Chapter 6

Capsule in capsule colon targeted ibuprofen delivery system containing menthol:
Chapter 6: Capsule in capsule ibuprofen colonic drug delivery system

6.0 Capsule in capsule colon targeted ibuprofen delivery system containing menthol

6.1 Introduction:

In recent years, colon-specific drug delivery system (CDDS) has been the focus of intense research.\(^1\) Colonic drug delivery system is preferred for treating 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 <1 mg/ml, 3.75 and 3.68 respectively. Ibuprofen is readily absorbed
Chapter 6: Capsule in capsule ibuprofen colonic drug delivery system throughout the gastrointestinal tract. In the present study ibuprofen was selected as a drug for formulating colonic drug delivery system to avoid gastrointestinal discomforts associated with ibuprofen therapy. Further, Min Yao et al., reported that low dose of ibuprofen decreases both tumor growth and metastatic potential in mice.

The aim of the present research work was to develop a novel pH and time-dependent system for delivering ibuprofen in the colon. The ibuprofen capsules (size 0) containing adsorbate of eutectic mixture of ibuprofen and menthol and pregelatinized starch were over-coated with a semi-permeable polymer (ethyl cellulose) to provide 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 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 min at pH 7.2 (mimicking transition time of solid dosage form from proximal ileum to terminal ileum) was obtained. 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. In addition, menthol is well known intestinal and dermal permeation enhancer and anti-tumor agent. Hence, the traces of menthol present in the formulation may improve in vivo performance.
6.2 Methods:

6.2.1 Determination of eutectic composition of ibuprofen and menthol:
Ibuprofen and menthol were mixed in different ratios, on weight basis, at 35±2°C for 15 min in a mortar and pestle. The undissolved solids, if any, were carefully collected and weighed. The presence of only liquid phase indicates eutectic composition.

6.2.2 Formulation:
Polyvinylpyrrolidone (0.75 gm) was dissolved in 15 ml of eutectic mixture consisting of 60 parts of menthol and 40 parts of ibuprofen in a closed container. The solution was then adsorbed onto 25 gm of pregelatinized starch (PGs). The wet mass was passed through 20# mesh screen (850 μm opening) and dried at 50±2°C to facilitate evaporation of menthol. The dried granules (20#, batch D1) were mixed with 1.5 gm of sodium starch glycolate and the blend was characterized for angle of repose. The batches D2-D4 additionally contained 0.1, 0.5 and 1.5% w/w extragranular fraction of Cab-O-Sil M5 respectively. In batch D5, the granules of batch D1 were co-grinded with mannitol (1:0.25) in a mortar and pestle for 15 min. Granules of batch D5 containing 50 mg ibuprofen (347 mg) were filled into HPMC capsule (size 0) and characterized for in vitro drug release (Figure 6.a). The capsules of batch D5 were dip coated using solution of ethyl cellulose. The percentage weight gain of ethyl cellulose was varied to get the desired in vitro lag time of 90 min in phosphate buffer with pH 7.2 (mimicking fasting conditions of terminal ileum, Figures 6.b). Batches D6-D9 contained 1.5, 2.2, 3 and 2% weight gain of ethyl cellulose respectively. The composition of
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covering 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.

Figure 6.a Formulated ibuprofen colonic drug delivery system; (a) Hydroxypropyl methylcellulose empty capsule, (b) Hydroxypropyl methylcellulose capsule containing ibuprofen, (c) Ethyl cellulose coated capsule and (d) Eudragit® S100 coated capsule.

The capsules of batch D9 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). A lag time of 30 min was desirable at pH 7.2 (mimicking fasting conditions of proximal ileum). The composition of Eudragit® S100 solution was similar to that of ethyl cellulose. The Eudragit® S100 coated capsules (batches D10-D12 containing 4, 6.5 and 7.5% weight gain of Eudragit® S100 respectively) were characterized for enteric test and in vitro drug release (Figure 6.b).
6.2.3 Evaluations:

6.2.3.1 Angle of repose:

The angle of repose was measured using the fixed height funnel method.21-22

6.2.3.2 Assay of ibuprofen:

The amount of ibuprofen present in the formulation was determined as per IP 1996.23

6.2.3.3 In vitro drug release from ibuprofen uncoated capsule:

The capsules of batch D5 were subjected to in vitro drug release for 3 h 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

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temperature of 37±0.5° C. Ten ml samples were withdrawn and analyzed spectrophotometrically at 221 nm employing Shimadzu-1700 UV/visible spectrophotometer after suitable dilution of the samples. 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 ($r^2>0.999$).

