RESEARCH ARTICLE

# A novel colonic drug delivery system of ibuprofen

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The present endeavor was directed towards fabrication of the novel colonic drug delivery system of ibuprofen. To begin with, the hydroxypropyl methylcellulose capsules containing adsorbate of eutectic mixture of ibuprofen and menthol and pregelatinized starch were coated with ethyl cellulose. These ethyl cellulose coated capsules were filled in another capsule and the capsules were coated with a Eudragit® S100. The *in vitro* drug release study was conducted using sequential dissolution technique at pH 1.2 (two hour), 6.0 (1hr), 7.2 (two hour) and 6.4 (three hour) mimicking different regions of gastrointestinal tract. The optimized batch with two per cent and 6.5% weight gain of ethyl cellulose and Eudragit® S100 showed less than eight per cent drug release in stomach and intestinal pH. The remaining 92% drug release was obtained thereafter from the optimized batch within two hours in colonic pH. Scanning electron microscopy study of the optimized batch confirmed presence of ibuprofen crystals (rod shape) in the formulation. The infrared spectroscopy study of the optimized batch indicated stability of ibuprofen during processing of the formulation.

***Key words:*** *Ethyl cellulose, eutectic mixture, Eudragit® S100 and capsule within capsule, ibuprofen, menthol*

## INTRODUCTION

In recent years, colon-specific drug delivery system (CDDS) has been the focus of intense research.[1] Colonic drug delivery system is preferred in the treatment of localized diseases such as ulcerative colitis, Crohn's disease and constipation. Colon is a promising site for systemic absorption of peptides and proteins.[2,3] The different approaches for targeting orally administered drugs to the colon include coating with pH-dependent polymers, design of timed-release dosage forms and utilization of carriers that are degraded exclusively by colonic bacteria.[4,5]

The poor site-specificity of pH-dependent systems, because of large variation in the pH of the gastrointestinal tract, is very well established.[6,7] The site-specificity of timed-release dosage forms is considered poor because of large variations in gastric emptying time and passage across the ileo-caecal junction.[8,9] Microbially triggered systems give good site specificity. However, it is worthwhile to note that diet, antibacterial drugs and disease states of an individual can affect colonic microflora. Enzymatic degradation may be excessively slow. [10,11]

Ibuprofen, a non-steroidal anti-inflammatory agent, is widely used in treatment of mild to moderated pain and fever.[12] Aqueous solubility, partition coefficient (log P) and calculated partition coefficient (clog P) values of ibuprofen are less than one mg/mL, 3.75 and 3.68 respectively. Ibuprofen is readily absorbed throughout the gastrointestinal tract.[13] This study selected ibuprofen as a drug for formulating colonic drug delivery system to avoid gastrointestinal discomfort associated with ibuprofen therapy. In addition, Min Yao *et al*. reported that low dose of ibuprofen decreases both tumor growth and metastatic potential in mice.[14]

The aim of the present research work was to develop a novel pH and time-dependent system for delivering ibuprofen in the colon. Ibuprofen capsules (size 0) containing adsorbate of eutectic mixture of ibuprofen and menthol and pregelatinized starch were over-coated with a semipermeable polymer (ethyl cellulose) to provide a lag time of 90min at pH 7.2 (mimicking transition time of solid dosage form from terminal ileum to ascending colon).[15] The ethyl cellulose coated capsules were then filled into another capsule (size 00) and the capsules were coated with an enteric polymer (Eudragit® S100) to a level such that a lag time of 30 minutes at pH 7.2 (mimicking transition time of solid dosage form from proximal

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ileum to terminal ileum) was obtained.[15] The formulation was prepared using eutectic mixture of ibuprofen and menthol to uniformly distribute the drug in the dosage form and surpass existing patents on colonic drug delivery systems of ibuprofen.[16] In addition, menthol is a well known intestinal and dermal permeation enhancer[17,18] and anti-tumor agent.[19] Hence, traces of menthol present in the formulation may improve *in vivo* performance.

