ORIGINAL ARTICLES

Controlled Delivery of Ranitidine in the Stomach using Magnetic Field

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ABSTRACT

An attempt has been made to localize ranitidine loaded microspheres in the stomach by magnetic means. Since ranitidine undergoes metabolism by microbial enzymes in the intestine, it is ideal to localize the controlled drug delivery system within the stomach to get uniform release and absorption of the drug for the desired period. Gelatin magnetic microspheres loaded with 9.1, 17.9, 26.3 and 33.3% w/w of ranitidine hydrochloride were prepared by emulsification-cross linking technique. The formulated microspheres were characterized by magnetite content, particle size and in vitro drug release. The efficiency of microspheres to be localized in the stomach is tested in vivo in rats. The prepared microspheres were spherical and had a size distribution from 10 to 105 µm. The in vitro study revealed the capability of microspheres to release the drug over a period of 8 to 12 hours, depending on drug loading. The release was found to be diffusion controlled and followed fickian diffusion principle. The in vivo study showed the efficiency of microspheres to be retained in the stomach over a period of 8 hours.

Administración Controlada de Ranitidina en el Estómago Usando Campos Magnéticos

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RESUMEN

Se ha hecho el intento por localizar las microesferas cargadas de ranitidina en el estómago mediante medios magnéticos. Como que la ranitidina experimenta metabolismo mediante enzimas microbianas en el intestino, resulta ideal localizar el sistema de administración del medicamento controlado dentro del estómago para alcanzar la liberación y absorción uniformes del medicamento por el período deseado. Microesferas de gelatina magnética cargadas con 9.1, 17.9, 26.3 y 33.3% p/p de hidrocloruro de ranitidina, fueron preparadas mediante una técnica de emulsificación-entrecruzamiento. Las microesferas formuladas se caracterizaron por su contenido de magnetita, el tamaño de las partículas y la liberación del medicamento in vitro. La eficiencia de las microesferas a ser localizadas en el estómago se prueba in vivo en ratas. Las microesferas preparadas eran esféricas y tenían una distribución de tamaño de 10 a 105 µm. El estudio in vitro reveló la capacidad de las microesferas para liberar la droga en un período de 8 a 12 horas, en dependencia de la carga de la droga. Se halló que la liberación estaba sujeta difusión controlada y seguía la ley de Fick para la difusión. El estudio in vivo mostró la eficiencia de las microesferas para ser retenidas en el estómago por un período de 8 horas.

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INTRODUCTION

Conventional drug delivery systems such as tablets, pills, capsules, liquid orals and injections guarantee a prompt release of drug; but they fail to maintain drug concentration within the therapeutically effective range for the required

period. To maintain effective plasma concentration of the drug, these dosage forms must be administered frequently (1, 2). Presently, controlled drug delivery systems have emerged largely to overcome the problems experienced with the conventional dosage forms. These controlled drug delivery systems are being formulated for oral and parenteral administration (3).

Basically, oral controlled drug delivery systems consist of a drug reservoir from which the drug is released slowly during its transits in the gastrointestinal tract in a predetermined rate to maintain constant absorption of the drug. Drugs used in oral control drug delivery must have uniform absorption throughout the gastrointestinal tract in order to have constant absorption. The development of oral controlled drug delivery poses a problem for drugs whose absorption is reduced due to various factors such as dissolution, solubility, pH, enzymes and microbial flora.

Ranitidine HCl is a H_2 receptor antagonist (4) used in the treatment of peptic ulcer. Since the biological half-life of the drug is between 2–3 hours, it is necessary to administer the drug frequently which may produce sawtooth kinetics and result in ineffective therapy. The drug can be administered preferably in controlled release dosage forms to obtain better effect. Ranitidine HCl has variable absorption in the gastrointestinal tract and the absorption in the intestine is less due to microbial degradation (5). Hence, an oral controlled release preparation of ranitidine should be preferably placed in the stomach to achieve uniform drug absorption.