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

The procedure was identical to that described above except the capsules of batches D6-D9 were subjected to in vitro drug release study for 5 h employing 900 ml phosphate buffer (pH 7.2) for first 2 h (mimicking fasting conditions of proximal ileum (30 min) and terminal ileum (90 min)) and finally in phosphate buffer (pH 6.4) for the remaining period (mimicking conditions of ascending colon). In vitro lag time, calculated by interpolation, was expressed as $t_{10\%}$, i.e. the time required to release 10% of the drug.

**6.2.3.5 In vitro drug release from Eudragit® S100 coated capsule:**

Hydrochloric acid (pH 1.2, mimicking fasting stomach), phosphate buffer (pH 6.0, mimicking fasting upper intestine), phosphate buffer (pH 7.2, mimicking fasting proximal and terminal ileum) and phosphate buffer (pH 6.4, mimicking ascending colon) were sequentially used as dissolution media for 2, 1, 2 and 3 h respectively. 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.
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6.2.3.6 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 2 h.25

6.2.3.7 Scanning electron microscopy:

The samples of batch D5 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 6.c.

![Scanning electron photograph of drug and formulated batch D5; (a) pure ibuprofen and (b) batch D5](image)

Figure 6.c Scanning electron photograph of drug and formulated batch D5; (a) pure ibuprofen and (b) batch D5
6.2.3.8 Fourier transformation infrared microscopy:

Pure ibuprofen and powder blend of batch D5 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$^{-1}$. The results are shown in Figure 6.d.

![Figure 6.d Results of Fourier transformation infrared spectroscopy; (a) pure ibuprofen and (b) batch D5](image)

Figure 6.d Results of Fourier transformation infrared spectroscopy; (a) pure ibuprofen and (b) batch D5
6.2.3.9 Short term stability study:

Optimized batch D11 was stored in polyethylene zip bags for 2 months at 40±5°C and 60% RH. At the end of two months, the HPMC capsules were subjected to drug content measurement and in vitro drug release studies (Figure 6.e). The procedures employed for drug content measurement and in vitro release were identical to that described above.

![Graph](image.png)

**Figure 6.e** In vitro drug release from batch D11 after short term stability study
6.3 Result 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. The 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 eutectic mixture. Ibuprofen exhibits poor flow (strong cohesive behavior) and poor tablettability. Improvement in compressibility and flow behaviour can be achieved by crystallization of ibuprofen from solvents. 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.

Menthol is chemically (1R, 2S, 5R)-5-methyl-2-(1-methylethyl)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 well known intestinal and dermal permeation enhancer and anti-tumor agent. The aim of the present 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 counterfeitors. 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...
Chapter 6: Capsule in capsule ibuprofen colonic drug delivery system to solid-solid mixing. Numbers of patents are filed on colonic drug delivery system.\textsuperscript{16} However, none of them uses 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±3.5, 81±3.5, 60±3.5 and 31±3.5 and 10±3.5 respectively. Complete liquification was observed in case of 6:4, 7:3, 8:2 and 9:1 of menthol to ibuprofen at 35±2\textdegree C. The results show that percentage undissolved solids are inversely related to percentage menthol upto 50\%. The eutectic blend consisting of 60 parts of menthol and 40 parts of ibuprofen was used for further studies. Menthol is well known intestinal and dermal permeation enhancer\textsuperscript{17-18} and anti-tumor agent.\textsuperscript{19}

Figure 6.a shows 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.\textsuperscript{33} Pregelatinized starch markedly reduces sticking, binding and ejection force in direct compression formulations. The self-lubrication property of pregelatinized starch lie 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).\textsuperscript{15} Batch D1 showed exhibited poor flow (angle of repose of 39\textdegree). Vasanthakumar and Vijaya described that the
angle of repose <30° indicates free flowing material.\(^3^4\) Hence, Cab-O-Sil, fumed silicon dioxide, was added upto 1.5% as an extragranular excipient in batches D2-D4 to resolve the issue of poor flow. The angle of repose of batches D2-D4 was 36, 34 and 31° respectively. 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.\(^3^5\) Hence, in batch D5, co-grinding technique with mannitol was adopted.

