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Original Article

Ion-exchange, an Approach to Prepare an Oral Floating Drug Delivery System for Diclofenac

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Abstract

Using ion-exchange resins, a multiple-unit type of oral floating dosage system has been prepared to prolong gastric emptying time of dosage form. The system is composed of beads of drug-resin complex, which are loaded with bicarbonate ions and coated with a hydrophobic polymer. The system is so designed that when the beads reach the stomach, chloride ions are exchanged with bicarbonate and drug ions. The generated CO_2 is entrapped in the polymeric coated resins and causes the beads to float.

In this study, Amberlite-IRA 900 was loaded with diclofenac and bicarbonate ions, using a batch method. The beads were encapsulated with a hydrophobic polymer (ethyl cellulose or Eudragit RS-100). To find an appropriate formulation, the factors affecting the drug loading, floating ability and drug release were investigated.

Based on the result obtained, maximum loading efficiency was attained at 3 h, using an aqueous diclofenac solution and resin beads measuring 430 μm in diameter. Drug release from both uncoated complexes of diclofenac-resin, and diclofenac-bicarbonate-resin occurred via particle-diffusion. The ethyl cellulose-coated beads have a desirable floating capability in comparison with the Eudragit RS-100 coated beads on HCl 0.1M solution containing 0.02% polysorbate 80.

Keywords: Floating system; Ion exchange resins; Diclofenac sodium; Bicarbonate sodium; ethyl cellulose; Eudragit RS-100.

Introduction

In recent years scientific and technological advancements have been made in the preparation and development of rate controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence time (GRT) and unpredictable gastric emptying time (GET) (1-7). The following means are currently being utilized in the prolongation of the GRT: the use of passage-delaying agent, large single-unit dosage forms, bioadhesive drug delivery systems, heavy pellets, sham feeding of indigestible polymers and buoyant forms (1-10).

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Up to now, it seems that floating delivery systems offer the best protection against early and random gastric emptying of non-digestible forms (1, 2, 9). The floating systems remain lastingly buoyant on the gastric content because of their low density compared to that of the gastric fluid. Several techniques have been adopted for the preparation of these systems (1-8 ,10).

Atyabi et al. (7) have described a novel gastric retentive system based on ion exchange resins. Resin beads are loaded with bicarbonate and coated with a semi-permeable membrane. On exposure to gastric media, exchange of bicarbonate and chloride ions takes place, releasing carbon dioxide. The gas is trapped within the membrane causing the particles to

Table 1. Various conditions used for preparing of the coated DBRCs

Formula	Loading time (h)	$NaHCO_3$ 0.1M (ml/g)	Polymer	Polymer ratio (%)
R1	2	200	EU	6
R2	2	200	EU	10
R3	2	200	EU	14
V1	2	200	EC	6
V2	2	200	EC	10
V3	2	200	EC	14
F1	3	200	EC	20
F2	3	300	EC	20
F3	3	450	EC	20
F4	3	600	EC	20

float. *In vivo* studies on this system in human volunteers showed prolonged gastric retention, compared to a control, after the ingestion of a light mainly fluid meal (9).

The aim of this investigation was to study the capability of ion exchange resins to offer an oral sustained release dosage form for diclofenac (as an anionic model drug) with gastric retentive properties. In previous works we showed that the amount of drug released from ion exchange resins loaded with diclofenac in simulated gastric fluid is negligible, suggesting that diclofenac could be protected from release in the stomach by loading it onto the ion exchange resins. Drug release in simulated intestinal fluid from drug-resin complexes with and without any exposure to acidic medium was not significantly different ($P>0.4$), showing that there is no relationship between the profile of drug release and its presence in the acidic media (11). Delayed and progressive sedimentation of the beads of a multiple unit floating system in stomach could resulting a sustained drug delivery within the intestinal lumen.

Experimental

Materials

Materials were obtained from commerical sources:Amberlite IRA 900 (RÖhm and Haas, France), diclofenac sodium (Ciba-Geigy, Swithzerland), ethylcellulose 100 cPs (Dow Chemicals), Eudragit RS-100 (RÖhm-Pharma, Germany, supplied as a gift) and dibutyl phthalate (Merck, Germany).