Microspheres loaded with magnetic particles are formulated to anchor the microspheres in a particular part of the organ or blood vessel (6) using an external magnetic field. This enables localization of drug in the desired site and also avoids distribution to unwanted organs. In the present study, we attempted to develop gelatin magnetic microspheres loaded with ranitidine HCl, after oral administration, which can be localized in the stomach by placing a suitable external magnet in the upper quadrant of abdomen. The controlled release of the drug in the stomach can be achieved from the localized magnetic microspheres.

MATERIALS AND METHODS

Neodymium magnet, 8000 Gauss field strength and 400 Gauss/cm field gradient, 30 mm diameter and 4 mm thickness was purchased from ABY systems (PVT) Ltd., Red Hills, Chennai, India. Healthy Wistar rats weighing 175 to 225 g were procured from the animal house, Vel's College of Pharmacy, Chennai, India. All other reagents used were of analytical/HPLC grade.

Preparation of Microspheres, Determination of Drug Loading and Magnetite Content

The Microspheres were prepared by emulsification and cross-linking method. The amount of ranitidine HCl present in gelatin microspheres was determined by digestion method. The magnetite content in microspheres was estimated quantitatively by atomic absorption spectroscopy at 248 nm. Particle size analysis was done by microscopical method. The detailed procedures were published previously (7). From the particle size distribution, various statistical diameters were calculated.

In vitro Release Studies

The *in vitro* release studies of drug-loaded microspheres were carried out at 37°C using 0.1 N Hydrochloric acid (HCl). Each batch of microspheres containing 25 mg of ranitidine HCl was individually added to 200 ml of 0.1 N HCl in flasks (8, 9). The flasks were shaken (60 oscillations/min) in an incubator (Remi, India) at 37°C. One millilitre of samples was withdrawn at regular time intervals and after suitable dilution, ranitidine HCl content in 0.1N HCl was estimated at 315 nm using UV visible spectrophotometer (Shimadzu 1601).

Release Kinetics

Data obtained from *in vitro* release studies were fitted to various kinetic (9, 10) equations. The kinetic models used are zero order, first order and Higuchi equation. The following plots were made: Q_t *versus t* (zero order kinetic model); $\log (Q_0 - Q_t)$ *versus t* (first order kinetic model); Q_t *versus* square root of *t* (Higuchi model); $Q_t^{1/3}$ *versus t* (Hixson and Crowell model) and $Q_t^{2/3}$ *versus t* (modified root cube equation). Where Q_t is the amount of ranitidine HCl released at time *t* and Q_0 is the initial amount of ranitidine HCl present in microspheres. Further, to find out the mechanism of drug release, the first 60% drug released (9, 10) was fitted in the Korsmeyer-Peppas model:

$$M_t/M_\alpha = k_t^n$$

where M_t/M_a is the fraction of drug released at time *t*, *k* is rate constant and *n* is release exponent. The *n* value is used to characterize different release mechanisms.

In vivo Studies

In vivo studies were performed to determine the efficacy of microspheres to be retained within the stomach. The experiments were performed in Wistar albino rats. Before the administration of microspheres, magnet with strength of 8000 G is placed in the upper quadrant of the abdomen with help of adhesive tape. The quantity of microspheres equivalent to 25 mg of drug was dispersed in water and administered orally to 6 rats. Animals (n = 3) were sacrificed by the end of the 4th and the 8th hour and the stomach was removed. Magnetic microspheres retained in the stomach were carefully transferred to a beaker containing 10 ml of concentrated HCl and kept overnight, after suitable dilution and filtration, analyzed spectrophotometrically for ranitidine HCl.

RESULTS AND DISCUSSIONS

In this work an attempt has been made to localize gelatin magnetic microspheres containing ranitidine HCl in the stomach (by placing a magnet near the stomach) in order to get better bioavailability from oral controlled release dosage form. By changing gelatin/ranitidine ratio microspheres with 9.1, 17.9, 26.3 and 33.3% w/w drug loading was formulated (7).

