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Development of Pulsatile Systems for Targeted Drug Delivery of Celecoxib for Prophylaxis of Colorectal Cancer

V. R. Sinha  
University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India

J. R. Bhinge  
Ranbaxy Research Laboratories, Gurgaon, India

Rachna Kumria  
Ind-Swift Laboratories, Parwanoo, India

Manoj Kumar  
Ranbaxy Laboratories Ltd, Paonta Sahib, India

The aim of the present study was to formulate fast release enteric-coated tablets for drug delivery to the colon. Two different approaches were used for the preparation of these tablets. The first included making use of superdisintegrant (SD) in the tablet. The amount of super disintegrant (cross-linked PVP) in the tablet and the coat weight were varied to formulate a suitable time-controlled release system, that would provide colon-specific drug delivery. The second approach consisted of development of osmogen-based tablets for drug delivery into the tracts of the colon. Two different osmogens, sodium chloride and potassium chloride, were used. These also were coated at different coat levels. Celecoxib was used as a model drug. In vitro drug release studies showed that superdisintegrants were more effective in showing burst effect in the tablets and therefore showed a rapid drug release as compared with osmogens, which would show a sustained drug release all through the colon. Osmotic tablets were formulated making use of a high concentration of osmogen sodium chloride (OM-SC) and potassium chloride (OM-KC) were further enteric-coated. These also were found to be useful in providing a sustained delivery of nearly 80–90% of the drug into the colonic region. The coat weight required in these tablets for protection in the upper gastrointestinal conditions varied from 9.69% in OM-KC tablets to 4.65% in OM-SC tablets.

Keywords  
Celecoxib, Cross-linked PVP, Osmogen, Potassium Chloride, Sodium Chloride, Superdisintegrant

During the past few decades there has been a considerable development in the field of colon-specific drug delivery. This is because the colon has a large amount of lymphoma tissue (which would facilitate a direct absorption into the blood), negligible brush border membrane peptidase activity, and much less pancreatic enzymatic activity as compared with the small intestine (Sarsija and Hota 2000; Lee 1991; Ikesue, Kopeckova, and Kopecek 1991). The colon also is considered as a suitable site for delivery of proteins, peptides, and acid labile drugs (Reddy, Sinha, and Reddy 1999). Development of locally acting colorectal-targeted drug delivery systems may revolutionize the treatment of such colonic diseases as, ulcerative colitis, Crohn’s disease, carcinomas, and infections.

Various approaches have been used for colon-targeted delivery systems including use of prodrugs, pH sensitive systems (Sinha and Kumria 2003a), microbially triggered systems (Sinha and Kumria 2001a, 2001b, 2002, 2003b), osmotically controlled drug delivery systems, pressure-dependent release systems, and timed release systems. Of all the systems formulated for colon-specific drug delivery, the use of pH sensitive systems (enteric-coated systems) have much more practical significance due to ease of their formulation (Leopold 1999). These systems find rationale in the fact that the pH of human gastrointestinal (GIT) increases progressively from the stomach (pH 1–3), small intestine (pH 6.5–7) and reaches up to 7–8 in the colon (Ashford and Fell 1994).

Enteric-coated systems provide protection to the formulation from drug release in the stomach. A thicker coat of these polymers on the delivery systems additionally would provide a lag phase to the formulation. This lag phase can be tailor-made to equate the small intestinal transit time. However, in case of a thicker coat of the polymer, the dosage form may pass through the upper GIT, intact without showing a drug release (Ashford...
et al. 1993). Alternatively some drug release retarding agents can be introduced into the formulation (Sinha and Kumria 2002). Osmotic agents generally have been used in the formulation to show burst effect. The present study was designed making use of superdisintegrants in the formulation as bursting agents, and these were evaluated against the osmogens to show such an effect. In vitro drug release studies were performed and drug release behavior characterized.

The aim of the present formulation was to provide a rapid drug release after a lag time of 5–6 hr into the proximal colon. The proximal colon is the most absorptive site of the colon since the chyme is in a semiliquid form when it arrives there. Thus, the chance of drug absorption from this site is maximum. These dosage forms also can be useful when a local pathology is restricted to this region of the colon.

The rationale of keeping the lag phase of 5–6 hr is that the usual gastric transit time in the fed state is 2 hr though this may vary (Rubinstein 1995). However, since the dosage form is enteric-coated, the variations in gastric transit time can be overcome. Further, the small intestinal transit time is relatively constant and is around 3–4 hr (Kinget et al. 1998). The thicker coat providing a lag or silent phase of 5–6 hr would be able to carry the dosage form into the proximal colon where drug release is desired. To ensure rapid drug release upon arrival into the proximal colon, the dosage form was designed to include superdisintegrants/osmotic agents (osmogens) so that during the transit through the small intestine when the dissolution of the polymer coating starts, a pressure starts building up in the tablet and as the pressure exceeds, the tablet bursts. The duration of this lag phase can be increased or decreased depending upon the site at which drug release is desired. This time of bursting of the tablet with respect to the coat weight thickness, the quantity of superdisintegrant and the type of osmogen used was investigated.

