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Cross-Linked Guar Gum Hydrogel Discs for Colon-Specific Delivery of Ibuprofen: Formulation and In Vitro Evaluation

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Hydrogel discs of guar gum cross-linked with glutaraldehyde were prepared as vehicles for colon-specific drug delivery. Ibuprofen was chosen as model drug. The discs were evaluated for such parameters as size, shape, weight, and drug loading. Swelling (buffer uptake) and in vitro drug release study, in presence and absence of rat caecal contents, was performed in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4) to evaluate the effect of various formulation parameters like guar gum concentration, amount of cross-linking agent, and cross-linking time on drug release. Cross-linking resulted in significant reduction in swelling of guar gum. Significant increase in drug release was observed in medium containing rat caecal content. Percent drug release increased with increasing glutaraldehyde concentration. Cross-linking time and guar gum concentration did not have any significant effect on drug release in the range studied.

Keywords Colon Delivery, Cross-Linking, Guar Gum, Hydrogel, Ibuprofen

The delivery of drugs to colon either for local action or for systemic action has gained importance in recent times. The reason for this is the thrust to deliver drugs at the site of action to produce minimum or no side effects and the unique physiological environment for systemic absorption of drugs. Use of polysaccharides is one of the various strategies developed to target drugs specifically to colon (Chourasia and Jain 2003; Vandamme et al. 2002). They remain intact in the hostile environment of the stomach and small intestine and are degraded by polysaccharidases upon arrival in colon (Rubinstein et al. 1993). Guar gum is a widely used polysaccharide for colon-specific drug delivery (Krishnaiah et al. 2002; Rama Prasad, Krishnaiah, and Satyanarayana 1998). It is degraded by Bacteroides and Ruminococcus present in the colon (Englyst, Hay, and Macfarlane 1987; McCleary et al. 1983).

Its enormous swelling is a drawback in its use as colonic carrier as there is a risk of drug leakage. Reduced swelling of the gum by cross-linking it with different cross-linking agents has been achieved (Gliko-Kabir et al. 1998, 2000a, 2000b). Cross-linking and reducing the macromolecular mesh size available for drug diffusion modify the macromolecular structure and consequently prolong drug release (Kim and Lee 1992). Cross-linking density and extent of swelling regulate rate of drug release (Peppas and Korsmeyer 1986).

Ibuprofen was used as model drug. It is a water insoluble (Herzfeldt and Klummel 1983), nonsteroidal anti-inflammatory drug indicated for rheumatic condition and treatment of primary dysmenorrhoea, among others (Katzung 2001). The present investigation aimed at developing cross-linked hydrogel discs of guar gum, with clutaraldehyde used as a cross-linking agent. The feasibility of the system as colon-specific drug carrier also was investigated.

MATERIALS AND METHODS

Ibuprofen was generously gifted by Albert David Limited, Kolkata, India. Other materials like guar gum (Dabur Research Foundation, Ghaziabad, India), glutaraldehyde (S. D. Fine Chemicals Limited, Boisar, India), and sodium bisulfite (Central Drug House, New Delhi, India) were obtained commercially and used as such.

Fabrication of Hydrogel Discs

Hydrogel discs using different concentration of guar gum (8–14 mg/ml) were prepared according to previously described method (Gliko-Kabir et al. 1998) with slight modifications. Weighed quantities of guar gum were added to distilled water and stirred at 45°C to disperse the gum. Different volumes of glutaraldehyde (1–15 ml) (25% w/v) were added to the dispersion in acidic conditions. The reaction mixture was stirred for different duration for different batches and subsequently was poured into petri dishes. The petri dishes were covered and kept at 40°C for 2–4 days. After the formation of wet hydrogels, excess water was drained out, and the hydrogel mass was collected and cut into discs of 1 cm diameter. The discs were

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stirred in aqueous solution (5% w/v) of sodium bisulfite for 2 hr and washed with distilled water until no traces of glutaraldehyde could be detected spectrophotometrically at 235 nm (polymeric glutaraldehyde) and 280 nm (monomeric glutaraldehyde) in the rinsing water. Further, the discs were dried at 40°C until no more weight loss was observed.

Drug Loading into Fabricated Discs

Drug loading was accomplished by immersing the oven-dried discs into 1 mg/ml solution of ibuprofen in methanol: SIF (simulated intestinal fluid) (1:4) for 24 hr. The discs were then washed with water to remove drug excesses on the surface. The drug-loaded discs were dried in the oven at 40°C until no weight loss was observed.

Characterization of Hydrogel Discs

The discs were weighed before and after drying to observe the effect of drying on surface morphology. The diameter of the discs also was measured after drying using screw gauge. Drug-loaded discs were immersed in SIF for exhaustive extraction of drug. The resultant solution was analyzed spectrophotometrically at 221 nm. The results were expressed as percent drug loading (DL).