Localization of magnetic microspheres in a desired area depends on the magnetic property of microspheres as well as external magnetic field applied to retain it. The magnetite content in the microspheres was theoretically fixed to 30% w/w, with an objective to have maximum possible magnetic property (6), so that it can be retained in the stomach by a magnet of 8000 G strength. As indicated in Table 1, all

Table 1:   Physical and chemical parameters of gelatin magnetic micro-spheres loaded with ranitidine hydrochloride

Batch	Percentage of drug Loading	% w/w Magnetite
A	9.1 ± 0.3	28.7 ± 1.4
B	17.9 ± 0.7	29.1 ± 1.8
C	26.3 ± 1.1	27.5 ± 1.1
D	33.3 ± 1.9	28.4 ± 2.3

Data shows mean ± SEM (n = 3).

formulated microspheres were loaded with 28–29% w/w of magnetite.

The particle size distributions of prepared microspheres were ranged from 10 to 105 µm. The average particle size of microspheres loaded with, 9.1, 17.9, 26.3, 33.3% w/w of drug was found to be 50.4, 56.6, 61.65 and 66.16 µm, respectively. The release rate of drug depends on the size and surface area of the microspheres. Since smaller particles have more surface area, under identical conditions, it will produce faster release than that of the larger particles. Hence before proceeding to drug release studies, it is essential to determine the size of the particles. Statistical diameters of formulated microspheres calculated from data obtained by the microscopic particle size analysis are given in Table 2. As far as drug release is concerned volume-surface mean diameter (d_s) is the most significant (11) and inversely proportional to release rate. The prepared microspheres had good spherical geometry as evident by the photomicrograph (Fig. 1).

The cumulative percentage releases of ranitidine HCl from microspheres are shown in Fig. 2. The formulated microspheres controlled the drug release over a period of 12 hours. The drug release was found to be fast in higher drug loading. About 90% of drugs was released by the end of the 8th hour from microspheres loaded with 33.3% drug, whereas only 63% of drug was released from microspheres loaded

Table 2:   Statistical diameters of formulated microspheres calculated from data obtained (n = 100) by the microscopic method.

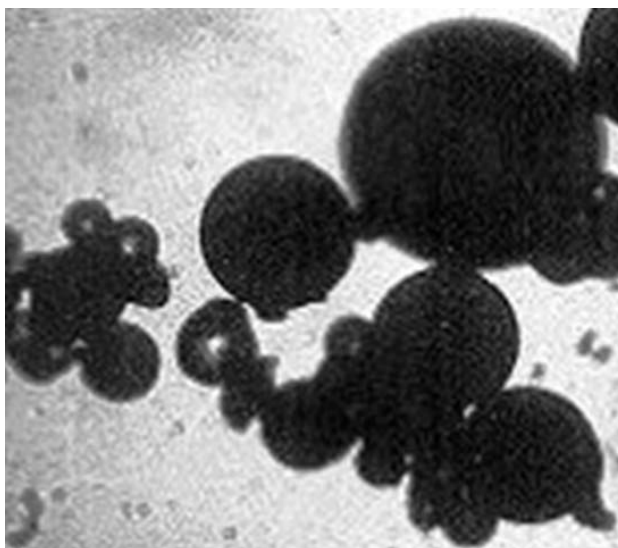| Statistical diameters	Batch A	Batch B	Batch C	Batch D
Length number mean, $d_{ln} = \Sigma nd/\Sigma n$	50.40	56.56	61.65	66.16
Surface number mean, $d_{sn} = \sqrt{\Sigma nd^2/\Sigma n}$	54.24	58.58	62.87	67.84
Volume number mean, $d_{vn} = \sqrt[3]{\Sigma nd^3/\Sigma n}$	56.95	60.32	64.05	69.52
Surface length mean, $d_{sl} = \Sigma nd^2/\Sigma nd$	58.38	60.67	64.12	69.56
Volume – surface mean, $d_{vs} = \Sigma nd^3/\Sigma nd^2$	62.77	63.97	66.46	73.02
Weight-moment mean, $d_{wm} = \Sigma nd^4/\Sigma nd^3$	65.98	66.72	68.63	76.38