## MATERIALS AND METHODS

### Material

Ibuprofen I.P, ethyl cellulose (Ethocel standard 10FP premium) and sodium starch glycolate were received as gift samples from Zydus Cadila (Ahmedabad, India). Pregelatinized starch (PGs) was a gift from Colorcon Pvt. Ltd. (Goa, India). Eudragit® S100 was a gift from Degussa Pvt. Ltd. (Mumbai, India) and Cab-O-Sil M5 from Cabot Sanmar Pvt. Ltd. (Chennai, India). Menthol was purchased from Shreeji Pharma International (Ahmedabad, India). Mannitol, polyethylene glycol 400 and isopropyl alcohol (IPA) were purchased from S.D. Fine Chemicals (Boisar, India). Polyvinylpyrrolidone (PVP K30) was purchased from Laser Laboratories (Ahmedabad, India). The hydroxypropyl methylcellulose (HPMC) capsules were purchased from Nature Caps Ltd. (Ahmedabad, India). The other chemicals and reagents were of analytical grade.

### Determination of eutectic composition of ibuprofen and menthol

Ibuprofen and menthol were mixed in different ratios, on weight basis, at 35 plus/minus 2° C for 15 minutes in a mortar and pestle. The undissolved solids, if any, were carefully collected and weighed. The presence of only liquid phase indicated eutectic composition.

### Formulation

Polyvinylpyrrolidone was dissolved in eutectic mixture consisting of 60 parts of menthol and 40 parts of ibuprofen in a closed container. The solution was then adsorbed onto pregelatinized starch (PGs). The wet mass was passed through 20# mesh screen (850 $\mu$m opening) and dried at 50 plus/minus 2°C to facilitate removal of menthol from the formulation. The dried granules (20#, batch A1) were mixed with sodium starch glycolate and the blend was characterized for angle of repose. The batches A2-A4 additionally contained extra granular fraction of Cab-O-Sil M5. In batch A5, the granules of batch A1 were co-grinded with mannitol in a mortar and pestle for 15 min. Granules of batch A5 containing 50 mg ibuprofen (347 mg) were filled into HPMC capsule (size 0) and characterized for *in vitro* drug release. The capsules of batch A5 were dip coated using polymeric solution of ethyl cellulose. The percentage weight gain of ethyl cellulose was varied from 1.5-3% (batches A6-A9) to get the desired *in vitro* lag time of 90 minutes in phosphate buffer with pH 7.2 (mimicking fasting conditions of terminal ileum).[15]

The capsules of batch A9 were filled in another HPMC capsule (size 00). The capsules were coated with Eudragit® S100 solution to a level such that the drug release was prevented in media with pH 1.2 (mimicking fasting conditions of stomach) and pH 6.0 (mimicking fasting conditions of upper intestine).[15,20] A lag time of 30 minutes was desirable at pH 7.2 (mimicking fasting conditions of proximal ileum).[15] The Eudragit® S100 coated capsules (batches A10-A12) were characterized for enteric test and *in vitro* drug release. [Table 1] represents the composition of different formulated batches A1-A12. The composition of coating solution of ethyl cellulose is given below: (a) Ethyl cellulose - 5% w/v, (b) polyethylene glycol 400-12.5% w/w of polymer, and (c) Sudan red and isopropyl alcohol- quantity sufficient. The composition of Eudragit® S100 solution was similar to that of ethyl cellulose.

## EVALUATIONS

### Angle of repose

The angle of repose was measured using the fixed height funnel method.[21,22]

**Table 1: Composition of various formulated batches A1-A12**

| Batch code | Ingredients | | | | | | |
|---|---|---|---|---|---|---|---|
| | *SP (% w/v) | +PGs (g) | !SSG(g) | Cab-O-Sil (mg) | Mannitol (g) | ^%ECWG | ◊%ES100WG |
| A1 | 5 | 25 | 1.5 | - | - | - | - |
| A2 | 5 | 25 | 1.5 | 33.25 | - | - | - |
| A3 | 5 | 25 | 1.5 | 166.2 | - | - | - |
| A4 | 5 | 25 | 1.5 | 498.6 | - | - | - |
| A5 | 5 | 25 | 1.5 | - | 8.31 | - | - |
| A6 | 5 | 25 | 1.5 | - | 8.31 | 1.5 | - |
| A7 | 5 | 25 | 1.5 | - | 8.31 | 2.2 | - |
| A8 | 5 | 25 | 1.5 | - | 8.31 | 3 | - |
| A9 | 5 | 25 | 1.5 | - | 8.31 | 2 | - |
| A10 | 5 | 25 | 1.5 | - | 8.31 | 2 | 4 |
| A11 | 5 | 25 | 1.5 | - | 8.31 | 2 | 6.5 |
| A12 | 5 | 25 | 1.5 | - | 8.31 | 2 | 7.5 |

