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Research paper

Leaky enteric coating on ranitidine hydrochloride beads: Dissolution and prediction of plasma data

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Abstract

The present research is based on the hypothesis that leaky enteric-coated pellets formulations are able to provide sustained input for drugs that have an absorption window, such as ranitidine hydrochloride, without jeopardizing their bioavailability. Leaky enteric-coated pellets formulations are defined as enteric-coated pellets that allow some of the drug to be released from the formulation in gastric fluid. Different approaches to making leaky enteric-coated pellets were investigated using extrusion–spheronization followed by spray coating. Leaky enteric coats were formulated using a commonly used enteric polymer, Eudragit® L 30 D-55, combined with soluble compounds including lactose, PEG 8000 and surfactants (Span 60 (hydrophobic) or Tween 80 (hydrophilic)). The rate of drug release from the formulations in simulated gastric fluid can be tailored by varying the additive's amount or type. All leaky enteric-coated formulations studied completely released the drugs within 30 min after changing dissolution medium to phosphate buffer, pH 6. Predictions of plasma concentration–time profiles of the model drug ranitidine hydrochloride from leaky enteric-coated pellets in fasted conditions and from immediate-release formulations were performed using computer simulations. Simulation results are consistent with a hypothesis that leaky enteric-coated pellets formulations provide sustained input for drugs shown to have an absorption window without decreasing bioavailability. The sustained input results from the combined effects of the formulation and GI transit effects on pellets.

The present research demonstrates a new application of knowledge about gastrointestinal transit effects on drug formulations. It also shows that enteric-coating polymers have new applications in areas other than the usual enteric-coated formulations. The hypothesis that a leaky enteric-coated pellets formulation may maintain or increase the bioavailability of drugs that have a window of absorption is still to be confirmed by further in vivo studies.

Keywords: Leaky enteric-coating; Pellets; Ranitidine hydrochloride; Extrusion–spheronization; Computer simulations; Absorption window; GI transit

1. Introduction

Many drugs are known to have an absorption window, for example, furosemide, hydrochlorothiazide, riboflavin, amino acids and digoxin [1–3]. This means that the absorption of drugs takes place in certain regions of the gastrointestinal (GI) tract, usually the upper intestinal tract. Some drugs, such as ranitidine, have significantly limited absorption once they reach the large intestine [4]. Williams et al. [4] showed that the relative bioavailability of ranitidine following cecal administration (via a nasoenteric tube) was less than 15% of that observed after administration into the stomach or the jejunum. There are currently limited formulation methods and no marketed products to provide sustained input for such drugs (with an absorption window in the gastrointestinal tract) from an oral formulation without reducing the bioavailability.

Ranitidine hydrochloride, a specific H_2-receptor antagonist used to treat peptic and duodenal ulcers [5], was chosen as the model drug in this study. Bioavailability of 100 mg immediate-release ranitidine was 51–58% in the fasted con-

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dition [6–8]. Ranitidine is absorbed only in the initial upper part of the small intestine [9–11]. Hence, prolonging ranitidine delivery into the upper small intestine may result in increased absorption while reducing frequent dosing and side effects.

For drugs that have an absorption window, administering the drugs as sustained-release formulations while maintaining similar bioavailability is not feasible. Typical sustained-release formulations, depending on the types of formulation, may begin releasing drugs as soon as the formulations are ingested. The release continues even when the formulations are in the lower intestinal tract. This causes absorption of the drugs to become significantly reduced once the formulations have passed an absorption window region of the GI tract. A few approaches studied attempt to produce sustained-release formulations of drugs exhibiting an absorption window by retaining the formulations in the stomach or in the upper intestinal tract as long as possible. These approaches include the use of mucoadhesive microspheres [1], a floating system [12] and a gastroretentive dosage form [13].

Extrusion–spheronization generates multiunit matrix-based particulate systems that produce pellets with spherical shape, good flow properties, low friability and uniform packing characteristics. Pellets can accommodate high drug load, and modified drug release can be achieved by incorporating release-modifying agents such as ethylcellulose, acrylic polymers, chitosan and glyceryl monostearate [14–16], and by further coating the pellets.

The present research proposes a concept of using the modified enteric-coated pellets that provide immediate release in the small intestine and simultaneously provide sustained input of drugs that have an absorption window and, at the same time, may improve or maintain similar bioavailability compared to an immediate-release formulation. The enteric coat was modified such that weakened enteric polymer allowed some amounts of drugs to release while the pellets are in the stomach. The modified enteric-coated pellets formulations are identified in this research as “leaky” enteric-coated pellets formulations.

