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Coating polymers for colon specific drug delivery: A comparative *in vitro* evaluation

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Colon is being extensively investigated as a drug delivery site. This study a comparison of the usual enteric coating polymers viz. Eudragit, a cellulose acetate phathalate with shellac and ethyl cellulose, as carriers for colon specific drug delivery. Lactose based indomethacin tablets were prepared. These were coated with one of the coating polymers to a varying coat thickness. The coated formulations were evaluated for dissolution rates under simulated stomach and small intestine conditions. From the dissolution data obtained, it was found that the dissolution rate varied with the type and concentration of the polymer applied. Comparative dissolution data revealed that, of all the various polymers and coat thicknesses used, a 3% (*m/m*) coat of shellac was most suitable for colonic drug delivery. It retarded drug release by 3–4 h (the usual small intestinal transit time) in simulated small intestinal fluid, whereafter a rapid drug release was observed.

Keywords: enteric coating, enteric coating polymers, shellac, CAP, Eudragit-S, ethyl cellulose

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Colon is being evaluatied as a site for drug delivery, not only for local colonic pathologies but also for systemic drug delivery and for delivery of protein and peptide drugs (1, 2). This site may also be useful in treatment of diseases susceptible to diurnal rhythm such as asthma, arthritis, *etc*.

As a site for drug delivery, colon offers a near neutral pH, reduced digestive enzymatic activity a long transit time (3) and an increased responsiveness to absorption enhancers. This has led to the development of various systems for targeting drugs to the colon.These include pH- controlled release systems, enzyme-controlled delivery systems (4, 5) (including prodrugs and polysaccharide based delivery systems), time- controlled release systems (3) and pressure/osmotically controlled release systems (1). However, the coated dosage forms, especially the enteric coated dosage forms are most popular (6).

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Enteric-coated systems are designed to provide protection to tablets in the stomach. Application of a thicker coat causes a delay in drug release in the small intestine and slows down drug release, which is both pH and time controlled. This time-controlled drug release may be retarded by 3–4 h. This ensures drug delivery to be colon specific. For the preparation of such tailor- made formulations, the selection of a polymer with a suitable coat level is crucial (6).

Most of the commercially available systems for colon specific drug delivery utilize Eudragit (L-100/S-100) or cellulose acetate phthalate (CAP). Other coating polymers such as shellac (SH) and ethyl cellulose (EC) may provide an alternative polymer for the development of these systems. Eudragit S-100 (ES) is a methacrylic acid methylmethacrylate co-polymer, which is soluble at a pH of 7 (7). Cellulose acetate phthalate is also an effective enteric film coating material as it dissolves at a pH of 6.0 (6). As an enteric-coating polymer, it is used at a concentration of 0.5–0.9% (7).

Shellac is a naturally occurring material obtained from lac, a resinous secretion of the insect *Laccifero lacca* Kerr. *(Coccidae)* (7). It is an inexpensive and abundantly available polymer and is used for enteric coating of tablets and beads. Ethyl cellulose is a hydrophobic polymer used as a tablet coating material.

For a formulation to act as an effective colon specific drug delivery system, the primary condition is that a minimum amount of drug should be released in the environment of the upper gastrointestinal tract, *i.e.*, in stomach and small intestine. The normal transit time in the stomach is 2 h (though this may vary), while in the small intestine it is relatively constant and is around 3 h (1). The usual colonic transit time varies from 20–30 h (3). This, for a dosage form to be effective as a colon drug delivery system, the drug release is required to be retarded in the upper GIT conditions. Thereafter, the drug release should be complete within the next 20–30 h.

The present study explores the comparative utility of the above polymers in developing a suitable dosage form, exhibiting a minimum drug release in the upper regions of the GIT in order to provide targeted drug delivery to the colon. For this purpose, varying concentrations of polymers were applied and the effect of the coating on drug release and site specifity was evaluated *in vitro*.

EXPERIMENTAL

Materials

Indomethacin was a generous gift from Indian Drugs and Pharmaceuticals Limited (India). Eudragit L-100 was donated by Panacea Biotech (India). Shellac flakes were procured from NAMCO Pharmaceuticals, (India), ethyl cellulose and CAP from S.D. Fine Chemicals (India). All the other excipients used to prepare and coat the tablets were of analytical/ pharmacopoieal grade.