Swelling (Buffer Uptake) Studies

Swelling studies were performed separately in SIF and simulated gastric fluid (SGF) for 4 hr. The discs were immersed in 20 ml of medium at 37 ± 0.5°C, removed at hourly intervals, blotted dry, and weighed. Percentage buffer uptake was expressed as:

$$\% \text{ Buffer uptake} = (\text{weight of the swollen disc-dry weight of the disc})/\text{dry weight of the disc}$$

In Vitro Drug Release

The discs were placed in a stainless steel mesh (no. 100) bag. The bag was dipped in a tightly screw-capped bottle containing 20 ml of SGF and placed on a mechanical shaker at 100 rpm. The temperature was maintained at 37 ± 0.5°C. After 2 hr the bag was transferred to another bottle containing 20 ml of SIF and shaken for another 3 hr. Samples were withdrawn at hourly intervals and replaced with same amount of fresh prewarmed medium.

Drug release studies also were conducted in presence of rat caecal contents (4% w/v) for 5 hr to assess the biodegradation of the discs by colonic bacteria. Rat caecal content medium was prepared as described previously (Rama Prasad et al.1998). The guidelines of Committee for Purpose of Control and Supervision of Experimental Animals, India, were followed in taking care of animals. Phosphate buffer pH 6.8 (10 ml) containing rat caecal contents was taken into a screw-capped bottle and the discs contained in a stainless steel mesh (no. 100) bag were introduced into the medium. The medium was shaken at 100 rpm in a mechanical shaker thermostated at 37 ± 0.5°C. Samples were withdrawn every hour and replaced with same volume of fresh medium, previously bubbled with nitrogen. Sampling was done in anaerobic environment with the help of a nitrogen cylinder. The samples were analyzed spectrophotometrically at 221 nm.

All the experiments were performed in triplicate. The results were expressed as mean ± S.D. values. Student's *t*-test was performed to determine the level of significance. One-way analysis of variance (ANOVA) was performed to determine significant difference among fabricated batches. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Effect of Drying on Size and Shape of Hydrogel Discs

Preliminary studies were performed to determine the effect of formulation variables on physical properties of the discs. Freshly prepared discs showed uniform and smooth surface. Drying caused marked shrinkage but the circular shape was retained. The shrinkage was irreversible in nature, i.e., the discs did not regain their original diameter even upon rehydration, although some increase in diameter was observed. It was evident that drying process introduces a permanent change in hydrogels due to W physical cross-linking (Korsmeyer and Peppas 1981). Hydrogel discs prepared using different concentrations of guar gum showed an increased shrinkage with increasing guar gum concentration. The diameter of the discs varied between 8.28 mm (discs prepared using 0.4 g/ 50 ml guar gum) and 5.25 mm (discs prepared using 0.7 g/50 ml guar gum). The weight of dried discs was in between 32–36 mg.

Drug-Loading Capacity

Drug loading into the discs, calculated as the percentage of drug present per disc, was fairly constant, being around 1.5% per disc. Drug loading was unaffected by the amount of polymer, amount of cross-linking agent added, or the cross-linking time.

Swelling (Buffer Uptake) Studies

The swelling studies were performed separately in SGF and SIF for 4 hr. Buffer uptake by the discs in the 2 media did not differ significantly. Cross-linking with glutaraldehyde does not interfere with the nonionic nature of the polymer (Gliko-Kabir et al. 1998); therefore, swelling is independent of the pH of medium. The equilibrium swelling for most of the batches was observed after 3 hr.

- Effect of cross-linking agent: The swelling of the discs markedly decreased in both the buffers with increasing amount of cross-linking agent (Figure 1). Presumably, cross-linking interferes with the free access of water to hydroxyl groups of guar gum. An increased cross-linking density also can conttributes to decreased swelling of the polymer.
- Effect of guar gum concentration: Buffer uptake increases with increasing amount of guar gum in both

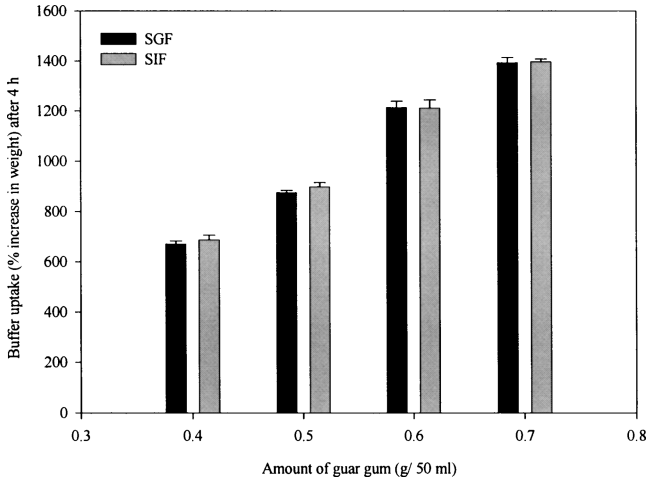

FIG. 1. Effect of guar gum concentration on buffer uptake by hydrogel discs in SGF and SIF (bars represent mean ± S.D.).

media (Figure 2). Higher amount of guar gum accounts for larger number of free hydroxyl groups available to react with water, thereby resulting in an increased buffer uptake (Gliko-Kabir et al. 2000a).

