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# Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application

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**Abstract**

A new drug delivery system for a water-soluble beta-blocker drug, sotalol HCl, was developed utilizing both the concepts of adhesiveness and of flotation, in order to obtain a unique drug delivery system which could remain in the stomach for a much longer period of time. The floating and controlled-release properties of tablets consisting of cellulosic polymers were investigated. In order to validate the technological design of the new system, two different batches were made. In both cases, the time necessary for the tablets to begin to float was less than 30 min. Moreover, 90% of the drug content was released during the first 14 h. The bioadhesive property of the tablets was determined using rabbit tissue and a modified tensiometer. The new oral controlled-release system shows, at least in vitro, good characetristics in relation to three parameters: controlled release of the drug, bioadhesiveness in the stomach and intestine of rabbits and buoyancy in an acid medium.

*Key words:* Bioadhesion; Flotation; Drug delivery system; Hydrophilic polymer; Matrix tablet; Sotalol

## 1. Introduction

It is well known that drug molecules presenting no difficulties in their solubility and/or absorption problems along the gastrointestinal (GI) tract are good candidates for sustained-release formulations. However, a significant obstacle may arise if there is a narrow window for drug absorption in the GI tract and/or if a stability problem exists in GI fluids. Controlling the placement of a drug delivery system in a particular region of the GI tract often improves absorption of those drugs which may involve these kinds of problems. Furthermore, it would be desirable to achieve a longer transit time, especially in the upper part of the GI tract, in order to maximize drug absorption and thus enhance the therapeutic effect (Bechgaard and Ladefoged, 1978; Welling, 1983).

Recently, interest has been focused on the development of two different types of solid dosage forms, mainly bioadhesive oral controlled-release and intragastric floating drug delivery systems. Studies have already demonstrated some of the benefits of these kinds of drug delivery systems (Sheth and Tossounian, 1984; Tossounian et al., 1985; Erni and Held, 1987; Jiménez-Castellanos

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et al., 1993a). However, each system may also have its own problems. For example, in the case of bioadhesive formulations, gastrointestinal motility may be a dislocating force for the dosage form or permanent renewal of the mucus may become an essential limiting factor and/or specific pH may not be adequate for creating sufficient adhesiveness (Gupta et al., 1990; Junginger et al., 1990). On the other hand, if a drug delivery system has positive buoyancy it will float in the semi-liquid contents of the stomach only when the stomach is full. However, as the stomach empties it is most likely that the dosage form will pass through the pyloric sphincter and enter the small intestine (Muller-Lissner and Blum, 1981; Timmermans et al., 1989a).

In this investigation, studies were carried out to design a drug delivery system for a water-soluble beta-blocker drug, sotalol HCl, as model drug in order to improve the variations in bioavailabilty of the drug, using FDA-approved cellulosic polymers while utilizing the technological concepts of adhesiveness and flotation in order to obtain a unique drug delivery system which could solve the above problems and remain in the stomach for a much longer period of time. Also, tests in vitro for release of drug, floating and bioadhesion of tablets were performed.

## 2. Materials and methods

In this study the following were used: sotalol hydrochloride (Bristol Myers-Industrial, U.S.A., lot no. N0C07), sodium carboxymethyl cellulose (SCMC 7MF cellulose gum, Aqualon Co., U.S.A., lot no. 67108), hydroxypropyl cellulose (HPC, HXF NF, Aqualon Co., U.S.A., lot no. 6232), and sodium stearyl fumarate (Pruv®, Zurich, lot no. 139-01). All materials were fractioned and particles of 500–1000 $\mu$m size range were used in the entire study. Also, all materials were stored under controlled humidity conditions (RH = 40%) before use.

Tablets containing sotalol HCl (240 mg) were made by mixing first the active ingredient with SCMC, HPC, a dry binder to improve the physical strength of the tablets and a carbonate to generate gas. Finally, the lubricant (Pruv®) was added. The final weight of tablets was 700 mg. Tablets were compressed using an instrumented Rotary Tablet Press with 12 mm diameter normal circular punches. Compression was controlled to produce a 6 kg tablet crushing strength.

The following standard physical tests were performed on the tablets produced:

Weight: the weight (mg) of each of 20 individual tablets was determined by dusting each tablet off with a camel-hair brush and placing it on an electronic balance (Mettler AE240 Erweka Tap). The weight data from the tablets were analyzed for sample mean, standard deviation and coefficient of variation (relative standard deviation).