Methods

Preparation of diclofenac-bicarbonate-resin complex (DBRC)

Amberlite IRA 900, an anionic exchange resin in chloride form, was purified and regenerated by conventional method.

Exchange of diclofenac ions for chloride ions was achieved by the addition of one gram of resin beads (either 430 μm or 600 μm) to 400 ml of sodium diclofenac (0.025N) aqueous solution or 200 ml of sodium diclofenac (0.05N) hydroalcoholic solution and stirring at 500 rpm for 2 or 3 h, followed by washing and drying at room temperature. Drug loading was determined gravimetrically. The results were statistically analyzed using the unpaired student's t-test. Bicarbonate ions from different volumes (160, 200, 300, 450 and 600 ml) of 0.1 M sodium bicarbonate solutions were loaded onto the diclofenac-resin complex beads (DRC), which were prepared in an aqueous medium. The released diclofenac within the loading solution was measured using a spectrophotometer at 276 nm.

Process of microencapsulation

DBRC beads (430 μm) were coated by an emulsification-solvent evaporation method for ethyl cellulose (EC), and a coacervation method using non-solvent addition technique for Eudragit RS 100 (EU RS-100). One gram DBRC was brought into contact with 10 ml of a double distilled water for 15 min. The excess water was removed and the resin beads transferred to the coating formulation containing different amounts of either EU RS-100 or EC as the coating polymers and dibutyl phthalate (DBP) (20% weight of the coating polymer) as plasticizer in dichloromethane. The suspension was stirred at a rate of 500rpm. Slow addition of 120 ml of water containing 0.02% *v/v* of polysorbate 80 for EC formed an o/w emulsion. The mixture was stirred at 1000 rpm for an additional 2 h. Evaporation of dichloromethane led to the formation of microcapsules. The solidification of EU RS-100 on the surface of other beads was obtained with

slow addition of 120 ml n-hexan as a non-solvent. Various microcapsules were prepared under different conditions (table 1).

The fractional coat on the microcapsules was determined (in triplicate) by extracting 0.1 g of dried microcapsules for 2 h with three 15 ml aliquots of dichloromethane and drying to a constant weight. The weight of coat (Wc) was taken to be the difference in dry weight before (Wm) and after extraction. The fractional coat (Fc) was determined from the following equation:

$$Fc=Wc/Wm$$

Bouyancy test

To assess the floating properties, the microcapsules were placed in 0.1 M HCl containing 0.02% *v/v* polysorbate 80 to simulate gastric conditions. Using a rotator, the solution was stirred at 100 rpm for 6 h (usual time span for stomach to stay in a fed state), the buoyant beads were counted and the percentage calculated. The data were statistically analyzed using the One-way ANOVA method.

Drug release studies

Since diclofenac is a weak acid (pKa=4), inherently has a negligible solubility in acid (11-13) and detection of the released drug in simulated gastric fluid is not possible. Hence, drug release testing was performed by placing 100 mg of coated or uncoated resin beads into a USP dissolution apparatus II containing 900 ml of a pH 6.8 phosphate buffer (USP), preheated and maintained at 37±0.5ºC. A paddle stirrer set at 50±2 rpm was used. Aliquots, withdrawn at predetermined intervals, were analyzed at 276 nm.

Results and discussion

Diclofenac loading

Table 2 shows the mean amount of drug loaded on 1g of resin beads (either 430 μm or 600 μm) from aqueous and hydroalcoholic loading solutions. In spite of increasing diclofenac solubility in hydroalcoholic medium, the drug loading capacity was slightly decreased ($P < 0.0001$). This is due to the reduction in acid dissociation constant of sodium diclofenac as a result of the presence of alcohol (50 %*v/v*) in the solution (14) which brings about a decrease in the proportion of ionized diclofenac for ion exchange with the chloride ions.

Table 2. Effect of loading medium and particle size on the drug content of diclofenac-resin complex (n=3, mean±SD).