It was hypothesized that leaky enteric-coated pellets formulations provide sustained drug input without decreasing the bioavailability because saturation of absorption sites at the absorption window occurred minimally or not at all. When leaky enteric-coated pellets are administered, some portion of drug will be released in the stomach. At the same time, intact pellets will slowly enter the duodenum and then quickly disintegrate and release any remaining portion of the drug due to an already weakened enteric coat. Therefore, high concentrations of drug are not present at an absorption site, therefore reducing a chance to saturate the site [17]. Also, since the formulation disintegrates and drug dissolves rapidly once it reaches the duodenum, it is unlikely that the formulation will pass the absorption window before completely releasing the drug [18].

Objectives of the present research are to produce leaky enteric-coated pellets formulations that release some drug in gastric fluid in a controlled fashion and then instantaneously release the remaining drug when transferred into intestinal fluid, and to demonstrate effects of leaky enteric-coated pellets formulations on plasma concentration–time profiles of drugs that have an absorption window by using computer simulations.

2. Materials and methods

2.1. Materials

All chemicals used in this study were obtained from standard sources. Ranitidine hydrochloride (Avocado Research Chemicals Ltd., Heysham, Lancs, UK), lactose monohydrate (J.T. Baker Chemical Co., Phillipsburg, NJ), methacrylic acid copolymer [Eudragit® L 30 D-55] (Röhm Tech Inc., Malden, MA), polyoxyethylene-20-sorbitan monooleate [Tween 80], sodium chloride, sodium phosphate tribasic, concentrated hydrochloric acid (Fisher Chemicals, Fair Lawn, NJ), talc (Mallinckrodt, Inc., St. Louis, MO), triethyl citrate (Aldrich Chemical Company, Inc., Milwaukee, WI), microcrystalline cellulose [Avicel PH 101] (FMC Corporation, Philadelphia, PA), sorbitan monostearate [Span 60] (Sigma Chemicals Co., St. Louis, MO), polyethylene glycol 8000 [PEG 8000] (Union Carbide Corporation, Danbury, CT), water were deionized using the Milli-Q® Reagent Water System (Millipore, Bedford, MA).

2.2. Pelletization using extrusion–spheronization

The formulation composition used is presented in Table 1. All ingredients were mixed using geometric mixing and the deionized water was added slowly until a uniform distribution of water was achieved to produce a lightly moistened mass which was free flowing but cohesive under slight compression.

The lightly moistened mass was passed through a Caleva laboratory extruder model 10/25 (GEI international, Inc., Wayne, PA) with a perforated (1 mm diameter) cylinder and a pressure cylinder rotating at 10–18 rpm. Extrudes were cut at 1 cm in length by using a spatula during extrusion. Sphere formation was facilitated using a Caleva laboratory spheronizer model 120 (GEI international, Inc.,

Table 1
Weight percentage compositions of different formulations for pelletization of ranitidine hydrochloride

Ingredients	Formulations					
	I	II	III	IV	V	VI
Ranitidine HCl	70	70	70	70	61	62.5
Avicel	25	18	18	18	15	15
Polyox	5	5	5	5	3	3
PEG 600	–	7	–	–	15	17
PEG 8000	–	–	7	–	–	–
Gelucire 50/13	–	–	–	7	6	2.5
D·H_2O	QS	QS	QS	QS	QS	QS

Wayne, PA) rotating at 1800 rpm for 10 min. Drug beads were dried overnight by tray drying in a hot air oven with temperature of 40–45 °C and sieved through screen sized 25 mesh.

2.3. Compositions and preparations of coating dispersion

A weighed amount (100 g) of ranitidine hydrochloride beads (formulation VI) (mesh size 18–20) was placed into the chamber of an Aeromatic fluid bed spray coater (Niro-Aeromatic, model STREA-1, Niro-Aeromatic, Ltd., AG, Bubendorf, Switzerland) with a Wurster column insert and fluidized to equilibrate to the temperature of 40 °C used in the coating process.

Sufficient coating dispersion was prepared to coat 100 g of drug beads. Compositions of the coating polymer dispersion are presented in Table 2 and were prepared as follows. Talc was dispersed in 20 ml of deionized water. Eudragit L 30 D-55 was accurately weighed into a beaker. One hundred millilitres of deionized water was added to the Eudragit suspension and mixed gently using a magnetic stirrer. Triethyl citrate was added to Eudragit suspension with continuous gentle mixing. The talc dispersion was then added into the Eudragit mixture and gently mixed. This mixture must be kept gently stirring.

Compositions of the leaky enteric-coating dispersions are presented in Tables 3–6. Each coating dispersion was prepared generally as the same as the basic enteric-coating polymer dispersion, but lactose, PEG 8000, Span 60 or Tween 80 was first dissolved in the 100 ml of warm deionized water and then added to Eudragit suspension and the procedures continued as before.