*SP is the solution (15ml) of polyvinylpyrrolidone in eutectic mixture consisting of 60 parts of menthol and 40 parts of ibuprofen, +PGs is pregelatinized starch, !SSG is sodium starch glycolate, ^%ECWG is the percentage ethyl cellulose weight gain and ◊%ES100WG is the percentage Eudragit® S100 weight gain

**Assay of ibuprofen**

The amount of ibuprofen present in the formulation was determined as per IP 1996.[23]

***In vitro* drug release from ibuprofen uncoated capsule**

The capsules of batch A5 were subjected to *in vitro* drug release for three hours in a calibrated USP dissolution test apparatus equipped with paddles employing 900 mL phosphate buffer (pH 6.4, mimicking conditions of ascending colon).[15] The paddles were rotated at 50 RPM. The dissolution media was maintained at a temperature of 37 plus/minus 0.5°C. Samples (10 mL) were withdrawn and analyzed spectrophotometrically at 221 nm employing Shimadzu-1700 UV/visible spectrophotometer after suitable dilution of the samples.[23] The fresh dissolution medium was replaced after each withdrawal. The percentage of ibuprofen released over time was calculated using the standard calibration curve obtained using linear regression analysis ($r^2$ greater than 0.999).

***In vitro* drug release from ethyl cellulose coated capsule**

The objective of depositing ethyl cellulose coat was to successfully carry the coated HPMC capsule from terminal ileum (pH 7.2) to ascending colon (pH 6.4). Hence, *in vitro* drug release from ethyl cellulose coated capsules (batches A6-A9) was carried out for five hours in two different media namely phosphate buffer (pH 7.2, 900 mL) for first two hours (mimicking fasting conditions of proximal ileum (30 min) and terminal ileum (90 min)) and finally in phosphate buffer (pH 6.4, 900 mL) for the remaining period (mimicking conditions of ascending colon).[15] The *in vitro* lag time, calculated by interpolation, was expressed as $t_{10\%}$, i.e. the time required to release 10% of the drug.[24]

***In vitro* drug release from eudragit® S100 coated capsule**

The purpose of depositing the outermost Eudragit® S100 coat was to protect the dosage form from the fluids present in stomach (pH 1.2) and upper intestine (pH 6.0). A lag time of 30 min at pH 7.2 (proximal ileum) was desirable. Hence, *in vitro* drug release from Eudragit® S100 coated capsules (batches A10-A12) was carried out for eight hours in four different media namely hydrochloric acid (pH 1.2, mimicking fasting stomach), pH 6.0 phosphate buffer (mimicking fasting upper intestine), pH 7.2 phosphate buffer (mimicking fasting proximal and terminal ileum) and pH 6.4 phosphate buffer (mimicking ascending colon) for two, one, two and three hours respectively, using sequentially dissolution technique.[15,20] The lag time, provided by Eudragit® S100 coat, was calculated by subtracting the lag time of ethyl cellulose coated capsule from lag time exhibited by Eudragit® S100 coated capsule.

**Enteric test**

Enteric test was performed according to the British Pharmacopoeia (BP 2001) using phosphate buffer with pH 6.8, following storage of the formulations in 0.1N HCl for two hours.[25]

**Scanning electron microscopy**

The samples of batch A5 and ibuprofen powder were subjected to scanning electron microscopic study (Model ESEM TMP-EDAX, Philips, Netherlands) at an accelerating voltage of 30kV. The results are displayed in Figure 1.

