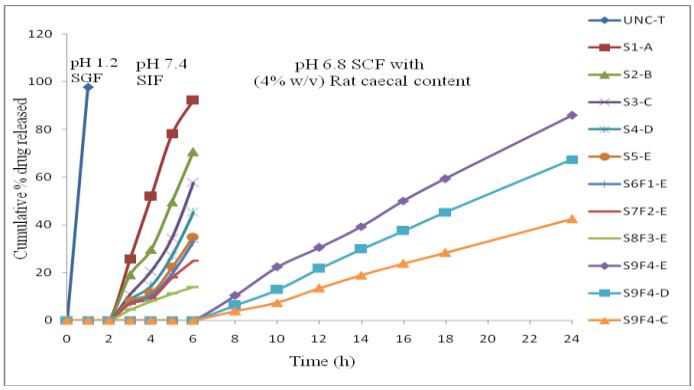


**Figure 4: Dissolution release profile of mebeverine hydrochloride from un-coated, coated and modified MAP-CT-OT formulations**

Effect of membrane variables on the drug release profile of MB-HCL was investigated. Firstly the cellulose acetate membrane was plasticized with 10% of PEG-400 in S1-A. **Figure 5** shows that this level led to an increase in drug release rate. Since PEG-400 is a hydrophilic plasticizer and after dissolution of enteric coat layer when such system came in contact with gastrointestinal milieu, PEG-400 leached out, leaving behind a micro-porous structure. The more void space was formed after leaching and as a result higher the permeability of membrane, higher the drug release rate was obtained.

In order to retard the drug release rate, another channeling agent DBT was used instead of PEG-400. From **Figure 5** it could be seen that the *in-vitro* release of S2-A was slower as compared to the formulation S1-B. The retardation of drug release was achieved due to the well-known hydrophobic nature of DBT (di butyl phthalate).

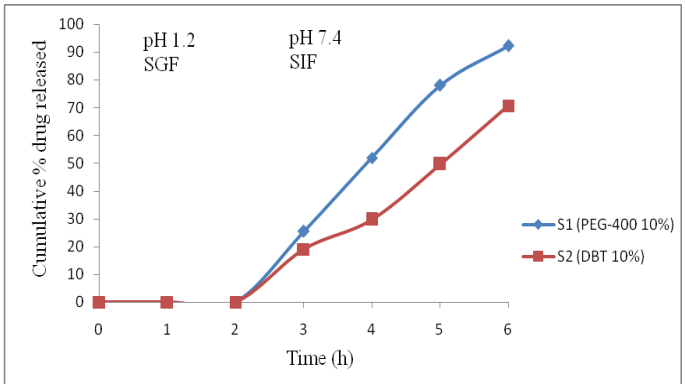


**Figure 5: Effect of plasticizing agent on cumulative (%) drug release**

The drug release rate from microporous membrane was affected by concentration of cellulose acetate in coating solution. Tablets with different concentration (3% and 5% w/v respectively) of microporous membrane were prepared to demonstrate the effect on drug release. *In-vitro* release profiles from these formulations are shown in **Figure 6**. It was evident that drug release rate decreased as the concentration of cellulose acetate in the membrane was increased.