The outlet temperature was adjusted at 40 °C; the atomizing air pressure was set at 15 psi; the fluid application rate was 1.5 ml/min, using nozzle diameter of 1 mm. in a laboratory Aeromatic Strea Spray Coater.

Five hundred and fifty micrograms of coated beads containing 300 mg of ranitidine was filled into capsules size OOCS.

2.4. In vitro dissolution testing of the studied formulations

In vitro drug release profiles of the studied formulations were obtained using the United States Pharmacopeia (USP) XXX dissolution apparatus II, Paddle method (VK 7000, Vankel Industries, Inc., Cary, NC). Dissolution was studied at a paddle rotation speed of 100 rpm and temperature of dissolution bath was maintained at 37.5 °C. Dissolution testing of all formulations was performed in triplicate.

Table 2
Composition (in grams) of different coating solutions

Ingredients	Formulations		
	C1	C2	C3
Eudragit L 30 D-55	25	33.33	50
TEC	0.75	1	1.5
Talc	6	6	6
D·H_2O	100	110	120

N.B. Eudragit amount is calculated as % from the suspension (30%).

Table 3
Composition (in grams) of coating solutions containing different amounts of lactose

Ingredients	Formulations		
	CL1	CL2	CL3
Eudragit L 30 D-55	50	50	50
TEC	1.5	1.5	1.5
Talc	6	6	6
Lactose	3	4.5	6
D·H_2O	120	120	120

N.B. Eudragit amount is calculated as % from the suspension (30%).
N.B. Lactose amount is calculated as % from the solid Eudragit L.

Table 4
Composition (in grams) of coating solutions containing different amounts of PEG 8000

Ingredients	Formulations		
	CP1	CP2	CP3
Eudragit L 30 D-55	50	50	50
TEC	1.5	1.5	1.5
Talc	6	6	6
PEG 8000	1.5	2	4
D·H_2O	120	120	120

N.B. Eudragit amount is calculated as % from the suspension (30%).
N.B. PEG amount is calculated as % from the solid Eudragit L.

Table 5
Composition (in grams) of coating solutions containing different amounts of Span 60

Ingredients	Formulations		
	CS1	CS2	CS3
Eudragit L 30 D-55	50	50	50
TEC	1.5	1.5	1.5
Talc	6	6	6
Span 60	1.5	2	4
D·H_2O	120	120	120

N.B. Eudragit amount is calculated as % from the suspension (30%).
N.B. Span 60 amount is calculated as % from the solid Eudragit L.

Table 6
Composition (in grams) of coating solutions containing different amounts of Tween 80

Ingredients	Formulations		
	CT1	CT2	CT3
Eudragit L 30 D-55	50	50	50
TEC	1.5	1.5	1.5
Talc	6	6	6
Tween 80	0.75	1	2
D·H_2O	120	120	120

N.B. Eudragit amount is calculated as % from the suspension (30%).
N.B. Tween 80 amount is calculated as % from the solid Eudragit L.

The capsules containing coated ranitidine beads were placed into dissolution vessels, containing 500 ml of simulated gastric fluid. Dissolution testing was run in simulated gastric fluid for 2 h. At the end of the 2-h period, the gastric fluid was discarded and replaced with 500 ml of phosphate buffer, pH 6.0. Dissolution testing was continued in phosphate buffer for another 2 h.

Five millilitres samples were automatically collected without medium replacement at 15, 30, 45, 60, 90 and 120 min for the first 2 h and at 10, 20, 30, 40, 50, 60, 90 and 120 min for the other 2 h. The samples were centrifuged at 3000 rpm for 20 min. Supernatant was then collected and measured by UV spectrophotometer at 313 nm. The amount of drug released was determined using an appropriate standard curve. Average drug releases and their standard deviations were calculated from three replications in all dissolution experiments. Dissolution profiles are presented as percent drug release versus time curves.

2.5. Pharmacokinetic model of leaky enteric-coated pellets

The equation used to calculate the concentration of ranitidine hydrochloride in plasma after the administration of oral single dose of IR formulations is presented in Eq. (1).

$$C_t = \frac{K_a \cdot F \cdot D}{V \cdot (K_a - K_{el})} \cdot (e^{-k_{el} \cdot t} - e^{-k_a \cdot t}) \qquad (1)$$