Methods

Tablet preparation. – Indomethacin tablets were prepared by wet granulation, using lactose as the main filler. Starch was used as binder. For a batch of 300 tablets, 7.5 g of indomethacin and 54 g of lactose were mixed. Starch (1.35 g) was added as disintegrant. The prepared powder mix was granulated using starch paste (10%). The wet mass formed was passed through a sieve with a nominal aperture size of 2 mm and dried in an oven for 6 h. The dried granules were screened through another sieve with a nominal aperture of 1 mm. The sieved granules were blended with talc (1.5%) and magnesium stearate (1%). Tablets weighing 225 mg and containing 25 mg of indomethacin were individually punched on a single punch tabletting machine (Modern Engineering Works, India) using a 7.9 mm concave die-punch and a compression force of 500 kg cm^2. Tablets were tasted for mass (Table I) and content uniformity, friability, disintegration, *etc*. Tablets conformed to USP limits for all the above-mentioned tests. Thickness of tablets was found to be 3.3 ± 0.1 mm, *i.e*, within the permissible limits.

Tablet coating. – Coating solutions were prepared using the usual concentrations of polymers used for coating (7). For Eudragit- S100, 12.5% (*m/V*) Eudragit S-100 (ES) was prepared using *iso*propyl alcohol and PEG-400 (1.25% *m/m*) as plasticizer. In the case of cellulose acetate phthalate, a 15% (*m/V*) solution in acetone was used for coating and propylene glycol (1.5% *m/m*) was used as plasticizer. In the case of coating with shellac, a 30% (*m/V*) solution in isopropyl alcohol was used. For ethyl cellulose, a solution of 5% (*m/V*) in acetone was used and ethyl alcohol (1.5% *m/m*) was used as plasticizer.

The tablets were coated with different polymers, at two or three different concretrations. The desired volume of coating solution was poured on the prewarmed tablet (batch size 50 g) bed in a pan coater. The tablets were coated and dried with the help of inlet air (temperature 35–45 °C). The coating process was repeated till the desired level of coating was achieved. The percent mass increase of the tablets upon coating was taken to be indicative of the coat thickness.

Dissolution studies

The USP 24 (8) method for enteric-coated tablets (basket method, 75 rpm, 37 ± 0.5 °C) using a USP dissolution test apparatus was used for all experiments. For the initial 2 h, the study was conducted in 750 ml of 0.1 mol L^{-1} HCl, followed by dissolution at a pH of 6.8 (adjusted by addition of 250 mL of 0.2 M trisodium phosphate) (8–11). Aliquots were collected manually at predetermined time intervals and analyzed for indomethacin using a UV-visible spectrophotometer at a λ_{max} of 318 nm (Shimadzu 1601, Japan).

Data analysis

The raw dissolution data were analyzed using the ZOREL software (12). The software has an inbuilt provision for applying the correction factor for volume and drug losses during sampling. The software was used to calculate the values of the amount of drug dissolved, percent of drug released, rate of drug release and the fraction released at various time intervals. Using the software, the values of the diffusional release exponent

(*n*) are obtained using logarithmic transformation of the relationship proposed by Korsmeyer *et al.* (13). For non-swellable matrices, for *n* ## 0.45 drug diffusion obeys fickian kinetics, for $n = 0.45–0.9$ the drug release behavior follows non-fickian, for $n > 0.9$, the drug release follows zero-order kinetics and for $n > 1$ the drug release is anomalous. The statistical parameter for each tablet unit and their mean values were computed and the type of release, whether fickian, non-fickian or zero-order, predicted.

ANOVA was applied for statistical comparisons.

RESULTS AND DISCUSSION

All the enteric-coated systems showed no drug release in the first 2 h in the simulated gastric environment. Ethyl cellulose-coated tablets also showed negligible drug release in the initial 2 h of dissolution. Afterwards, a different drug release profile was evident for each polymer..