Hardness: the crushing strength (kg force) of 20 individual tablets was determined by placing each tablet in an electronic hardness tester (Erweka). The sample mean, standard deviation and coefficient of variation (C.V.) were calculated.

Thickness: the individual crown-to-crown for the thickness of 20 individual tablets was determined after dusting off the tablet surface, and then placing it in and parallel to the jaw of a micrometer (Mitutoyo N.2416, sensitivity 0.001–1.000 inch). The measurements were recorded and the sample mean, standard deviation and coefficient of variation were calculated.

Friability: this was determined by weighing 15 tablets after dusting, placing them in a Roche-type friabilimeter and rotating the basket vertically at 25 rpm for 4 min (100 drops). After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated according to:

$$\% \text{ friability} = (\text{weight}_{\text{final}} - \text{weight}_{\text{original}}) / \text{weight}_{\text{original}}$$

Content uniformity: 10 individual tablets were crushed. Then, the exact weight of the powder was measured and the powder was put into a volumetric flask (500 ml) with 300 ml of 0.1 N HCl. After stirring for 45 min, a further 200 ml of HCl was added. 2 ml of solution (filtered twice) was diluted to 50 ml with 0.1 N HCl and analyzed spectrophotometrically using an 8451A Diode Ar-

ray spectrophotometer (Hewlett Packard) at 228 nm.

In vitro dissolution studies: drug dissolution was carried out on a USP XXII/NF XVI apparatus (Vanderkamp 600 six-spindle dissolution tester), using the basket method and two media at pH 1.2 and 3. Samples were withdrawn at different intervals of time and replaced by dissolution medium at sampling times. Sample solutions were diluted to 10 ml with 0.1 N HCl or with 0.001 M HCl + 0.099 M NaCl and analyzed spectrophotometrically at 228 nm. Three different batches of sotalol HCl standards were prepared on three different days and calibration curves were established for each one.

Measurement of time to float: 15 individual tablets were put in individual flasks with 400 ml of 0.1 N HCl. Then, the time (min) necessary for each tablet to go from the bottom to the top of the flask was measured. The sample mean, standard deviation and coefficient of variation were calculated.

In vitro evaluation of tablet bioadhesion: the maximum adhesion force and the work of adhesion-shear to separate the tablet from freshly excised rabbit stomach tissue or small intestine were measured using a modified tensile tester (Instron, model 1122) (Jiménez-Castellanos et al., 1993b) adapted for bioadhesion measurements. A section of tissue was cut from the fundus of the rabbit stomach (or first portion of small intestine) and secured, mucosal side out, onto a polyacrylic cylinder (3 cm diameter) using a rubber band to adequately fix tissue onto the cylinder without deforming it. The polyacrylic cylinder was fastened to the wall of a polyacrylic square vessel (13 cm). In addition, a rectangular aluminium piece with a hole in the middle was used as support for the tablets. This hole had a diameter 2 mm greater than that of the tablets to allow swelling of tablet due to absorption of medium. The experiment was carried out in a constant volume of test medium (USP simulated gastric or intestinal fluid). After 30 min, the adhesional and shear forces required to separate two parallel surfaces (tablet-tissue) were recorded as a function of time, until the tablet had crossed the tissue surface (crosshead speed 1 mm/min; chart speed 20 mm/min; full scale load 1 kg). The mechanical parameters were then calculated.

## 3. Results and discussion

In order to validate the technological design of the new system, two different batches of system formulation were prepared. Table 1 presents the physical test data of both batches. The data are the average of 10–20 individual measurements of random tablets. The variabilities of the data, described as a relative variation (C.V. %) or an absolute variation (S.D.), were small. The coefficient of variation and standard deviation of compression force of batch 2 could not be calculated because the compression force data were difficult to record.