From the scheme presented in Fig. 7, a pharmacokinetic model for drug release and absorption from leaky enteric-coated pellets in fasted condition was designed. The plasma drug concentration can be calculated according to this model as described in Eq. (2)

$$\begin{aligned} C_1 = \frac{k_a D}{V} \Bigg[& \frac{(k_c k_s - k_{em} k_c) e^{-k_c t}}{(k_a - k_c)(k_s - k_c)(k_{el} - k_c)} \\ & + \frac{(k_c k_s - k_{em} k_s) e^{-k_s t}}{(k_a - k_s)(k_c - k_s)(k_{el} - k_s)} \\ & + \frac{(k_c k_s - k_{em} k_a) e^{-k_a t}}{(k_s - k_a)(k_c - k_a)(k_{el} - k_a)} + \frac{(k_c k_s - k_{em} k_{el}) e^{-k_{el} t}}{(k_a - k_{el})(k_s - k_{el})(k_c - k_{el})} \Bigg] \end{aligned} \qquad (2)$$

where X_{PS}, the amount of drug in pellets form in the stomach; X_{SS}, the amount of dissolved drug in the stomach; X_{SI}, the amount of dissolved drug in the intestine; X_1, the amount of drug in plasma/blood; Dose, a leaky enteric-coated dose; k_{em}, a first-order rate of drug input into the intestine corresponding to the first-order gastric emptying of pellets in fasted condition; k_r, a first-order release rate of drug from pellets within the stomach (which equals the first-order release rate of drug from pellets in the dissolution vessel); k_s, a first-order rate of drug input into the intestine corresponding to the first-order gastric emptying of liquid; k_a, a first-order absorption rate constant of drug; k_{el}, a first-order elimination rate constant of drug.

C_1 is the concentration of drug in blood compartment at time t; V is the volume of distribution; D is the administered dose; $k_c = k_{em} + k_r$.

In the case of fed condition, k_{em} is replaced by k_0, which is a zero-order rate of drug input into the intestine corresponding to the zero-order gastric emptying of pellets in fed condition.

Assumptions underlying pharmacokinetic models of leaky enteric-coated pellets used in simulations are pharmacokinetics of drug are linear in the dosing range of interest, leaky enteric-coated formulation is in multiunit pellet/granule (multiparticulate) form, drug release from leaky enteric-coated formulation in the stomach is a first-order process, upon transfer into the intestine, drug release from leaky enteric-coated formulation in the intestine is instantaneous, once being released from the formulation into the intestine, the drug is absorbed by a first-order process. The elimination of the drug from the body is a first-order process.

Pharmacokinetic parameters of ranitidine hydrochloride used in simulations were obtained by fitting of plasma concentration–time data from the literature [19]. All data fittings were performed on data from immediate-release formulations using WinNonlin Professional software, version 3.2 (Pharsight Corporation, Mountain View, CA). Table 7 summarizes pharmacokinetic parameters of ranitidine used in simulations.

Bioavailability of leaky enteric-coated pellets of ranitidine hydrochloride was assumed to be equal to that of immediate-release formulation.

GI transit parameters involved in simulations were gastric emptying of pellets and gastric emptying of liquid. Gastric emptying of drug pellets in fasted and fed conditions are first-order and zero-order processes, respectively [20,21]. Gastric emptying of liquid was a first-order process [22] and was assumed to be at a similar rate for fasted simulation.

All simulations were performed using MATLAB software, version 7 (The MathWorks, Inc., Natick, MA). The simulated plasma concentration–time curve of ranitidine hydrochloride was visually compared to published literature data of immediate-release formulation.

3. Results and discussion

3.1. Pelletization of ranitidine beads

The process of pellet formation produces a greater densification of materials compared with other granulation techniques. It also allows incorporating high drug concentrations into spherical particles which is an ideal preparation for presenting a high dose or low potency drug in the form of a multiparticulate oral sustained release dosage form.

A series of six formulations (I–VI) were systematically designed as shown in Table 1. For each formulation, the critical water content necessary to achieve the desired con-

Table 7
Pharmacokinetic parameters of ranitidine hydrochloride used in simulations

Dose (mg)	F	V (L)	k_a (h^{-1})	k_{el} (h^{-1})	k_{em} (h^{-1})	k_r (h^{-1})	K_s (h^{-1})	GET fasted condition (h)
300	0.5	98	0.641	0.293	1.386	0.345	1.386	0.5

GET is the gastric emptying time.

sistency for extrusion varied from formulation to formulation. It is worthy to note that formulations containing soluble drugs as ranitidine require less water for successful extrusion and spheronization than is required for insoluble drugs [23].