Particle size (μm)	Loaded diclofenac (mg/g)		
	In alcoholic solution	In aqueous solution	
	During 2h	During 2h	During 3h
430	-	742.9 ± 34.5	902.4 ± 45.5
600	604.4 ± 21.5	672 ± 19.2	736.2 ±17.7

Results also showed that a more desirable drug loading was achieved during the 3-h period in comparison with the 2-h duration ($P < 0.004$). The particle size is also an important factor in drug loading, since the smaller the beads, the more the drug loading ($P < 0.0001$).

Bicarbonate loading

As could be seen in figure 1, an increase in the volume of utilized sodium bicarbonate leads to a lowering of the loading capacity of the resin for diclofenac due to the displacement of diclofenac from a number of its binding sites by bicarbonate.

Drug release from uncoated DRC and DBRC

Drug release from drug-resin complex normally occurs via particle-diffusion. The process could be modeled by the following equation (15):

$$f = \frac{Q_t}{Q_\infty} = 1 - \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot \exp\left[- \frac{4\pi^2 . n^2 D . t}{dp^2} \right]$$

Where F is the fraction of the drug released from the resin at time t; Q_∞, the initial drug content of the drug-resin complex (g.g-1); Q_t, the cumulative drug released from the drug-resin

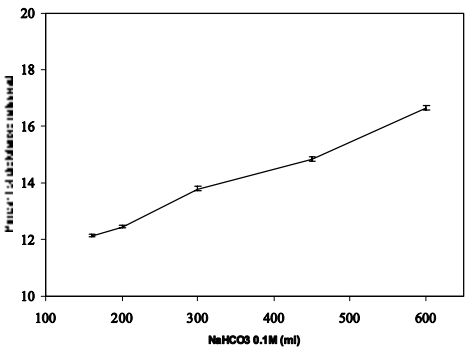

Figure 1. Diclofenac released from DRC after contact with different amount of 0.1M NaHCO3(n=3, mean±SD).

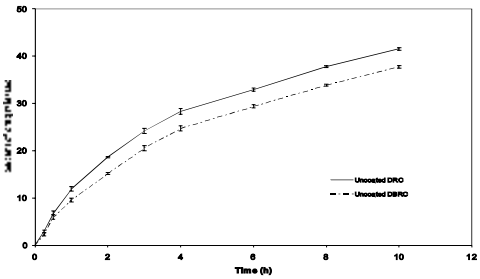

Figure 2. Diclofenac released from the uncoated DRCs and DBRCs (430 µm) in pH 6.8 phosphate buffer (n=3, mean±SD).

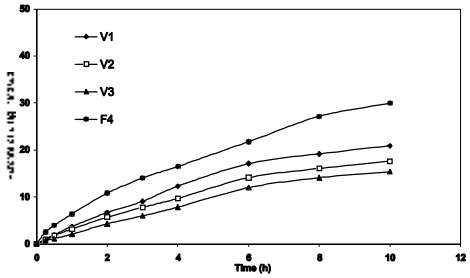

Figure 3. Diclofenac released from the coated DBRCs in pH 6.8 phosphate buffer (n=3, mean±SD)

complex at time t ($g.g^{-1}$); D, the diffusion coefficient of drug within the resin ($m^2.min^{-1}$); n, the natural number between 1 to ∞; d_p, the mean diameter of resin particles (m) and t, the time into dissolution (min). A "B" term ($B= \pi^2 D/d_p^2$) is also defined. If the release of drug is particle-diffusion controlled, the plot of Bt against time provides a linear plot (15). Profile of drug release for DRC and DBRC would be the same (Figure 2). The plot of Bt against time for both of them provides a linear plot (R2 for DRC and DBRC are 0.9988 and 0.9976, respectively). The results showed that diclofenac ions released from DBRC is independent of the presence of bicarbonate ions.

Studies of floating properties

As shown in tables 3 and 4, EC-coated microcapsules (V-series) have a higher floating capability compared to the EU RS-100-coated microcapsules (R-series). This may be due to the difference in density of coating resulted from the polymers undertaken in this study. Therefore, selection of a proper polymer could play an important role in prolongation of the DBRC beads.