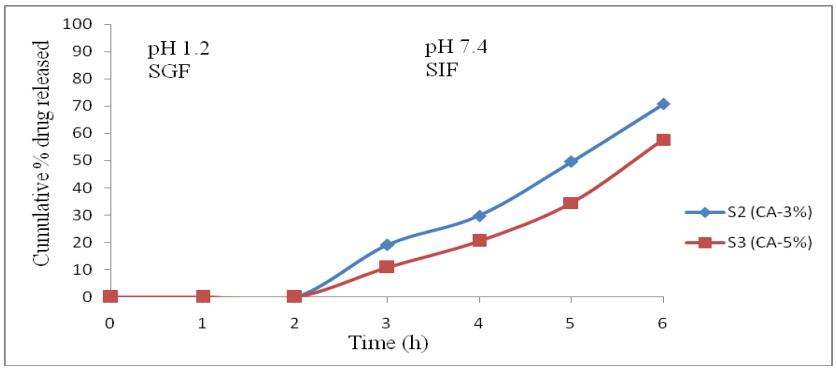


**Figure 6: Effect of concentration of cellulose acetate on cumulative % drug release**

In initial trials, core tablet of mebeverine hydrochloride coded as S1, S2, S3, S4 and S5 was coated with coating composition of A, B, C, D and E as shown in **Table 4** and enteric coated with EC1 given in **Table 3**. Result of release studies showed that 92.19%, 70.67%, 57.64%, 45.12% and 35.03% respectively of drug was delivered in 6 h or in small intestine. This phenomenon could be expected because of high solubility of mebeverine hydrochloride. To decrease the osmotic pressure of core compartment, solubility modifier sodium bicarbonate was added. This approach was also successful as there was no drug release at the end of small intestine transit time. Osmotic pumps are suitable for delivery of drugs having intermediate water solubility. It has been reported that in case of highly water soluble drugs, meaningful release rates may not be obtained using elementary osmotic pump (EOP) or controlled-porosity osmotic pump (CPOP). This is because the kinetics of osmotic drug release is directly related to solubility of drug within the core [19].

Four batches of (MAP-CT-OT) were further prepared in which concentration of sodium bicarbonate was varied. Batch S6F1, S7F2, S8F3 and S9F4 coated with SPM coating composition E and enteric coat EC1 containing 25, 50, 75 and 100 mg of sodium bicarbonate respectively were prepared. *In-vitro* release profiles of all four batches were compared with batch-S5 (core without sodium bicarbonate) and in **Figure 7** it is clearly evident that with the increase in concentration of sodium bicarbonate, there was significant decrease in rate and extent of drug release from developed formulations in small intestine.

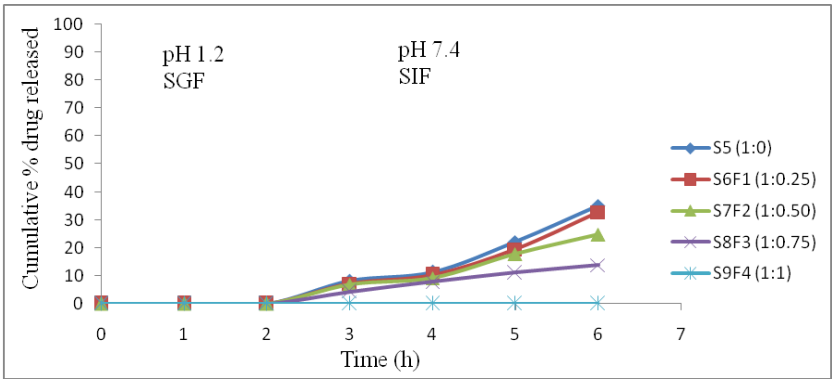


**Figure 7: Effect of solubility modifier (sodium bicarbonate) on Cumulative % drug release in small intestine**

The guar gum is degraded by anaerobic bacteria of colon and it is not degraded by the aerobic bacteria of small intestine. This property of guar gum was used to retard the drug release in small intestine. As the proportion of guar gum was increased in coating solution, decrease in release rate of drug in small intestine and increase in release rate in colon was observed. To elaborate the effect of concentration of pore forming agent (guar gum) on drug release the core formulation of (batch-S9F4) of MB-HCL were coated with semipermeable membrane coating formulation C and D containing 20% and 30% *w/w* (of cellulose acetate) level of guar gum respectively as shown in **Table 2** and enteric coated with EC1 as shown in **Table 9**. Release profiles of these formulations in comparison with formulation S9F4 containing 40% *w/w* of guar gum are shown in **Figure 4** in SCF region.