It was noticed that by using the extruder, formula I produced extrudes that dried quickly and became harder with time; so when these extrudes were placed into the spheronizer, the resulting pellets were of mixed shapes (mostly rods and few spheres). In order to improve the physical appearance and properties of the ranitidine pellets, a preliminary test was performed to test the physical properties of the compressed mass before extrusion and spheronization. This test is summarized as follows. After preparing the mass of required consistency of each formulation, each mass was left for 1 h at ambient temperature and the consistency of each mass was recorded every 10 min for a total period of 1 h. In order to complete extrusion and spheronization it was desired to use a formulation which was "workable" in consistency for at least one hour following initial wetting and mixing. For formula I (see Table 1), it was noticed that there is an increase of hardness of the mass after 10 min, and the mass became very hard after 50 min. This phenomenon may be due to lack of sufficient plasticity of this specific formulation. Addition of more Avicel is required in such cases to produce formulations with the necessary rigidity, plasticity and water absorbing capacity for extrusion–spheronization [24]. But the use of Avicel is undesirable because ranitidine is unstable in the presence of Avicel. The instability involves chemical degradation of drug by means of a complex three-way interaction between ranitidine, Avicel and water [25]. Therefore, Avicel amount was decreased in formula II and PEG 600 was added which produced a mass of desired consistency, but the resulting beads (after spheronization) were too soft. PEG of higher molecular weight was considered because higher molecular weight polyethylene glycols are quite hard "semi"-solids and can impart plasticity to granules [26]. In formula III, PEG 8000 was used instead of PEG 600 and produced a mass of desired consistency, but it became harder after 15 min of standing. In formula IV, PEG was replaced by Gelucire 50/13 which is a softer semi-solid than PEG 8000.

Gelucires are a family of vehicles derived from mixtures of mono-, di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires are available with a range of properties depending on their hydrophilic lipophilic balance (HLB 1–18) and melting point (33–65°C) range [27,28]. The Gelucires containing only PEG esters (Gelucire 55/18) are generally used in the preparation of fast release formulations, while Gelucires containing only Glycerides or a mixture of Glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in the preparation of sustained release formulations [29,30]. Formula IV was of desired consistency, but became harder after 30 min of standing. A mixture of PEG 600 and Gelucire 50/13 was used in formula V with reduction of the drug content. The resulting mass was of desired consistency but became harder after 50 min. Therefore, by modification of the ratio of PEG 600 and Gelucire 50/13 it was determined that increasing PEG and decreasing Gelucire to produce formula VI, the resulting mass was of desired consistency for 60 min, and then became harder. Formula VI (Table 1) was the formula of choice for the preparation of ranitidine hydrochloride beads. Formula VI beads after spheronization and drying were of regular spherical shape with acceptable smooth surfaces, high yield (85 ± 5%), adequate hardness to withstand spray coating procedures and of a narrow size distribution (0.85–1.15 mm).

Successful formulation of ranitidine beads containing reduced amount of Avicel is promising and complies with the previous work of Basit et al. [25] who concluded that due to ranitidine–Avicel incompatibility, a reduction in concentration or complete removal of Avicel from the formulation is necessary.

3.2. *In vitro release studies*

A dissolution profile of each formulation in a capsule containing 300 mg of ranitidine hydrochloride is presented as an average of three replicates in the figures. Vertical bars represent standard deviation and may not be visible when data are very consistent. Formulations C1–C3 contain enteric-coated beads using Eudragit L 30 D-55; their composition is described in Table 2. Amount of enteric-coating polymer as percent of Eudragit® L 30 D-55 polymer solid on ranitidine pellets for C1, C2 and C3 is 7.5%, 10% and 15%, respectively. Dissolution profiles of C1–C3 are shown in Fig. 1. Formulations C1, C2 and C3 released ranitidine approximately 98%, 75% and 4%, respectively, over 2 h dissolution in paddle stirred simulated gastric fluid. Drug release rate was initially very fast for the 7.5% and 10% weight gain (formulations C1 and C2) and then essentially stopped in gastric fluid. This release pattern is clearly not the desired sustained or continuous release. The 15% weight gain enteric-coating (formulation C3) blocked all but 4% of drug release in gastric fluid after 2 h. This release pattern is also not the desired sustained release in gastric fluid. After transfer into phosphate buffer medium (pH

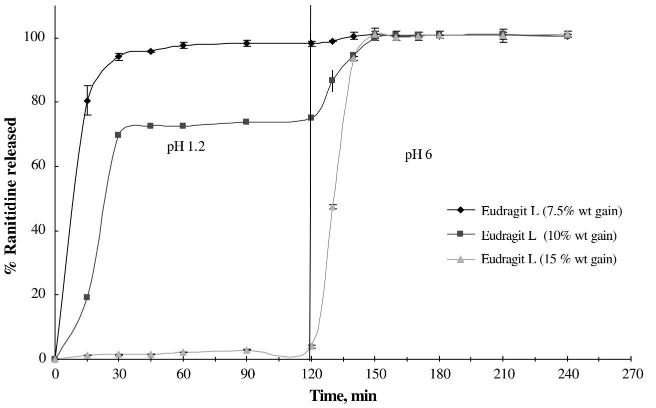

Fig. 1. In vitro release of ranitidine hydrochloride from beads coated with Eudragit L (different weight gains).