The quantity of the superdisintegrant in the tablet and the coat weight was varied and these tablets were evaluated for their drug release characteristics. Similarly enteric-coated tablets containing different osmogens were prepared. These were coated to different coat levels. The utility of osmogens as compared with the super-disintegrant to provide a rapid colon-specific drug delivery was evaluated. Osmotic agents are known to show bursting effects in the tablets.

**MATERIALS AND METHODS**

Celecoxib was obtained as gift sample from Hetro Drug Ltd, (Hyderabad, India). Methacrylic acid copolymers (Eudragit® L-100 and Eudragit® S-100) were supplied as gifts by COREL Pharma-Chem (Ahmedabad, India). Microcrystalline cellulose (Avicel PH 102) was obtained as gift samples from Ranbaxy Laboratories Limited, (Gurgaon). Cross-linked PVP was obtained from ISP Technologies (USA). Other ingredients such as lubricant, glidant, and plasticizer used to prepare the tablet were of standard Pharmacopoeial grade and all chemical reagents used were of analytical grade.

**Preparation of Core Tablets**

Core tablets containing 10 mg of celecoxib and superdisintegrant (SD)/osmogen (OM) were prepared with microcrystalline cellulose (MCC) as filler using direct compression method. The tablets containing celecoxib and other tableting excipients were mixed and then compressed into tablets on single punch machine (Modern Engineering New Delhi, India) using 7 mm deep concave punches. The granules weighing 125 mg were weighed and tabletted individually.

**Core Tablets with Superdisintegrant (SD)**

Core tablets were prepared making use of two different concentrations of superdisintegrants. One containing 3 mg (2.4% w/w) and the other had 1.5 mg (1.2%w/w) of cross-linked PVP. These were prepared as described above. Tablets containing 1.5 mg of SD were coated to two different coating levels, whereas those containing 3 mg cross-linked PVP were coated to three different coat levels. These were coded as depicted in Table 1.

**Core Tablets with Osmogens**

Core tablets were prepared making use of two different osmogens namely sodium chloride (NaCl) and potassium chloride (KCl). These were used at a concentration of 92% of the tablet weight. These tablets were further coated to two different coat levels. All the tablets containing SD, NaCl, and KCl were evaluated for appearance, uniformity of weight, hardness, thickness, drug content, and disintegration time to meet a predetermined criteria.

**Coating of Tablets**

The coating solution containing Eudragit® L-100; Eudragit® S-100 in the ratio of 1:5 was prepared in a mixture of acetone

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation code and the percentage of SD/OM present in the tablet and the coat weight</td>
</tr>
<tr>
<td>Formulation code</td>
</tr>
<tr>
<td>SD-1.5A</td>
</tr>
<tr>
<td>SD-1.5B</td>
</tr>
<tr>
<td>SD-3 A</td>
</tr>
<tr>
<td>SD-3 B</td>
</tr>
<tr>
<td>SD-3C</td>
</tr>
<tr>
<td>OM-KC-A</td>
</tr>
<tr>
<td>OM-KC-B</td>
</tr>
<tr>
<td>OM-SC-A</td>
</tr>
<tr>
<td>OM-SC-B</td>
</tr>
</tbody>
</table>

SD = Superdisintegrant, OM = Osmogen, KC = potassium chloride, SC = sodium chloride.
and isopropyl alcohol (1:1) using PEG 400 (1.25% w/w) as plasticizer. The solution was vortexed for 1 min to obtain a clear solution. The tablets containing celecoxib were coated at different levels of coating using dip-coat method and dried with the help of dryer with an inlet air temperature of 33–40°C. The coating process was repeated until the desired level coating thickness was achieved.

**Disintegration Test**

Disintegration testing was carried out according to the USP 23 on core tablets to check the effect of SD in comparison to the osmotic agents (such as sodium chloride and potassium chloride) in carrying out the disintegration. Disintegration testing was carried out in phosphate buffer pH 6.8.

**Bursting**

Bursting time was taken to be the time when the tablet coat was no longer able to withstand the internal pressure and the tablet opened up as noted visually. The test was carried out in the dissolution media by keeping the tablets in buffer (pH 6.8) at 50 rpm at 37 ± 0.5°C. The test was carried out 6 tablets for each formulation.