**Table 9.** Dissolution release profile of S9F4 in presence of (0.1%) enzyme

| Dissolution media | Time (h) | S9F4 with enzyme |
|---|---|---|
| Simulated gastric fluid | 1 | 0 |
| | 2 | 0 |
| Simulated intestinal fluid | 3 | 0 |
| | 4 | 0 |
| | 5 | 0 |
| | 6 | 0 |
| Simulated colonic fluid with enzyme(Galactomannanase) | 7 | 0 |
| | 8 | 0 |
| | 9 | 1.26 |
| | 10 | 5.89 |
| | 11 | 17.48 |
| | 12 | 28.57 |

It is clearly evident that the level of pore former had direct effect on drug release. As the level of guar gum increases the membrane becomes more porous due to the degradation of larger amount of guar gum by microflora of SCF resulting in higher drug release from the delivery pores of membrane. Another parameter affected by the concentration of pore forming agent was the lag time of drug release. Before SCF dissolution study it was expected that there was a lag time of 6 h to reach specific colon region which meant that the release of drug was only activated by SCF containing colonic bacteria. However in the SCF, dissolution study no lag time should be shown. The concentration of guar gum in the membrane might be the key factor to this lag time. The lag time was inversely related to the initial level of pore forming agent in the membrane. The lower concentration of pore forming agent in formulation C (20% *w/w*) showed longer average lag time (7±0.5h) and the higher concentration of pore forming agent 40% showed shorter average lag time (6±0.5 h) in the dissolution set-up. *In-vitro* drug release in presence of enzyme was also investigated as shown in **Figure 8**. It was demonstrated that the extracellular enzymes released from the microflora in rat caecal contents had more profound degradation effects on polysaccharide.

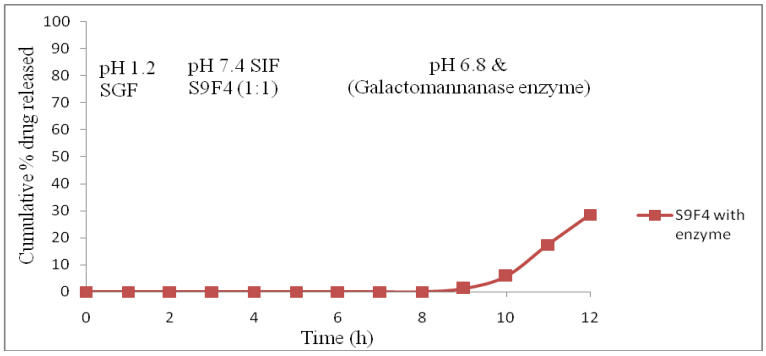


**Figure 8: Dissolution profile of optimized MAP-CT-OT (S9F4) formulation in the presence of enzyme in SCF**

It could be concluded that results are related only to the effect of the enzyme but not due to any acidic constituents in the faecal content. Literature survey reveals several guar gum-based colonic formulations using in simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 7.5) and simulated colonic fluids containing galactomannanase. As expected when compared with drug release in simulated gastric and intestinal fluids results showed that drug release was speeded-up only in the colonic fluid due to the presence of the galactomannanase that could hydrolyze the guar gum. Comparison of *in-vitro* drug release studies of optimal MAP-CT-OT (S9F4) with marketed formulation F-MR** was also investigated. The *in-vitro* dissolution study of conventional (sugar coated) marketed product F-MR** was found to show 98.62% drug release within 2 h. From this data as shown in **Table 10** and **Figure 9**, it was found that It was found that the drug release rate of conventional tablet was very high initially in acidic environment of stomach as compare to the modified MAP-CT-OT releasing the drug only in colon in controlled manner. From the *in-vitro* dissolution studies of prepared osmotic colon targeted tablet, it can be

concluded that the drug release was accelerated in the presence of rat caecal content. Prepared colon targeted osmotic tablet containing 40% guar gum in first cellulose acetate layer would able to release 85.92% of mebeverine hydrochloride in the presence of colonic microflora at target site. This was found to be promising formulation for the treatment of IBS as compared to the conventional market formulation.