The floating ability of F-series microcapsules prepared from the is enhanced when the level of loaded bicarbonate is increased (Table 5).

Although lower levels of bicarbonate were used in the preparation of V-series, as compared to the preparation of the F-series, the former exhibited a higher floating ability, because they have more exchangeable sites for bicarbonate ions due to the lower duration of diclofenac loading (2 h). In the presence of high levels of bicarbonate content, the V-series shows a better tendency for buoyancy.

Despite the exhibition of a desirable buoyancy, due to limited amount of loaded diclofenac (Table 6), V-series does not contain the proper dose of drug for therapy.

Drug release from EC-coated DBRC

The drug release profiles of V1, V2, V3 and F4 microcapsules are shown in figure 3. The most desirable diclofenac release was obtained from formulation F4 (the best formulation). Containing greater amounts of diclofenac compared to the V-series.

Although application of higher level of coating material (EC) in the microencapsulation process improved the floating ability of V-series beads, it had a detrimental effect on the release rates due to the greater diffusional path lengths in the microcapsules possessing thicker coats.

However, the maximum amount of drug released during 10 h, did not exceed 30%, even from formulation F4. Substitution of an anionic-exchange resin with smaller particle size as well as lowering the extent of lower cross-linking is suggested.

Table 3. Effect of the amount of Eudragit RS-100 as the coating polymer on the floating ability of the beads (n=3, mean±SD).

Formula	EU RS-100 (%)	Floated beads (%)
R	0	0
R1	6	30 ± 3
R2	10	20.5 ± 1.5
R3	14	0

Table 4. Effect of the amount of ethyl cellulose as the coating polymer on the floating ability of coated DBRC beads (n=3, mean±SD)

Formula	EC (%)	Floated beads (%)
V	0	0
V1	6	57.1 ± 2.3
V2	10	83.8 ± 3.5
V3	14	88.7 ± 3.8

Table 5. Effect of different volumes of bicarbonate sodium (0.1M) on the floating ability of EC coated DBRCs (n=3, mean±SD)

Formula	$NaHCO_3$ (ml/g)	Floated beads (%)
F1	200	27.4 ± 2.1
F2	300	37.0 ± 2.5
F3	450	45.5 ± 4.2
F4	600	73.5 ± 4.4

Conclusion

The present study reports the development of a novel multiple-unit floating dosage form based on an ion-exchange resins. It is shown that coated anionic resin beads loaded with bicarbonate and diclofenac ions (under an optimized condition) are able to float on the surface of HCl 0.1 M solution for a relatively long period. The generated and entrapped CO_2 within a membrane is responsible for the buoyancy of the beads. Ethyl cellulose (100 cPs) as a pH-independent coating polymer, improves the floating ability of the microcapsules. With selection of a proper amount of this polymer, the system could offer a suitable drug release pattern.

Consequently, this type of oral dosage form has potential for use as a controlled-release drug delivery system. These multi-unit dosage forms do not have the disadvantage of the "all or nothing" gastric emptying process. Also, the uniform distribution of these beads along the gastrointestinal tract could result in a more reproducible drug absorption and reduce the risk of local irritation, compared with single-unit dosage forms.

Table 6. Results of fractional coat and drug content of different formulations. (n=3, mean±SD)

Formula	Fractional coat (%)	Drug content (%)
R1	4.10 ± 0.10	33.08 ± 0.029
R2	6.70 ± 0.09	32.19 ± 0.032
R3	8.23 ± 0.40	31.66 ± 0.137
V1	5.16 ± 0.08	32.70 ± 0.028
V2	9.09 ± 0.12	31.36 ± 0.037
V3	12.30 ± 0.50	30.26 ± 0.176
F1	14.80 ± 0.40	40.06 ± 0.188
F2	14.00 ± 0.51	39.82 ± 0.236
F3	13.60 ± 0.56	39.50 ± 0.256
F4	15.10 ± 0.78	38.00 ± 0.349

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