**Dissolution**

Dissolution test was performed on the tablets to study the effects of different coating levels on release profiles of the tablets. The USP 23 Method A for delayed release tablets (paddle method, 50 rpm and 37°C), using a USP apparatus (Labindia Ltd.). Initial studies were carried out in 750 ml of 0.1 N HCl (pH 1.2) after which 250 ml of a 0.2 M trisodium phosphate solution was added into the dissolution media and the pH was adjusted to 6.8. To maintain the sink conditions, sodium lauryl sulphate (0.5%, SLS) was added. Samples were collected manually at predetermined time intervals and analyzed for celecoxib content using ultraviolet (UV) spectrophotometer (Shimadzu-1601, India). The UV readings were taken at 248 and 249 nm for samples tested in 0.1N HCl and the buffer media, respectively.

**RESULTS AND DISCUSSION**

**Disintegration Test Uncoated Tablets**

At the highest level, 3 mg of SD, the disintegration time was 1.16 min in buffer pH 6.8. In the other three formulations (tablets with 1.5 mg of SD, potassium chloride tablets, and sodium chloride tablets), disintegration time was 1.54 min, 9.17 min, and 7.76 min, respectively (Table 2). The result depicts that the SD tablets disintegrate at faster rate, once the tablet coat dissolves. Disintegration test carried out on coated tablets with lower coating level of 20% showed that disintegration time for tablets was greater than 330 min. Bursting times for each formulation with different levels of coating are given in Table 3.

**Table 2**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets with 3 mg of superdisintegrant</td>
<td>1.16</td>
</tr>
<tr>
<td>Tablets with 1.5 mg of superdisintegrant</td>
<td>1.54</td>
</tr>
<tr>
<td>Tablets with potassium chloride</td>
<td>9.17</td>
</tr>
<tr>
<td>Tablets with sodium chloride</td>
<td>7.76</td>
</tr>
</tbody>
</table>

**Dissolution Test on SD Tablets**

All the formulation met the USP criteria for enteric performance test in 0.1N HCl (for 2 hr). In tablets containing 3 mg of superdisintegrant (SD-3) coated with 30.46% coating, SD-3-A tablets, cumulative percent drug release was 53.84% in the first 5 hr of the study, and this increased to 80.36% in 6 hr and was 99.9% in 24 hr. We observed that only 46.06% drug release from the formulation takes place in the 6–24 hr intervals. The coating was further increased to 42.04% in SD-3-B tablets. SD-3-B tablets showed a cumulative percent drug release of 35.22% in the first 5 hr of the study, which increased to 60.25% in 6 hr and was 100% in 24 hr. We observed that only 64.78% drug release from the formulation takes place in the 6–24 hr intervals. The above two results of SD-3-A and SD-3-B indicate that a 3-mg content of SD in the tablet shows the desired bursting, but the initial duration of lag phase that is required from the present formulation needs to be increased. In SD-3-A tablets, nearly 80% of drug release is observed between 2–6 hr interval showing rapid drug release. Similarly in SD-3-B tablets this rapid drug release period was between 3–8 hr, showing nearly 65% drug release in these 5 hr intervals. So, the coat weight was further increased.

This burst effect phase needs to be tailored toward the right with a rapid disintegration phase starting 5 hr post-dose. Considering this, the coat weight was increased to 51.04% in the SD-3-C tablets. The SD-3-C tablets showed a cumulative percent drug release of 9.41% in the first 5 hr of the study, which increased to 22.11% in 6 hr and was 99.9% in 12 hr. The dissolution profiles of celecoxib tablets containing 3 mg of SD (SD-3-A, SD-3-B, and SD-3-C) are shown in Figure 1. Results show that by increasing the coat weight to 51.04% in SD-3-C tablets the rapid release period shifted further to right, and the
rapid release was seen in 5–10 hr interval with more than 80% drug release in this period.

To reduce the coat weight, the amount of SD in the tablet was reduced to 1.5 mg. The tablets SD-1.5-A containing 1.5 mg of SD, coated to 37.98% coat weight, showed a cumulative percent drug release of 4.36% in the first 5 hr of the study, which increased to 5.1% in 6 hr and was 95.19% in 24 hr. We observed that 90% drug release from the formulation takes place in the 6–24 hr intervals, i.e., during the colonic transit time. The lag time for drug release from the formulation was ∼6 hr. When coating was increased further from 37.98 to 46.64% in SD-1.5-B tablets, no drug release was observed until ∼8 hr and a total of 57.26% drug release was found in 24 hr (Figure 2). This may be explained by the coat weight of 46.64% is considerably higher, this much coat weight slows down the seeping in of dissolution media considerably. The small amount of disintegrant is unable to exert its effect within the desired time.