**Fourier transformation infrared microscopy**

Pure ibuprofen and powder blend of batch A5 were separately mixed with IR grade potassium bromide. Infrared spectra were taken using an infrared spectrophotometer (Model FTIR-8400S, Shimadzu, Japan) by scanning samples over a wave number of 4000 to 400/cm. The results are shown in Figure 2.

## RESULTS AND DISCUSSION

A eutectic mixture is a mixture of two or more components at a composition that has the lowest melting point and the components simultaneously crystallize from the solution at a particular temperature. Substances such as camphor, menthol, chloral hydrate, beta naphthol, lidocaine and prilocaine form eutectic mixtures. The primary criterion for eutectic formation is the mutual solubility of the components in the liquid. Ibuprofen and menthol also form a eutectic mixture. Ibuprofen exhibits poor flow (strong cohesive behavior) and poor tablet ability.[26,27] These properties lead to the formation of tablets with low crushing strength. Improvement in compressibility and flow behavior can be achieved by crystallization of ibuprofen from solvents.[28] However, the use of organic solvents is discouraged by regulatory agencies. Numbers of patents have been filed to overcome the problem of poor flow and compressibility of ibuprofen.[29-32]

Menthol is chemically (1R, 2S, 5R)-5-methyl-2-(1-methyethyl) -cyclohexanol with a molecular weight of 156 and melting point of 42°C. Menthol is widely used in pharmaceuticals, confectionery, and toiletry products as a flavoring agent or odor enhancer. In addition, menthol is a well known intestinal and dermal permeation enhancer and anti-tumor agent. [17-19]

The aim of this study was to develop a colonic drug delivery system of ibuprofen which is novel, industrial acceptable, functional yet difficult to copy creating a high barrier to reverse engineering by counterfeiters for preventing tumor growth and metastatic potential. The formulation was prepared by adsorbing eutectic mixture of ibuprofen and menthol over pregelatinized starch to get uniform drug distribution. Solid-liquid mixing is easier as compared to solid-solid mixing. The numbers of patents are filed on colonic drug delivery system.[16] However, none of them use eutectic mixture in the formulation. The dual advantages (easy mixing and surpassing of existing patents) offered by the eutectic mixture tempted us to undertake this study. When the proportion of menthol to ibuprofen was 1:9, 2:8, 3:7, 4:6 and 5:5, the percentage w/w of undissolved solids was 96 plus/minus 3.5, 81 plus/minus 3.5, 60 plus/minus 3.5 and 31 plus/minus 3.5 and 10 plus/minus 3.5 respectively. Complete liquification was observed in case