Eudragit S-100 coating. – Percent of drug release versus time plot shows that the dissolution rate was inversely proportional to the thickness of the coat applied (Fig. 1a). A significant difference ($p < 0.001$) was observed in the percentage of drug released for different coating concentrations, fromf 4 h, to 12 h during the dissolution study. Drug release was found to be of zero-order ($n > 0.9$) at all three coat concentrations. At a coat concentration of 1% (*m/m*), the percent drug release in the first 3 h of dissolution at pH 6.8 (small intestinal environment and transit time) was 39%. Increasing the coat thickness to 1.5% and 3% reduced the drug release to 28% and 18%, respectively. All the coated tablets showed a nearly complete drug release in the next 20 h. These results are in agreement with the results of Ashford *et al.* (14), who demonstrated that an increase in coat thickness of Eudragit S shows a decrease in the dissolution rate of salicylic acid. This can be explained by the fact that increasing the coat concentration made the coat more impermeable and drug release was retarded. Slowly as the coating solubilized, drug dissolution through it was facilitated.

Cellulose acetate phthalate coating. – Similarly, varying the coat thickness of CAP varied the percent drug release from the tablet significantly at the end of 3 h, up to 18 h ($p < 0.001$) (Fig. 1b). Drug release kinetics was found to follow non-fickian kinetics at a coat concentration of 1.5 % (*m/m*) ($n = 0.802$) whereas it was zero-order at the other two coat concentrations (3% and 5%) ($n > 0.9$). The formulation with a 5% coat showed as low as 25% drug release in the first 3 h of dissolution at pH a 6.8. A total of 90% drug was released in the next 20 h. The results for CAP are also in agreement with the studies conducted by Levine *et al.* (15), since they also found the usefulness of this polymer for delivery of beclomethasone dipropionate to the colon. Although an increase in coat concentration retarded drug release, no considerable retardation was observed. This may be attributed to the fact that the dissolution medium (pH 6.8) which is well above the pH of CAP solubilization.

Shellac. – Shellac, however, showed a different drug release profile (Fig. 1c) with a high *n* value (1.4–1.27), which is beyond the range of fickian, non-fickian or zero-order release. A significant difference ($p < 0.001$) was observed in the percent drug released from the tablets with different coating concentrations from the second hours up to 9

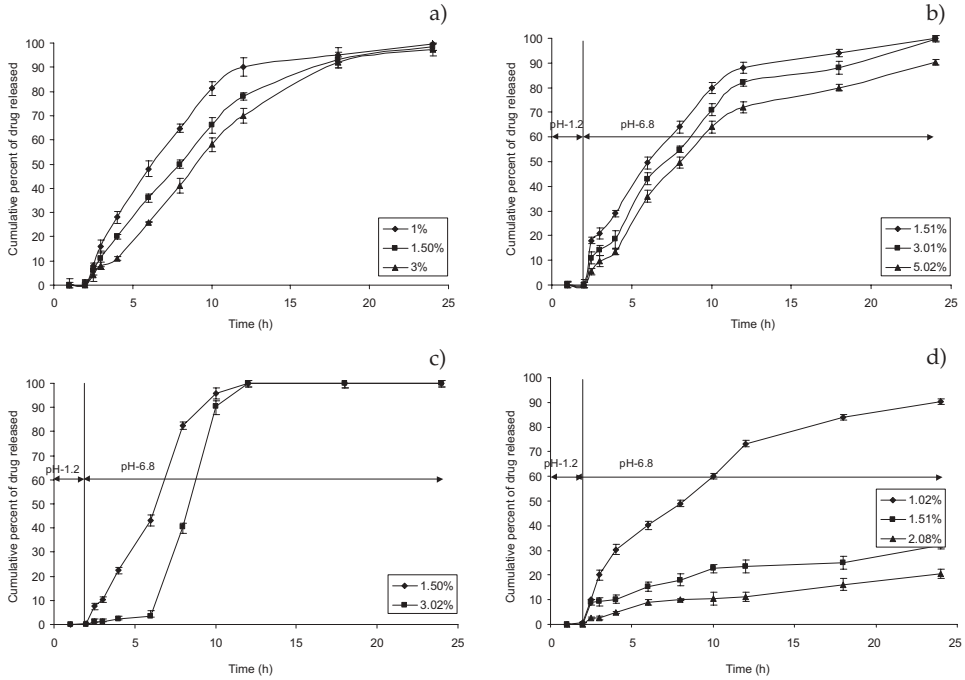

Fig. 1. Cumulative percent of drug released (mean ± S.D, $n = 6$) *versus* time profile for tablets coated with: a) Eudragit-S 100, b) CAP, c) shellac, d) ethyl cellulose.