In pharmaceutical formulations mannitol is used as a non-hygroscopic diluent in the concentration range of 10-90\% w/w.\(^3^3\) Mannitol exhibit excellent compressibility and flow property. In addition, mannitol is commonly used as a taste masking excipient in chewable and mouth dissolving/disintegrating tablets because of negative heat of solution, sweetness and mouth feel.\(^3^3\) Co-grinding with mannitol (batch D5) 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 machine, the problem of wet variation will not be observed if the flow is good. The uniform drug distribution is critical in pharmaceutical dosage form.\(^3^6\)-\(^3^7\) 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. Granules of batch D5 showed uniform drug content uniformity (94±2\% ) than physical mixture of ibuprofen, pregelatinized starch, mannitol and sodium starch glycolate (81±3\%). In vitro
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drug release study of uncoated ibuprofen capsule was carried out in phosphate buffer (pH 6.4, mimicking conditions of ascending colon).\textsuperscript{15} Figure 6.b depicts that ibuprofen was immediately released from the capsule of batch D5 (>85% drug release in 45 min). The UV spectrum remained unchanged during in vitro study, indicating stability of ibuprofen during analysis.

The pH in terminal ileum and ascending colon is 7.2 and 6.4 respectively.\textsuperscript{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\textsuperscript{®} RL or Eudragit\textsuperscript{®} RS. The results shown in Figure 6.b reveals that the time required for 10% of drug release (lag time) from batch D6 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 D7 and D8 showed lag time of 101 and 148 min respectively. The data were subjected to mathematical model using linear regression analysis. The percentage weight gain was chosen as an independent variable (X) and lag time (t\textsubscript{10%}) was chosen as a dependent variable (Y). Equation 6.a shows the relationship between the dependent and independent variables with r\textsuperscript{2} value of 0.99 and p < 0.05. The required amount of percentage weight gain was 2% to get lag time of 90 min at pH 7.2. Batch D9 exhibited a lag time of 93 min.

\begin{equation}
Y = 62.57(X) - 38.74
\end{equation}

\textsuperscript{6.a}
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 D9 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 ≥ 7.0. Polyethylene glycol 400 was added as a hydrophilic plasticizer in the coating solution containing Eudragit® S100. The formulated batches D10-D12 satisfied the pharmacopeial (BP 2001) requirements for the enteric test. Figure 6.b shows that the batch D10 containing 4% 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 % weight gain. Higher percentage weight gain of Eudragit® S100 was applied in subsequent batches (D11-D12). Batch D11 containing 6.5% Eudragit® S100 weight gain provided desired lag time of 30 min at pH 7.2 with little drug release (8%) before reaching pH of ascending colon (pH = 6.4). Complete drug
release was achieved within 2 h at pH 6.4. Batch D12 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 D11 was ranked as an optimized batch.

Scanning electron microscopy of pure drug and granules of batch D5
confirms presence of ibuprofen crystals (rod shape) in the formulation (Figure
6.c). The infrared spectra are shown in Figure 6.d. The infrared spectra of
ibuprofen and batch D5 were comparable. Ibuprofen showed two prominent
peaks at 2871 cm⁻¹ and 1701 cm⁻¹ because of presence of aliphatic alkyl and
carboxyl groups respectively. The peaks present in ibuprofen were retained in
batch D5 indicating stability of ibuprofen during processing.

Short term stability study of batch D11 was carried out for 2 months at
40±5°C with 60% RH. The HPMC capsules were examined for fracture of coats,
drug content and the change in vitro drug release (Figure 6.e). Cracks were not
noticed in coats on visual inspection of the HPMC capsule after 2 months. Drug
content was found to be 95±2%. Unpaired t-test with equal variance indicated
statistical insignificant difference in the in vitro drug release profile from the
HPMC capsules of optimized batch (D11) at 5% level of significance with t_{calculated}
(0.07)< t_{critical-one tail} (1.69).

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, whereas HPMC capsules contain <2% moisture.

6.4 Conclusion:

The colonic drug delivery system of ibuprofen was developed using the concept of eutectic mixture. The 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 (D11) showed about 92% drug release at ascending colonic pH (pH = 6.4) within 2 h. The traces of menthol left in the dosage form may function as a permeation enhancer and anti-tumor agent. The 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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6.5 References:


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