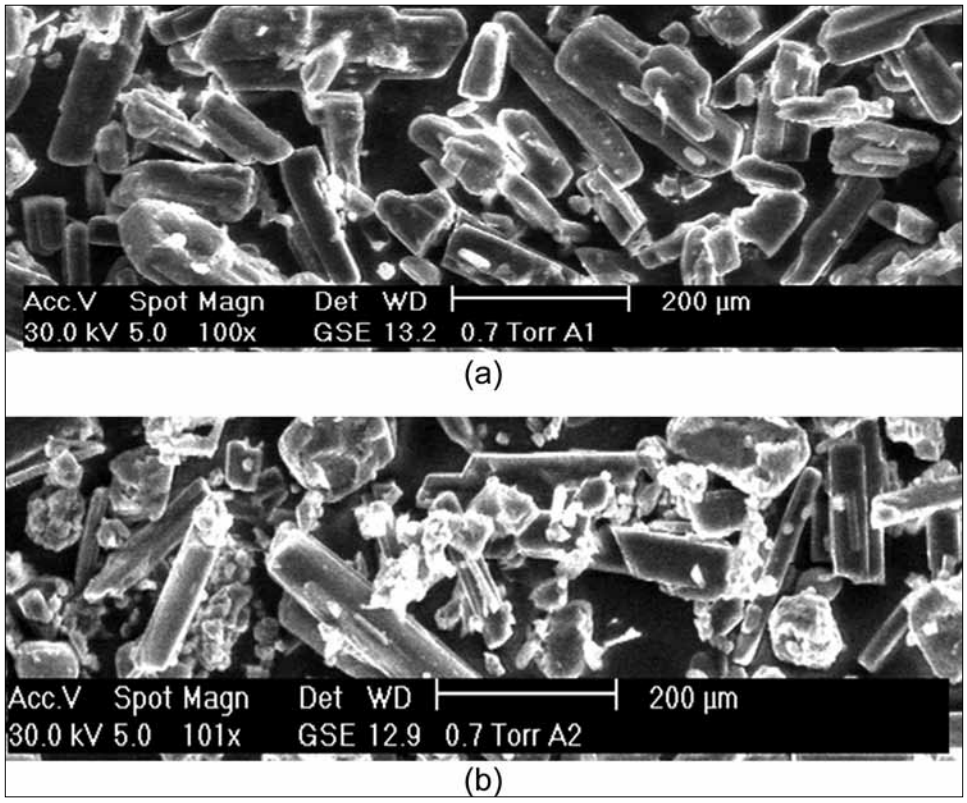


**Figure 1:** Scanning electron photograph of drug and formulated batch A5; (a) pure ibuprofen and (b) batch A5

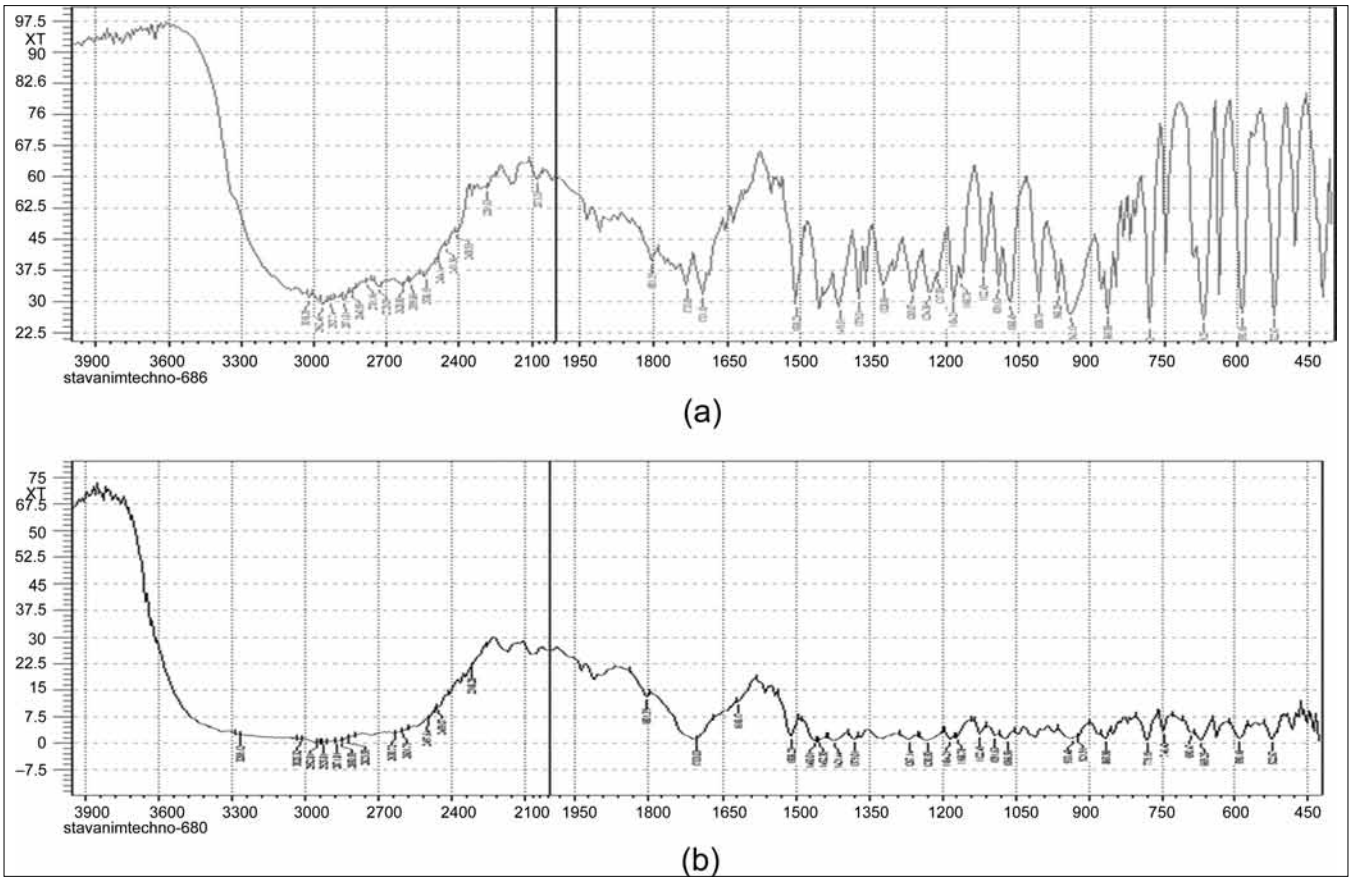


**Figure 2:** Results of fourier transformation infrared spectroscopy; (a) pure ibuprofen and (b) batch A5

of 6:4, 7:3, 8:2 and 9:1 of menthol to ibuprofen at 35 plus/minus 2° C. The results show that percentage of undissolved solids is inversely related to percentage menthol up to 50%. The eutectic blend consisting of 60 parts of menthol and 40 parts of ibuprofen was used for further studies. Menthol is a well known intestinal and dermal permeation enhancer [17,18] and anti-tumor agent.[19]

Figure 3 shows a formulated dosage form (a capsule within a capsule). Pregelatinized starch was selected as an inert carrier for adsorption of eutectic mixture of ibuprofen and menthol considering its compressibility, flow property and self disintegration nature.[33] Pregelatinized starch markedly reduces sticking, binding and ejection force in direct compression formulations. The self-lubrication property of pregelatinized starch lies in its viscoelastic behavior i.e., its time-dependent deformation. Polyvinylpyrrolidone (PVP K30) was employed as a binder. Sodium starch glycolate was employed as a swellable excipient to cause rupture of ethyl cellulose coat after a predetermined lag time of 90 min at pH 7.2 (mimicking fasting conditions of terminal ileum).[15] The batch A1 showed angle of repose of 39°. Vasanthakumar and Vijaya described that the angle of repose less than 30° indicates free flowing material.[34]

Hence, Cab-O-Sil, fumed silicon dioxide was added up to 1.5% as an extra granular excipient in batches A2-A4 to resolve the issue of poor flow. The angle of repose of batches A2-A4 were 36, 34 and 31° respectively and thus failed to give excellent flow property. The concentration of Cab-O-Sil M5 was not increased above 1.5% since normal concentration of Cab-O-Sil, as per inactive ingredient guide for oral film coated tablets is 3.6 mg.[35] Hence, in subsequent batch A5, co-grinding technique with mannitol was adopted.