Table 1
Summary of physical tests from two different batches of bioadhesive and floating drug delivery system

| Physical tests | Batch 1 | | | Batch 2 | | |
|---|---|---|---|---|---|---|
| | Mean | S.D. | C.V. (%) | Mean | S.D. | C.V. (%) |
| Compression force [c] (kN) | 20.59 | 0.46 | 2.23 | (between 18.88 and 19) | – | – |
| Uniformity of weight [a] (mg) | 704.67 | 4.02 | 0.57 | 702.47 | 4.42 | 0.63 |
| Crushing force [a] (kg) | 6.81 | 0.44 | 6.47 | 6.23 | 0.38 | 6.09 |
| Thickness [a] (cm) | 0.59 | 0.001 | 0.23 | 0.59 | 0.000 | 0.1 |
| Friability [b] (%) | 0.25 | | | 0.29 | | |
| Uniformity of content [c] (mg) | 230.46 | 2.55 | 1.10 | 227.8 | 3.7 | 1.62 |

[a] Average of 20 experiments; [b] average of 15 experiments; [c] average of 10 experiments.

It can be observed from Table 1 that the lower crushing strength and higher friabilities in batch 2 compared to batch 1 were a result of the lower compression force used to prepare this batch. Likewise, the lower drug content in the tablets in batch 2 compared to those in batch 1 was a result of the lower weight of the tablets.

The low drug content in the tablets of the two batches compared to drug dose (240 mg/tablet) was an inherent problem in the measuring procedure, since the polymers used produce matrix tablets in which drug release is controlled by the penetration of liquid through a gel layer. The average percent of drug detected was 96.1 and 95% from batch 1 and 2, respectively. Despite this, the data for the two batches were inside the limits permitted for this test by the USP XXII.

Dissolution tests (mean and S.D.) for each of the tablet batches are shown in Fig. 1, where we can see, once again, the good reproducibility of the results. In both cases, 90% of the drug content was released during the first 14 h. The graphs show curvilinear relationships between percent released and time. The above results were analyzed using the following diffusion equation (Peppas, 1985):

$$M_t/M_\infty = Kt^n$$

where $M_t/M_\infty$ is the fractional release of the drug, $t$ denotes the release time, $k$ is a constant incorporating structural and geometric characteristics of the controlled release device and $n$ is the release exponent, indicative of the mechanism of drug release. In both cases, $n$ was found to be equal to $0.5 \pm 0.02$, indicating Fickian diffusion.

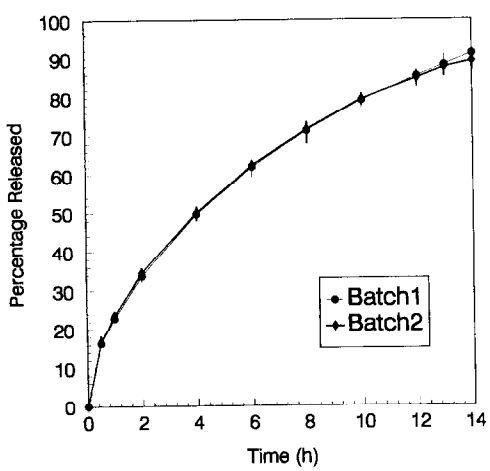


Fig. 1. In vitro release of sotalol HCl at pH 1.2 from two different batches of bioadhesive and floating drug delivery system.

Table 2
Values of correlation coeficients from release data of batch 1 (pH 1.2 and pH 3) and batch 2 for different models of mechanisms of release of drug

| Model | Batch 1 pH 1.2 | Batch 1 pH 3 | Batch 2 pH 1.2 |
|---|---|---|---|
| Zero-order | 0.958 | 0.952 | 0.950 |
| First-order | 0.780 | 0.783 | 0.758 |
| Higuchi | 0.990 | 0.991 | 0.993 |

In order to investigate this further, the release data were also fitted to models representing zero-order, first-order or Higuchi square-root of time (Higuchi, 1963) processes, indicative of release mechanisms related solely to time, drug concentration, or drug diffusion, respectively. The determination indices ($r^2$) are shown in Table 2. Again, the highest correlation coefficient for the Higuchi equation coincides with diffusion release behavior.

On the other hand, it is known that one important problem with any controlled-release formulation is the fact that many drug release rates depend on the pH of the environment (Delargy et al., 1989). In order to understand the influence of stomach pH after a meal on the controlled release of tablets, the dissolution test from batch 1 was carried out at pH 3.

Fig. 2 demonstrates clearly that at least with sotalol HCl these controlled-release matrices for drug release are slightly independent of pH. Similar results were obtained by Delargy and coworkers (1989) with verapamil using optimal levels of HPMC and sodium alginate.