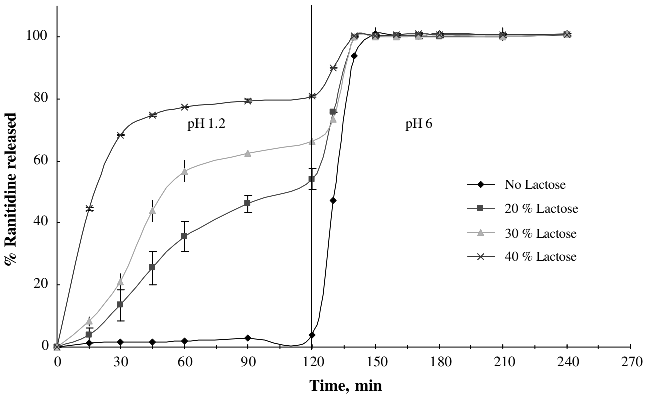

Fig. 2. In vitro release of ranitidine hydrochloride from beads coated with Eudragit L (15% wt gain) containing different amounts of lactose.

6.0), all formulations completely released the drug within 30 min as desired.

The functional enteric coating of 15% weight gain (formulation C3) was altered to prepare leaky enteric-coating formulations. The enteric coat was modified in such a way that weakened enteric polymer allowed some amounts of drug to release while the pellets were in simulated gastric fluid. Modified enteric-coated pellets formulations are recognized in this research as "leaky" enteric-coated pellets formulations to differentiate from traditional enteric coatings. This modification can be achieved by incorporating acid soluble substances such as lactose, PEG 8000, or non-ionic surfactants like Tween 80 (hydrophilic) or Span 60 (hydrophobic) in the enteric polymer coating solution. Dissolution tests were performed to study the effect of these specific additives on the release of ranitidine hydrochloride from the leaky enteric-coating formulations although other acid soluble excipients can also be used. Compositions of coating dispersions containing different amounts of lactose are shown in Table 3 (CL1–CL3), PEG 8000 in Table 4 (CP1–CP3), Span 60 formulations in Table 5 (CS1–CS3) and for Tween 80 (CT1–CT3) in Table 6.

Amount of lactose as percent of Eudragit® L 30 D-55 polymer solid on ranitidine pellets for CL1, CL2 and CL3 is 20%, 30% and 40%, respectively. Dissolution profiles of CL1–CL3 are shown in Fig. 2. Formulations CL1, CL2 and CL3 released ranitidine approximately 54%, 66% and 80%, respectively, at 2 h in simulated gastric fluid. More importantly, the 20% and 30% lactose in the coatings now produce drug release patterns which show some sustained drug release in gastric fluid. By increasing lactose amount from formulations CL1 to CL3, drug release was increased. After transfer into phosphate buffer medium (pH 6.0), all formulations completely released the drug within 15–30 min. Dissolution profiles of formulations CP1–CP3 are displayed in Fig. 3. PEG 8000 formulations (10%, 13.33% and 26.66% as percent of Eudragit solid polymer) released ranitidine approximately 48%, 50% and 77%, respectively, at 2 h in simulated gastric fluid. There is no significant difference between the release from CP1 and CP2 formulations in gastric solution. Ranitidine release in pH 6 was 100% within 30 min of dissolution testing.

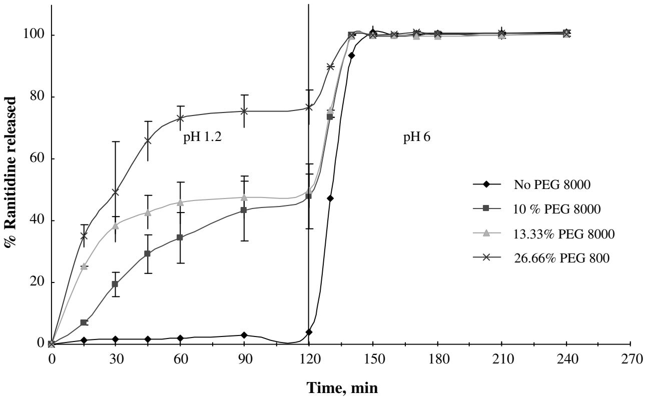

Fig. 3. In vitro release of ranitidine hydrochloride from beads coated with Eudragit L (15% wt gain) containing different amounts of PEG 8000.