In pharmaceutical formulations mannitol is used as a non-hygroscopic diluent in the concentration of 10-90% w/w.[33] Mannitol exhibits excellent compressibility and flow property. In addition, mannitol is commonly used as a taste masking excipient in the chewable and mouth dissolving/disintegrating tablets because of negative heat of solution, sweetness and mouth feel.[33] Co-grinding with mannitol (batch A5) resulted into improved flow of the granules with angle of repose less than 27° and thus it was selected for preparation of ibuprofen capsules. In high speed capsule filling machines, the problem of wet variation will not be observed if the flow is good. Uniform drug distribution is critical in pharmaceutical dosage form.[36,37] Uniform solid-solid mixing is difficult to achieve since, the proportion of solids, density of solids and size of solids affect the results. On the other hand, liquid can be easily mixed with solid, as done in the process of wet granulation. A layer of liquid is formed on the surface of carrier, giving uniform distribution of drug on the carrier. In the present study eutectic blend was used as a solvent for adsorption. The idea in the present study worked well as seen in the results of content uniformity test. Granules of batch A5 showed uniform content uniformity (94 plus/minus 2%) than physical mixture of ibuprofen, pregelatinized starch, mannitol and sodium starch glycolate (81 plus/minus 3%). An *in vitro* drug release study of uncoated ibuprofen capsule was carried out in phosphate buffer (pH 6.4, mimicking conditions of ascending colon).[15] [Figure 4] depicts that ibuprofen was immediately released from the capsule of batch A5 (greater than 85% drug release in 45 min). The UV spectrum remained unchanged during *in vitro* study, indicating stability of ibuprofen during the analytical procedure.