- Effect of cross-linking time: A gradual increase in cross-linking time from 15 min to 1 hr caused decreased swelling in both the buffers, due to increase in the cross-linking density of the products. However, increasing the cross-linking time beyond 1 hr did not significantly decrease the buffer uptake. The process of cross-linking reaches saturation after 1 hr, beyond which no chemical cross-linking takes place.

In Vitro Drug Release

In the absence of rat caecal contents, in vitro studies in the absence of enzymatic source were carried out for 2 hr in SGF, followed by 3 hr in SIF. Our aim was to find out whether the prepared hydrogels could restrict drug release in the gastric and intestinal environments. The cumulative percent release at the end of study was observed at 2–5% (Figures 3, and 4). It is evident that the fabricated discs release minimal amount of drug in gastric and intestinal environments.

In the presence of rat caecal contents (4%w/v), in vitro dissolution studies were conducted in phosphate buffer pH 6.8 in as the enzymatic source to assess the susceptibility of the prepared hydrogel discs to the bacterial enzymes. The drug release from the discs was significantly higher in presence of rat caecal contents when compared to with that in its absence (Figure 5 and

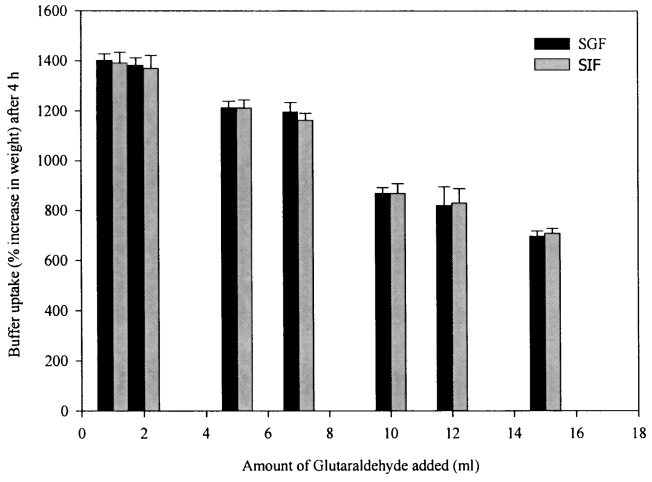

FIG. 2. Effect of amount of glutaraldehyde on buffer uptake by hydrogel discs in SGF and SIF (bars represent mean ± S.D.).

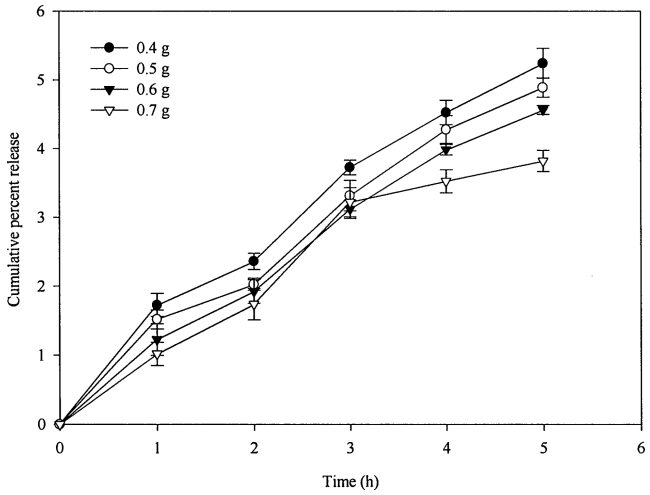

FIG. 3. In vitro drug release from hydrogel discs fabricated using different concentrations of guar gum in sequenced gastrointestinal fluid lacking rat caecal contents (bars represent mean ± S.D.).