Fig. 1:   Photomicrograph of gelatin magnetic microspheres loaded with 9.1% w/w of ranitidine hydrochloride (400 fold magnifications).
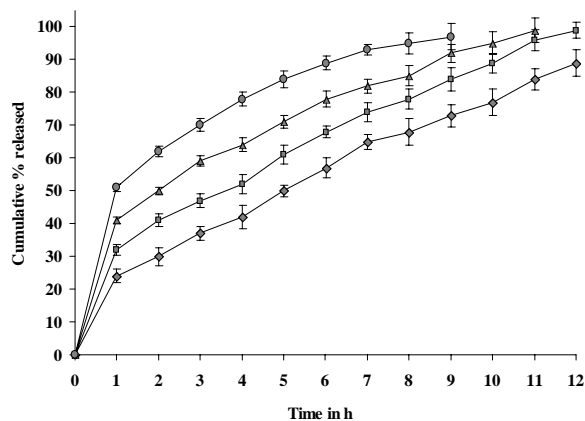

Fig. 2:   The *in vitro* release of ranitidine hydrochloride from (–♦–) 9.1, (–■–) 17. 9, (–▲–) 26.3 and (–●–) 33.3% w/w loaded gelatin magnetic microcrospheres. Values represent mean of six determinations and bars represent ± SE.

with 9.1% of drug by the end of the 8th hour. As loading increases, the release rate also increased and became fast. The given release profile is unique to the particle size data given in the Table 2.

The *in vitro release* profile was applied on various kinetic models in order to find out the mechanism of drug release. The best fit with the highest correlation coefficients was shown in Higuchi first order and followed by zero order equations as given in Table 3. The rate constants were cal-

given in Table 3, which in turn is another confirmation (13, 14) that the release from gelatin microsphere is diffusion controlled.

The data obtained from *in vitro* release studies were applied in Korsmeyer and Peppas equation in order to find out the *n* value, which describes the drug release mechanism. The *n* value of various batches of microspheres was between 0.28 and 0.48 indicating fickian diffusion principle. The re- lease also showed higher correlation for Korsmeyer and

Table 3:   Coefficients, *in vitro* release rate and the release exponent of ranitidine hydrochloride from formulated microspheres. r^2 is correlation co-efficient and the release rate constants k_0, k_1 and k_H was calculated from the slopes of the respective plots.

Batch	Zero order		First order		Higuchi		Korsmeyer-Peppas s		Log C vs Log t
	r^2	k_o (h^{-1})	r^2	k_1 (h^{-1})	r^2	k_H (h$^{-1/2}$)	r^2	n value	r^2
A	0.9452	8.15	0.9706	0.0159	0.9841	23.44	0.9730	0.48	0.9685
B	0.8975	9.08	0.9517	0.0178	0.9917	26.89	0.9998	0.35	0.9787
C	0.8387	9.85	0.9256	0.0202	0.9836	30.02	0.9905	0.33	0.9917
D	0.7912	12.46	0.8890	0.0299	0.9679	35.43	1	0.28	0.9973

culated from the slope of the respective plots (12). High cor- relation was observed in Higuchi model rather than first order and zero order. The drug release was proportional to the square root of time (Fig. 3), indicating that the drug re-
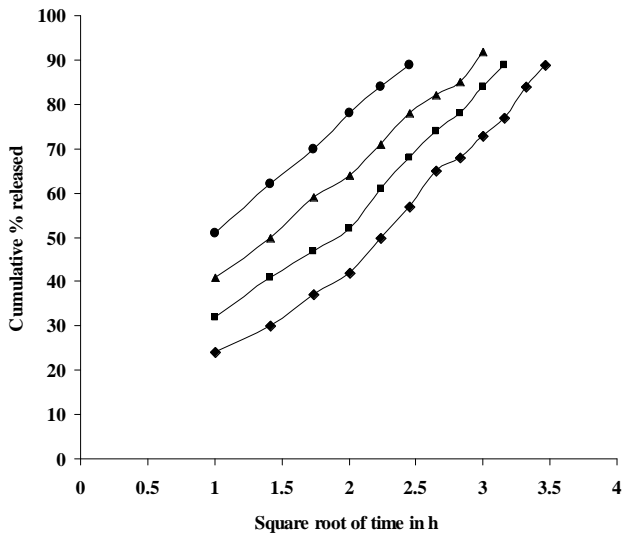