The pH in terminal ileum and ascending colon is 7.2 and 6.4 respectively.[15,20] Therefore, the pH dependent systems may not be successful in arresting drug release prior to reaching colon. The objective of depositing ethyl cellulose coat was to successfully carry the coated HPMC capsule from terminal ileum (pH 7.2) to ascending colon (pH 6.4). The lag time can be achieved by coating the capsule with semi-permeable film of ethyl cellulose, Eudragit® RL or Eudragit® RS. In the present study ethyl cellulose was selected as semi-permeable film

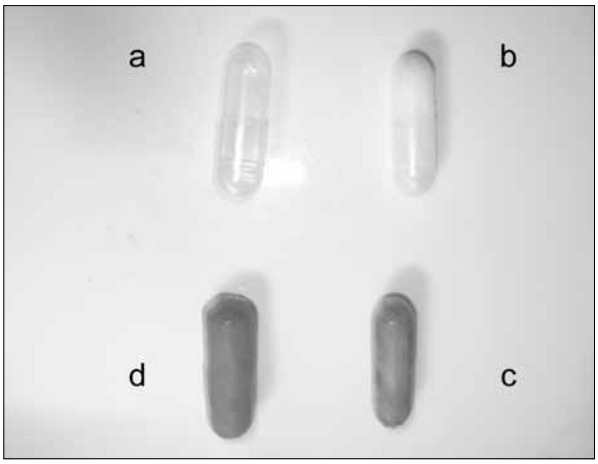


**Figure 3:** Formulated ibuprofen colonic drug delivery system; (a) hydroxypropyl methylcellulose empty capsule, (b) ibuprofen hydroxypropyl methylcellulose capsule, (c) ethyl cellulose coated capsule and (d) Eudragit® S100 coated capsule

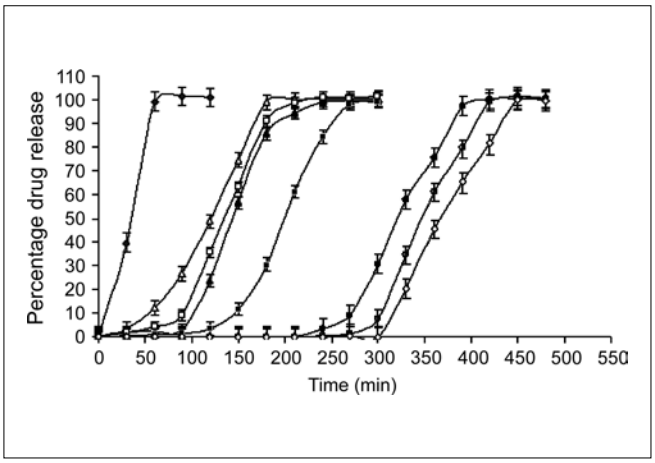


**Figure 4:** *In vitro* drug release from different formulated batches A5-A12; A5 (-♦-), A6 (-Δ-), A7 (-▲-), A8 (-■-), A9 (-□-), A10 (-●-), A11 (-○-) and A12 (-◊-)

forming polymer to coat HPMC capsule. The results shown in Figure 4 reveal that the time required for 10% of drug release (lag time) from batch A6 was 54 min. In order to increase the lag time to 90 min, the percentage weight gain of ethyl cellulose was increased in subsequent batches. Batches A7 and A8 showed a lag time of 101 and 148 min respectively. The data was subjected to mathematical model using linear regression analysis. The percentage weight gain was chosen as an independent variable (X) and lag time ($t_{10\%}$) was chosen as a dependent variable (Y). Equation 1 shows the relationship between the dependent and independent variables with $r^2$ value of 0.99 and *P* less than 0.05. The required amount of percentage weight gain was two per cent to get lag time of 90 min at pH 7.2. Batch A9 exhibited a lag time of 93 min.