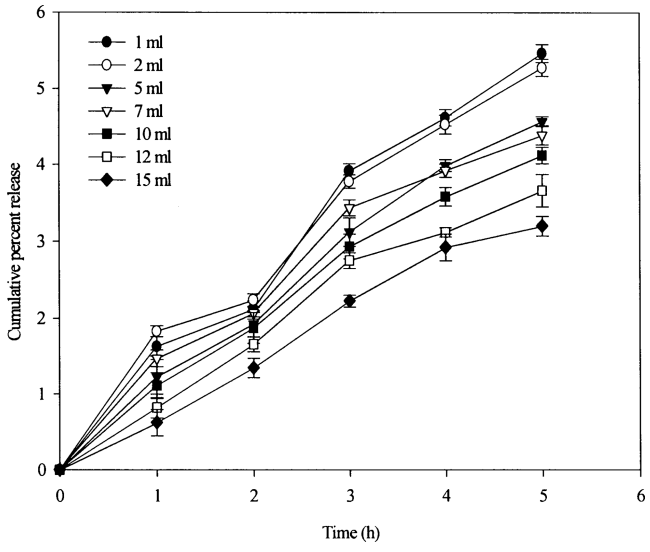

FIG. 4. In vitro drug release from hydrogel discs fabricated using different amounts of glutaraldehyde in sequenced gastrointestinal fluid lacking rat caecal contents (bars represent mean ± S.D.).

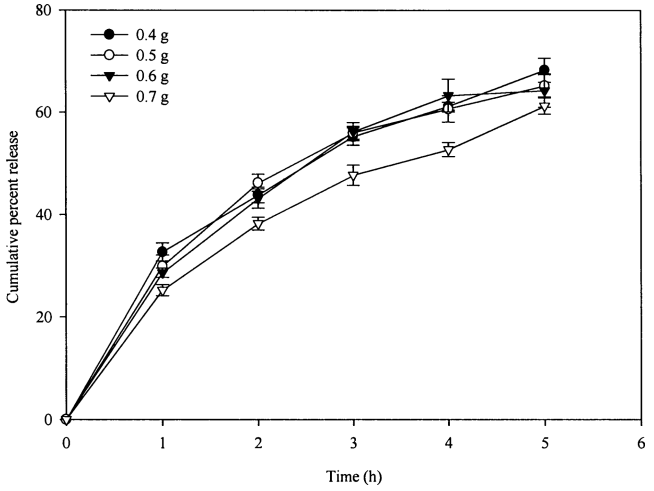

FIG. 5. In vitro drug release from hydrogel discs fabricated using different concentrations of guar gum in phosphate buffer pH 6.8 containing rat caecal contents (4% w/v) (bars represent mean ± S.D.).

Figure 6). Diffusion through gel matrix as well as the erosion of the polymer by bacterial enzymes contribute to increased drug release.

Increase in guar gum concentration caused reduction in percent drug release. This may be due to an increase in the diffusion barrier for the drug release with increased polymer concentration. But the effect was not statistically significant. Drug release decreased with increasing amount of glutaraldehyde. An increase in cross-linking density decreases the volume of swelling and drug release that are attributed to the decreased diffusion coefficient of drug and solvent (Korsmeyer and Peppas 1981). Swelling and in vitro drug release tend to decrease or increase together, and a direct relationship between the two variables was proved by Pearson's correlation analysis.

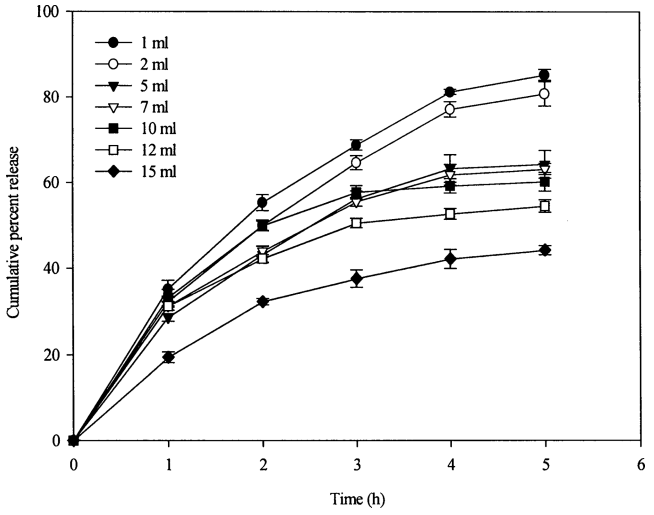

FIG. 6. In vitro drug release from hydrogel discs fabricated using different amounts of glutaraldehyde in phosphate buffer pH 6.8 containing rat caecal contents (4% w/v) (bars represent mean ± S. D.).

CONCLUSION

Hydrogel discs containing guar gum cross-linked with glutaraldehyde were fabricated using ibuprofen as a model drug. Cumulative percent release after 5 hr was significantly higher in presence of rat caecal contents than that observed in its absence, and the fabricated discs released minimal amount of drug in intestinal pH conditions. The fabricated discs could overcome enormous swelling of guar gum that turns out to be a drawback due to associated risk of leakage of the entrapped drug prior to its arrival to colon. The fabricated hydrogel discs may, thus, prove to be beneficial as colon-specific drug delivery vehicles for poorly water-soluble drugs like ibuprofen.

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