The dissolution test data at pH 3 were analogously analyzed. In this case the $n$ value was also 0.50, indicative again of Fickian diffusion. These results coincide with the highest correlation coefficient for the Higuchi equation, as can be seen in Table 2.

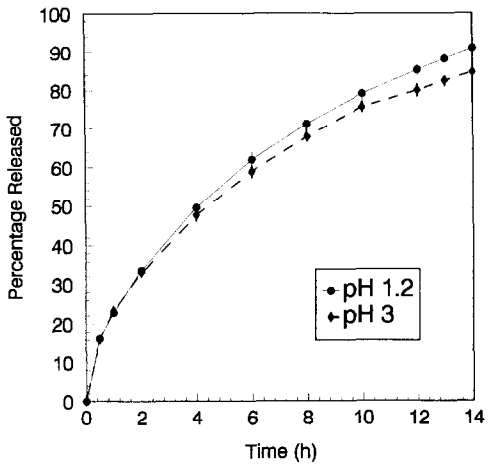


Fig. 2. In vitro release of sotalol HCl from batch 1 at pH 1.2 and 3.

Table 3 lists the time, expressed in min, that the tablets required to go from the bottom to the top of a beaker containing 0.1 N HCl. Once the tablets arrived at the top of the beaker, they remained in a buoyant state and the tablet shape was retained for more than 24 h. In this sense, floating hard gelatin capsules showed adequate floating capabilities in vitro (Sheth and Tossounian, 1984; Timmermans et al., 1989a,b), for at least 8 h.

It is interesting to point out that the mean time required for the tablets to begin to float during the dissolution test of batches (dynamic test) was 10.3 min (average of 12 tablets, with S.D. of 0.87 and C.V. (%) of 8.44%).

In vitro bioadhesion of batch 1 was also measured and the results are shown in Table 3. Saline solution at pH 2 and 5 was used as stomach and small intestine medium, respectively.

As shown in Table 3, the maximum adhesion force was higher in the small intestine tissue than in the stomach tissue. However, the opposite occurred with the work of adhesion-friction required to separate the two parallel surfaces of tablet and tissue; tablet adhesion appears to be better at high pH than at low pH.

In this sense, different results have been reported by the authors. Thus, Smart et al. (1984), for example, indicated that low pH favored adhesion of SCMC P75 and tragacanth. Lejoyeux and co-workers (1989) showed that pH had no significant influence on tablets containing HPMC and PAA as polymers. However, our results agree with those of Ch'Ng and co-workers (1985) who reported that with polycarbophil, maximum adhesion was observed at pH 5 and 6.

At present, we can state conclusively that the technological problems (direct compression, bioadhesion, flotation and controlled release) for the new oral controlled-release system were solved. However, more studies will be necessary to probe the availability of the system in vivo.

## 4. Conclusions

The following conclusions can be drawn from the results obtained in this study:

(1) A good reproducibility of the physical tests was found for the two different batches of system formulation.

Table 3
Characteristics of floating and bioadhesion to rabbit tissue using a modified tensiometer from two different batches of drug delivery system

| | Batch 1 | | | Batch 2 | | |
|---|---|---|---|---|---|---|
| | Mean | S.D. | C.V. (%) | Mean | S.D. | C.V. (%) |
| Time to float [a] (min) | 27.7 | 2.03 | 7.32 | 21.45 | 2.86 | 13.3 |
| Stomach [b]: force (N) | 1.21 | 0.44 | 36.4 | – | – | – |
| Stomach [b]: work (kg mm) | 0.83 | 0.46 | 55.4 | – | – | – |
| Small intestine [b]: force (N) | 1.68 | 0.98 | 58.3 | – | – | – |
| Small intestine [b]: work (kg mm) | 0.53 | 0.08 | 15.1 | – | – | – |

[a] Mean of 15 experiments; [b] mean of 3 experiments.

(2) Although the drug release data fitted better to difusion release behavior, a model representing zero-order was also very close.
(3) The mean time required for the tablets to begin to float during dynamic tests was 10.3 min.
(4) Although the maximum adhesion force was higher in the small intestine tissue than in the stomach tissue, the opposite occurred with the work of adhesion-friction required to separate the two parallel surfaces of tablet and tissue.
(5) The new oral controlled-release system shows, at least in vitro, good characteristics in relation to three parameters: controlled release of the drug, bioadhesiveness in the stomach and intestine of rabbits and buoyancy in an acid medium.

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