Fig. 3:   Higuchi plot of ranitidine HCl release from (–♦–) 9.1, (–■–) 17. 9, (–▲–) 26.3 and (–●–) 33.3% w/w loaded gelatin magnetic micro- spheres.
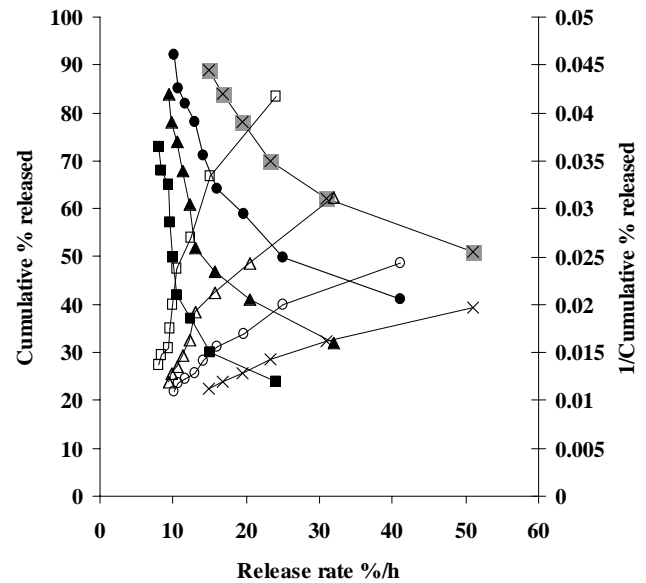

Fig. 4:   Plot of release rate of ranitidine HCl against cumulative percentage released (solid symbols) and reciprocal of the cumulative percentage released (open symbols) from gelatin magnetic micro- spheres (*n* = 6) (–□–) Batch A, (–△–) Batch B, (–○–) Batch C, (–✳–) Batch D

lease from gelatin microsphere is diffusion controlled. Plots (Fig. 4) of the release rate *versus* 1/cumulative % released were linear and plots of the release rate *versus* % released were curved, which confirms (13, 14) that the release is diffusion controlled. Moreover, the plots (not shown) of log % released *versus* log time showed a high level of linearity as

Peppas model as shown in Table 3. The release kinetics studies clearly indicate that the drug release is controlled by diffusion principle. Gelatin microspheres swell well if im- mersed in water and the swelling property may control the diffusion of drug from the microspheres. The release of the drug at the first hour was fast (also called as burst effect) and

may be due to release of surface drug or poorly entrapped drug. As time progress the release is slow and controlled, probably due to swelling of the gelatin matrix present in the microspheres. As shown in Fig. 2, the rate of drug release reduced with time, this may be due to the increase in path length through which the drug molecule is diffusing towards dissolution medium.

In vivo study was done using a minimum number of animals as *per* the recommendations given by the local ethical committee for animal experiments, Vel's College of Pharmacy, Chennai, India. The purpose of the study was to monitor the retaining ability of magnetic microspheres in the stomach. This was indirectly quantified by measuring ranitidine HCl present in the magnetic microspheres collected from the rat stomach at two different time intervals after oral administration as described in the experimental section. The microspheres of batch B equivalent to 25 mg of drug was administered orally and about 43.4 ± 4.5 and $10.7 \pm 3.1\%$ (mean $\pm$ SEM, $n = 3$) drug was recovered from the stomach of rats after the 4th and 8th hour of administration, respectively. This observation revealed the feasibility of localization of drug loaded magnetic microspheres in the stomach by placing an external magnet in the upper abdomen. The technique can be used to prepare oral sustained release dosage form for any drug whose absorption is reduced in the intestine. Similarly, it may be possible to localize the magnetic particles at any given part of the gastrointestinal trait placing the external magnet at a suitable position.

CONCLUSION

In the present work, we attempted to localize drug loaded particles of ranitidine in the stomach by magnetic means. The study confirms the efficiency of the formulated magnetic microspheres to be retained in the stomach by applied external magnetic field. *In vitro* release studies revealed the prolonged release of the drug from the formulated microspheres. Further studies are required with more number of animals and advanced techniques to support the concept of using magnetic microspheres in the localized drug delivery in

the stomach. These findings open up a new area in oral controlled drug delivery particularly for drugs which have variable absorption in the gastrointestinal trait.

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