For formulations, CS1–CS3, dissolution patterns are shown in Fig. 4. Amount of Span 60 as the percentage of Eudragit solid was 10%, 13.33% and 26.66% producing percentage ranitidine release of 43%, 70% and 88%, respec-

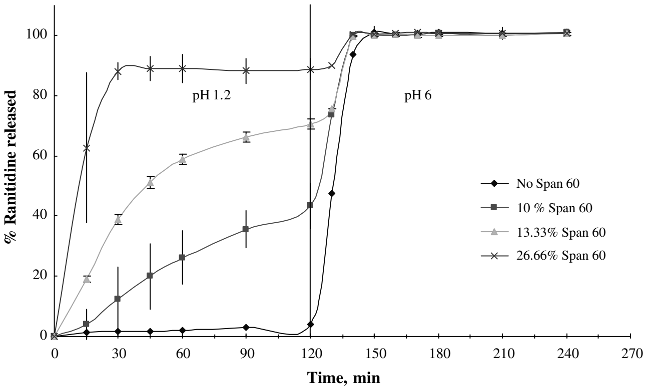

Fig. 4. In vitro release of ranitidine hydrochloride from beads coated with Eudragit L (15% wt gain) containing different amounts of Span 60.

tively, during 2 h in gastric pH, which became 100% when transferred to pH 6 within 30 min.

Dissolution profile for Eudragit formulations containing 5%, 6.66% and 13.2% Tween 80 (CT1–CT3) is presented in Fig. 5. There was no significant difference between 5% and 6.66% Tween 80 formulations; they released 47% and 53% of ranitidine after 2 h in gastric solution, while 13.2% Tween 80 released 77% after 2 h in gastric conditions. The release was complete (100%) when transferred to pH 6 within 30 min.

The drug release pattern of the enteric-coated ranitidine beads can be tailored using different excipients. To achieve about 50% release from the leaky enteric-coating formulations of ranitidine hydrochloride during 2 h in gastric fluid either 5% Tween 80, 10% Span 60, 10% PEG 8000 or 20% lactose can be incorporated into the Eudragit L 30 D-55 coating formula as shown in Fig. 6. And by changing the amounts of coating and additives, the release pattern can be tailored to produce a desired amount and rate of release over a desired time of retention in gastric fluid that may be encountered physiologically such as from as little as 1 h to as long as 16 h or more.

Preparation of leaky enteric-coated pellets using extrusion/spheronization and spray coating worked well. The coating process was simple and could be scaled up with ease. Eudragit® L 30 D-55 polymer was selected in formulations because the polymer dissolved in the duodenal pH (pH 5.5 or higher). Dissolution of polymer at this pH allows the formulation to rapidly disintegrate and instantaneously release drugs before it passes the upper intestinal region.

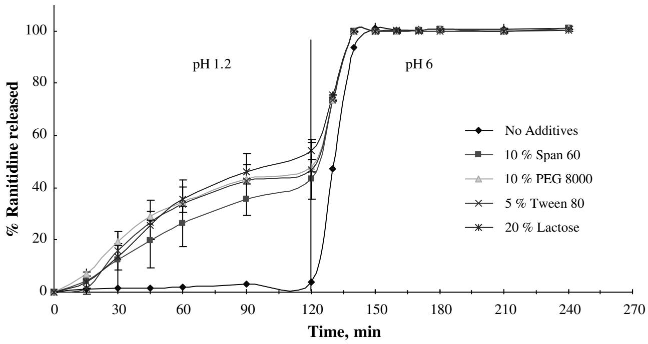

Fig. 6. In vitro release of ranitidine hydrochloride from beads coated with Eudragit L (15% wt gain) containing different types of additives.

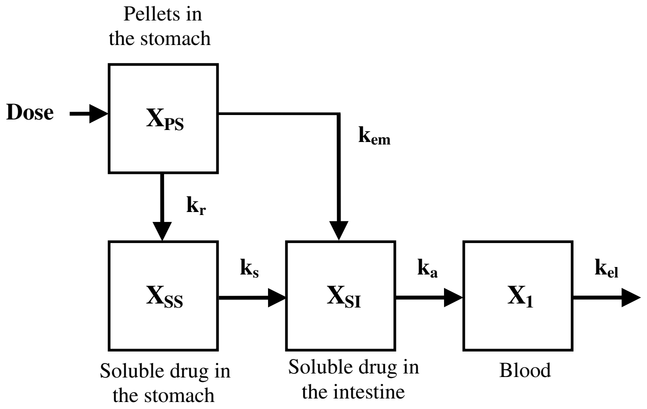

Fig. 7. Compartmental diagram of pharmacokinetic model for leaky enteric-coated pellets in fasted condition.