Considering the normally accepted GI transit time, 2 hr for stomach and 3–4 hr for small intestine, the SD-1.5-A and SD-3-C formulations release the drug directly into colon. The increase in lag time of SD-3-C tablets containing 3 mg of SD was due to increase in coat weight. The disintegration and dissolution time depends on the coating thickness (Ashford et al., 1993), as well as the amount of SD added. The coat weight of these systems may seem to be very high. But considering that in compression-coated systems, the coat weight may more than 200% of the core, these systems definitely have an upper edge in being able to be formulated using the usual enteric-coating procedures.

The above study shows that the dissolution time can be extended by increasing the coating thickness (Ashford et al., 1993), as well as the amount of SD added. The release of drug from the enteric-coated tablets can be attributed to pore formation and bursting of the coat due to the presence of SD. As the pH of solubilization of Eudragit® L-100 is 6 and that of Eudragit® S-100 is 7, Eudragit® L-100 get dissolved first and forms pores, at pH 6.8 (pH of dissolution media). The bursting of tablets with SD occurs because of rapid uptake of water from the pores, followed by swelling due to capillary action (Kibbe 2000). Cross-linked PVP, when added to the formulation has enhances dissolution of poorly soluble drugs from solid dosage forms (Kornblum and Stoopak 1973). This might have contributed to the faster dissolution. Bursting of tablets thus minimizes the risk of the dosage from coming out intact from the GI tract as demonstrated by Ashford et al. (1993) for Eudragit® S-100 coated tablets.

Dissolution Test on Osmogen Tablets

In tablets containing osmogens, those containing potassium chloride with a coat weight of 9.69%, OM-KC-A tablets, the cumulative percent drug release was found to be 5.16% in the first 5 hr of the study and a total of 94.25% of drug was released in 24 hr. These systems seem quite promising for a sustained delivery of drug into the colonic region. To refine these systems further, the coat level was increased. When coating was increased from 9.69 to 13.75% (in OM-KC-B tablets), a cumulative percent drug release of 3.57% was found in the first 5 hr of the study and this increased to 41.41% in 24 hr (Figure 3). These results may be attributed to the fact that an increase in coat weight led to decreased seeping of water into the tablet, due to a delayed pore formation in thicker coats. Thus, the tablets are not able to release the complete drug within the usual colonic transit time (taken as 20 hr for the purpose of the present study).
OM-KC-B systems were not suitable for delayed release systems for colonic drug delivery.

Tablets containing sodium chloride (OM-SC-A tablets) coated to 4.65% showed a cumulative percent drug release of 6.95% in the first 5 hr of the study, which increased to 90.26% in 24 hr. We observed that 83.31% drug was released from the formulation in the 6–24 hr intervals. When coating was increased further from 4.65 to 9.44% in OM-SC-B tablets, a cumulative percent drug release was 1.08% in the first 6 hr of the study and was 19.25% in 24 hr. We observed that only 18.17% drug release from the formulation takes place in the 6–24 hr interval. The dissolution profiles of celecoxib tablets containing sodium chloride (OM-SC-A and OM-SC-B) are shown in Figure 4. This may be explained similarly as in OM-KC tablets.

Even though sodium chloride has a higher osmotic pressure than potassium chloride, it requires lower percentage of coating for complete release of drug. At 9.44% of coating, the release of drug was found to be 19.25% in 24 hr. But after reducing the coat weight to 4.65%, the release was improved to 90.26% in 24 hr. The release from sodium chloride tablets was much slower as compared with potassium chloride tablets at approximately the same coating level. The release of drug from the tablets containing osmogens is due to development of hydraulic pressure; when dissolution medium imbibe the osmogen, it exerts hydraulic pressure on the film and ruptures the coating.

CONCLUSION

The presence of superdisintegrant/osmotic agent in the enteric systems formed time-controlled drug delivery systems that could facilitate drug delivery into different segments of the GIT depending upon the coat weight and the concentration of these agents. Fast melt tablets could be formulated making use of SDs rather than osmogens. Presence of 2.4% SD in the tablet coated to a coat weight of ~51% formed fast release tablets facilitating drug release in the proximal colon. The coat weight determines the silent/lag phase of the formulation, whereas the coat weight and amount of SD in the tablet determines the burst effect and rapid/sustained drug release.

Osmotic tablets could be formulated making use of potassium chloride/sodium chloride (92%) in the core tablets and further enteric-coated. A coat weight of 4.65% in sodium chloride tablets would deliver ~83% of the drug into the colon in a sustained manner. In potassium chloride tablets, a coat weight of 9.69% facilitated the delivery of more than 90% of drug into the colonic region.

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