$$Y = 62.57(X) - 38.74 \quad (1)$$

The purpose of depositing the outermost Eudragit® S100 coat was to protect the dosage form from the fluids present in stomach (pH 1.2) and upper intestine (pH 6.0). A lag time of 30 min at pH 7.2 (proximal ileum) was desirable. After dissolution of Eudragit® coat, dissolution medium will permeate in the ethyl cellulose coat since ethyl cellulose forms a semi-permeable film. On permeation of fluid in the capsules, increase in the core volume will cause rupture of ethyl cellulose coat. The ethyl cellulose capsules of batch B9 were not directly coated with Eudragit® to avoid probable partial dissolution of ethyl cellulose coat. The solvent used in both the coating solutions of ethyl cellulose and Eudragit® was isopropyl alcohol. Hence, in order to reduce bath-to-batch variability due to processing, ethyl cellulose coated capsules were put in another HPMC capsule, which were subsequently coated with Eudragit®. Eudragit® S100 is readily soluble in neutral to weakly alkaline media, i.e., pH greater than or equal to 7.0.[33] Polyethylene glycol 400 was added as a hydrophilic plasticizer in the coating solution containing Eudragit® S100. The formulated batches A10-A12 satisfied the pharmacopeial (BP 2001) requirements for the enteric test.[25] Figure 4 shows that the batch A10 containing four per cent Eudragit® S100 weight gain failed to show desired lag time of 30 min at pH 7.2 (proximal ileum). About 30% of the drug was released before reaching the colonic pH of 6.4. The dissolution time was again directly correlated with percentage weight gain. Higher percentage weight gain of Eudragit® S100 was applied in subsequent batches (A11-A12). Batch A11 containing 6.5% Eudragit® S100 weight gain provided desired lag time of 30 min at pH 7.2 with little drug release (eight per cent) before reaching pH of ascending colon (pH is equal to 6.4). Remaining drug release (92%) was achieved within two hours at pH 6.4. Batch A12 containing 7.5% Eudragit® S100 weight gain showed higher lag time of 44 min at pH 7.2. Considering the results of *in vitro* drug release, batch A11 was ranked as an optimized batch.

Scanning electron microscopy of pure drug and granules of batch A5 confirms presence of ibuprofen crystals (rod shape) in the formulation [Figure 1]. The infrared spectra are shown in Figure 2. The infrared spectra of ibuprofen and batch A5 were comparable. Ibuprofen showed two prominent peaks at 2871/cm and 1701/cm because of presence of aliphatic alkyl and carboxyl groups respectively. The peaks present in ibuprofen were retained in batch A5 indicating stability of ibuprofen during processing.

Hard gelatin capsules has tendency to undergo cross-linking at high humidity and high temperature, which is prevalent in tropical countries. Cross-linked gelatin capsules may exhibit problems in drug release. Hydroxypropyl methylcellulose capsules were used in the present investigation to prevent such problems. Gelatin capsules contain 10-12% moisture, where as HPMC capsule contain less than two per cent moisture.

## CONCLUSION

The colonic drug delivery system of ibuprofen was developed using the concept of eutectic mixture. Ibuprofen capsules containing the adsorbate of eutectic blend and pregelatinized starch were coated with ethyl cellulose which provided a lag time of 90 min at pH 7.2 (mimicking transition time of solid dosage form from terminal ileum to ascending colon). The ethyl cellulose coated capsule was filled into HPMC capsule and then it was coated with Eudragit® S100. The drug release was prevented for 30 min at pH 7.2 (mimicking transition time of solid dosage form from proximal ileum to terminal ileum). The optimized batch (A11) showed about 92% drug release at colonic pH 6.4 within 2 hr. The traces of menthol left in the dosage form may function as a permeation enhancer and anti-tumor agent. Knowledge of properties of excipients such as swelling, permeability, pH dependent solubility and glidant enabled us to develop functional colonic drug delivery system.

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