3.3. Computer simulations

The first-order release rate of drug from pellets in the stomach (k_r) used in simulations of 0.349 h^{-1} corresponded to the average release rates calculated from release pattern curves of the different additives that released about 50% drug in gastric pH at 2 h as shown in Fig. 6. Simulated plasma concentrations of ranitidine hydrochloride from leaky enteric-coated pellets and immediate-release (IR) formulations are presented in Fig. 8. The simulated plasma concentration profiles are presented with observed data of immediate-release ranitidine in fasted humans from the FDA database [18]. Bioavailability of ranitidine from leaky enteric-coated pellets used in the simulation was assumed equal to bioavailability of an immediate-release formulation of ranitidine. Ranitidine absorption has been previously studied. The upper small

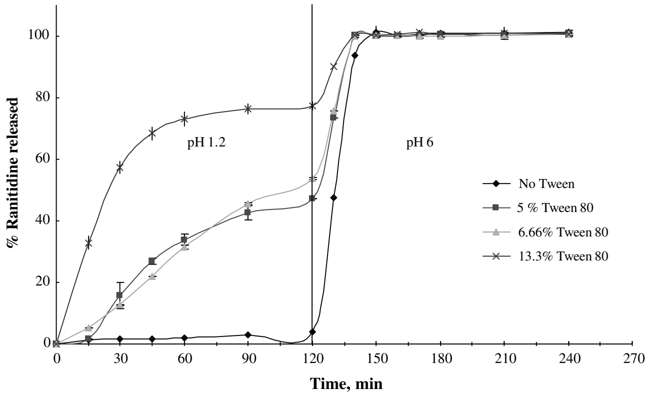

Fig. 5. In vitro release of ranitidine hydrochloride from beads coated with Eudragit L (15% wt gain) containing different amounts of Tween 80.

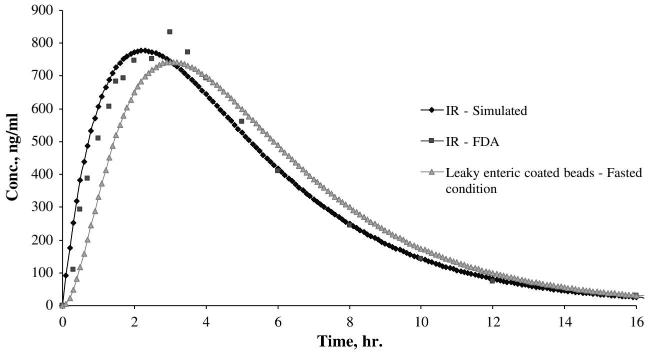

Fig. 8. Simulated plasma concentrations of ranitidine hydrochloride from leaky enteric-coated pellets (fasted condition) and immediate-release formulations.

intestine and jejunum were found to be the primary absorption sites of ranitidine while the drug absorption decreased significantly (over seven times compared to that in the jejunum) in the cecum [4]. The bioavailability of ranitidine therefore can be decreased when made into the sustained-release formulation because some of the drug will still remain in the sustained-release formulation when it arrives in the lower intestinal tract. The assumption for the bioavailability of ranitidine from leaky enteric-coated pellets in the simulation was based on the expectation that leaky enteric-coated pellets formulation will help retain the drug in the stomach for a longer time than that for an immediate-release dosage form followed by immediate release in the upper intestine and, as a result, prevent the drug from entering a region of poor absorption in the lower intestinal tract.

The difference in "leakage rate" is not expected to have much different effects on the bioavailability of ranitidine. It is expected that the bioavailability of ranitidine from any leaky enteric-coated pellets presented here will be similar to that from immediate-release formulation. The effect on pharmacokinetics of ranitidine caused by leaky enteric-coated pellets formulation is on the absorption process. Since the drug will slowly be available at the absorption sites due to slow emptying of drug pellets, the absorption process will be controlled compared to immediate-release formulations. Fig. 8 shows only a small sustaining effect which is expected in fasted patients as previously reported but, formulations of the leaky enteric-coated beads are expected to provide substantial and clinically important sustained drug input when administered with a meal.

4. Conclusion

Leaky enteric-coated pellets formulations in a clinically useful dose of ranitidine hydrochloride using all FDA approved excipients were successfully prepared by spray coating beads produced using extrusion/spheronization. Multiple wet masses were evaluated to obtain a formulation that avoids Avicel and remains sufficiently plastic for at least one hour to extrude and spheronize. Leaky enteric coats were formulated enteric polymer, Eudragit® L 30 D-55, combined with soluble compounds or surfactants including lactose, Tween 80, PEG 8000 or Span 60. Rate of drug release from the formulations in simulated gastric fluid was controlled by modifying the additive amount. All leaky enteric-coated formulations studied completely released ranitidine within 30 min after changing dissolution medium to phosphate buffer, pH 6.0.

Computer simulations were performed in order to predict plasma concentration–time profiles of ranitidine from leaky enteric-coated pellets in fasted conditions compared to immediate release formulations. It is hypothesized that leaky enteric-coated pellets formulations provide controlled release of clinically useful doses of ranitidine, without jeopardizing bioavailability.

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