**Table 10.** Dissolution release profile of mebeverine hydrochloride from conventional market formulation F-MR** and MAP-CT-OT (S9F4)

| Time (h) | F-MR** | MAP-CT-OT (S9F4) |
|---|---|---|
| 0 | 0 | 0 |
| 1 | 53.91 | 0 |
| 2 | 98.62 | 0 |
| 3 | - | 0 |
| 4 | - | 0 |
| 5 | - | 0 |
| 6 | - | 0 |
| 8 | - | 10.34 |
| 10 | - | 22.41 |
| 12 | - | 30.53 |
| 14 | - | 39.33 |
| 16 | - | 50.11 |
| 18 | - | 59.39 |
| 24 | - | 85.92 |

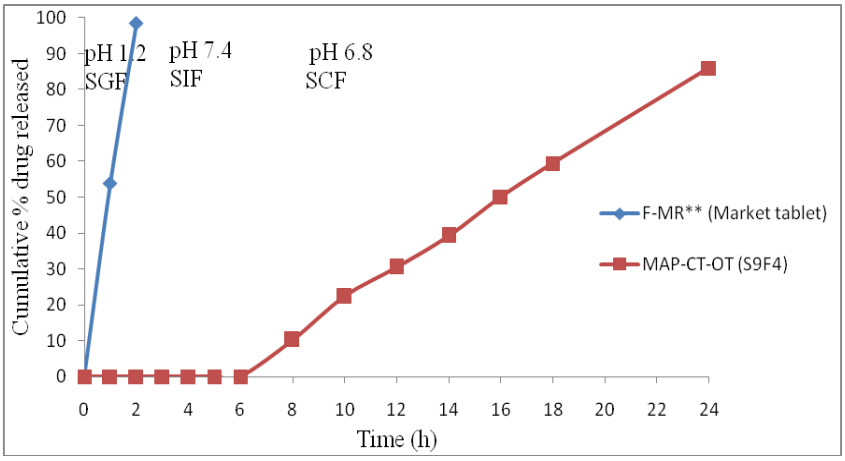


**Figure 9: Dissolution profile of mebeverine hydrochloride from conventional market formulation F-MR** and MAP-CT-OT (S9F4)**

In order to investigate the drug release kinetics, release data of promising batch was fitted to different models like Zero-order, First-order and Higuchi model as shown in **Figures 10, 11** and **12**.