hours of the dissolution study. A coat concentration of 1.5% retarded drug release for the first 2 h and percent drug release during this time was almost with after 6 h it was 42.2 ± 2.2% and around 100% drug was released in 12 h of dissolution (1c). However, increasing the coat concentration to 3% almost resisted drug release for the initial 4 h of dissolution at pH 6.8 where after, a rapid drug release was observed, which became 100% in the tenth hour. The typical drug release of shellac can be explained by the fact that at a lower coat concentration, after introduction into a medium of pH 6.8, there is a slow solubilization of shellac whereby channels within the film through which the drug diffuses are formed slowly. However, when the coat mass was increased, due to the slow solubilization of this polymer, formation of channels through thicker coat took some time, which in this case was 3–4 h. The ability of shellac to resist drug release for 3–4 h, followed by a rather rapid drug release, can be exploited for delivery of various drug molecules to the colon.

Ethyl cellulose coating. – The drug release from the EC coated tablets was zero-order ($n = 1.0$) at the lowest coat concentration and increasing the coat concentration changed the drug release kinetics to non-fickian ($n = 0.671$), and further to fickian diffusion ($n = 0.328$). These tablets also showed a decrease in drug release upon increasing the coat mass (Fig. 1d). Percent drug release varied significantly from the end of the third hour

up to 24 h ($P < 0.001$) at different coat concentrations. The amount of drug released (at pH 6.8) decreased upon increasing the coat concentration. The drug release from EC coated tablets can be explained by the fact that at a low coat thickness film formed retards drug release but diffusion of drug continues through such a film. Upon increasing the coat thickness, the release rate was highly suppressed, suggesting that the thicker film formed by ethyl cellulose was quite impermeable.

Different behavior observed in the case of shellac compared to other polymers can be explained by the fact that, unlike other polymers such as Eudragit and CAP, shellac solubilizes rather slowly. This is further confirmed by the observation that unlike other polymers, shellac needs to be soaked overnight before being used for enteric/seal coating purposes. This may be due to the presence of waxy substances in shellac, but once the polymer solubilizes, the coating loses its intactness and a rapid drug release is observed.

CONCLUSION

At a coat concentration of 3%, shellac provided the most appropiate polymer coat for colon specific drug delivery in the present study, which may be useful for local colonic pathologies and for systemic drug delivery. Shellac is a natural polymer that is also abundantly available and cost effective. Moreover, the study shows that it provides a site-specific drug delivery. Variation in shellac coat thickness can facilitate drug delivery to terminal ileum, distal or proximal colon.

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S A Ž E T A K

Polimeri za oblaganje za specifičnu isporuku lijeka u kolonu: usporedno *in vitro* vrednovanje

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Isporuka lijekova preko kolona intenzivno se istražuje. U ovoj studiji uspoređivani su uobičajeni gastrorezistentni polimeri Eudragit, celuloza acetat ftalat sa šelakom i etilceluloza kao nosači za specifičnu isporuku lijekova u kolonu. Tablete indometacina s laktozom obložene su s jednim od polimera za oblaganje. Debljina obloženog sloja je varirana. Određivana je brzina oslobađanja ljekovite tvari u simuliranom želučanom i crijevnom soku. Dobiveni podaci ukazuju da oslobađanje ljekovite tvari ovisi o vrsti i koncentraciji primjenjenog polimera. Za isporuku u kolonu bio je najpovoljniji pripravak sa 3% (*m/m*) otopinom šelaka, koji je usporio oslobađanje ljekovite tvari za 3-4 h (uobičajno vrijeme prolaza kroz tanko crijevo) u simuliranom crijevnom soku. Nakon tog vremenskog razdoblja slijedi brzo oslobađanje ljekovite tvari.

Ključne riječi: gastrorezistentna ovojnica, gastrorezistentni polimeri, šelak, CAP, Eudragit-S, etilceluloza

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