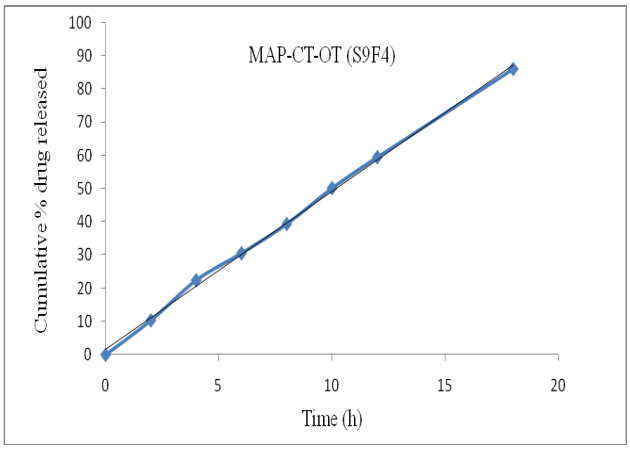


**Figure 10: Zero order release profile of MAP-CT-OT (S9F4) tablets**

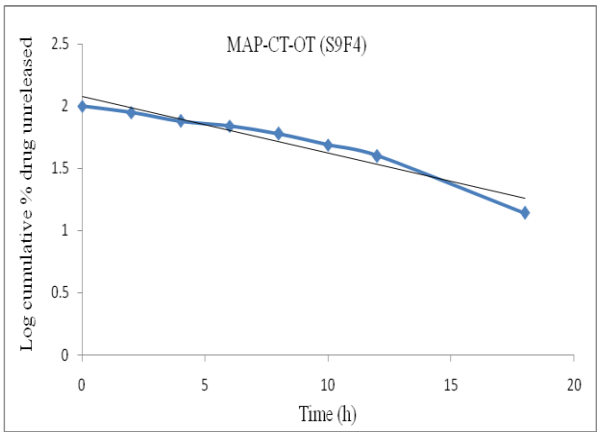


**Figure 11: First order release profile of MAP-CT-OT (S9F4) tablets**

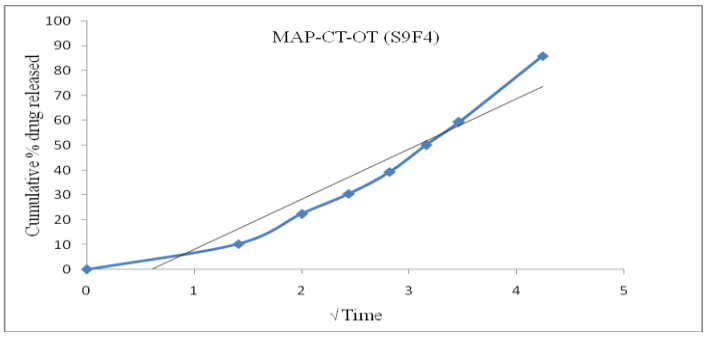


**Figure 12: Higuchi model of MAP-CT-OT (S9F4)**

On the analysis of regression coefficient value of all mathematical models as shown in **Table 11**, it was found that MAP-CT-OT (S9F4) followed the Zero-order kinetic ($R^2$=0.998). As observed from cumulative percent drug release in SCF pH 6.8 at time 8 h value was found 10.34% and up to 24 h it was approximately 86%. Data analysis of this release period showed to be zero order which indicates that when the release of the drug starts in colon follows zero order.

**Table 11.** Fitting of drug release data of optimized formulation according to various mathematical models

| Model | Equation of line | Regression coefficient ($R^2$) |
|---|---|---|
| Zero order | Y = 4.761X + 1.541 | 0.998 |
| First order | y = -0.045x + 2.074 | 0.930 |
| Higuchi model | y = 20.19x - 12.04 | 0.916 |

**Stability Studies:**

The formulation shows no significant variation in *in-vitro* drug release over the period of four weeks as shown in **Figure 13**. The difference factor and similarity factor between reference and test was found to be 3.4 and 75 respectively. Hence the results of stability studies confirm that the formulation is stable.

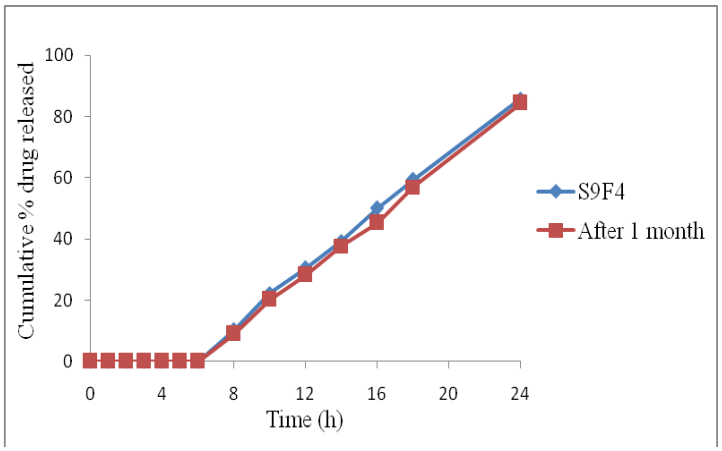


**Figure 13: Dissolution profile of MAP-CT-OT (S9F4) at different time interval**

## Conclusion:

Mebeverine hydrochloride colon-specific drug delivery with the combinations of polysaccharide (guar gum) and enteric polymer with the degradation mechanisms based on pH and micro flora appears to be potential as it permits specific drug delivery to the colon. Firstly the degradation products of polysaccharides are non toxic. Secondly Colon provides favorable factors and conditions for designing of delivery systems. A successful trigger could be obtained for drug release in the colon from specially two layer coated tablets. The result obtained using mebeverine hydrochloride as model drug can be extrapolated for other drug undergoing to first pass metabolism after oral administration.

## Acknowledgements:

The authors would like to thank Dr. Hasmukh Mehta G.M Chemicals (Mumbai), Mr. Reddy Rantus Pharmaceuticals Pvt. Ltd (Hyderabad), Mr. Garg Niche Marketing (Delhi) and N.B Pharma Pvt. Ltd (Yamuna Nagar). The authors gratefully acknowledge the generous financial support by Nidhi Sapra and Jatin Bagga.

**Declaration of interest:**

The authors report no conflicts of interest.

## References:

1. Kumar P, Mishra B. Colon targeted drug delivery systems: an Overview. Curr Drug Deliv., 2008;5(3):186-98.

2. Muraoka M, Hu Z, Shimokawa T, Sekino S, et al. Evaluation of intestinal pressure controlled colon delivery capsule containing caffeine as a model drug in human volunteers. J Control Release., 1998;52:119–129.

3. Elhady SSA, Mortada ND, Awad GAS, et al. Development of in-situ gelling and mucoadhesive mebeverine hydrochloride solution for rectal administration. Saudi Pharm J., 2003;11(4):159-171.

4. Shanahan F. Probiotics in inflammatory bowel disease-therapeutic rationale and role. Adv Drug Del Reviews., 2004;56:809-818.

5. Shimono N, Takatori T, Ueda M, Mori M, et al. Chitosan dispersed system for colon-specific drug delivery. Int J Pharm., 2002;245:45-54.

6. Aswar PB, Khadabadi SS, Kuchekar BS, Wane TP, et al. Development and in-vitro evaluation of colon-specific formulations for orally administered diclofenac sodium. Arch Pharm Sci Res., 2009;1(1):48-53.

7. Al-Dossary BN, AL-Gohary OMN, El-Khawaas MM. In-vitro and in-vivo availability of mebeverine hydrochloride suppositories. Sci Pharm., 2006;74:31-51.

8. Hosny EA, Abdel-Hady SS, E1-Tahir KEH. Formulation, in-vitro release and ex-vivo spasmolytic effects of mebeverine hydrochloride suppositories containing polycarbophil or polysorbate 80. Int J Pharm., 1996;142:163-168.

9. Naikwade SR, Kulkarni PP, Jathar SR, Bajaj AN. Development of time and pH dependent controlled release colon specific delivery of tinidazole. Daru., 2008;16(3):119-127.

10. Das NG, Das SK. Controlled-release of oral dosage forms. Formul Fill Finish., 2003;10-16.

11. Liu H, Yang XG, Nie SF, Wei LL, et al. Chitosan-based controlled porosity osmotic pump for colon-specific delivery system: Screening of formulation variables and in-vitro investigation. Int J Pharm., 2007;332:115–124.

12. Aulton ME. Pharmaceutics: The science of dosage form design. 3rd ed. Churchill livingstone; p. 112 & 134.

13. Ansel HC, Allen LV, Popovich NG. Pharmaceutical dosage forms and drug delivery systems. 8th ed. Lippincott Williams and Wilkins; p. 240.

14. Prasad RYV, Krishnaiah YSR, Satyanarayana S. In vitro evaluation of guar gum as a carrier for colon-specific drug delivery. J Control Release., 1998;51:281-287.

15. Krishnaiah YSR, Muzib YI, Bhaskar P, Satyanarayana V, et al. Pharmacokinetic evaluation of guar gum-based colon-targeted drug delivery systems of tinidazole in healthy human volunteers. Drug Deliv., 2003;10:263-268.

16. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci., 2001;13:123-133.

17. Rahman Z, Kohli K, Khar RK, Ali M, et al. Characterization of 5-fluorouracil microspheres for colonic delivery. AAPS Pharm Sci Tech., 2006;7(2):E1-E9.

18. Viness P, Reza F. Evaluation and comparison of dissolution data derived from different modified release dosage forms: an alternative method. J Control Release., 1998;55:45–55.

19. Kumar P, Singh S, Mishra B. Colon targeted delivery systems of metronidazole based on osmotic technology: development and evaluation. Chem Pharm Bull., 2008;56(9):1234-1242.