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Original research paper

Effect of formulation parameters on the drug release and floating properties of gastric floating two-layer tablets with acetylsalicylic acid

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Floating dosage forms of acetylsalicylic acid, used for its antithrombotic effect, were developed to prolong gastric residence time and increase bioavailability. In the two-layer tablet formulation, hydroxypropyl methylcellulose (HPMC) of high viscosity and an effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained the drug, direct tableting agent and different types of matrix-forming polymers such as HPMC of low viscosity, sodium carboxymethylcellulose and chitosan. Tablets were prepared using a direct compression technique. The effect of formulation variables on physicochemical and floating properties and the drug release from tablets were investigated. Floating ability was dependent on the amount of effervescent agent and gel-forming polymer of the floating layer. Drug release was prolonged to 8 hours by changing the type and viscosity of the matrix-forming polymer in the drug-loading layer and all formulations showed a diffusion release mechanisms.

Keywords: acetylsalicylic acid, two-layer floating tablet, gastric retention, hydroxypropyl methylcellulose, chitosan

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In recent years, scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming the physiologically unpredictable gastric emptying time. Oral dosage forms for gastric retention have drawn more attention for their theoretical advantage in permitting control over the time and site of drug release (1, 2). Prolonged gastric retention would be particularly valuable for drugs that are unstable in lower parts of the gastrointestinal tract and poorly soluble at high pH values (3). In addition, prolonged gastric retention of the therapeutic moiety may offer numerous advantages, including improved bioavailability and therapeutic efficacy and possible reduction of dose size (4, 5).

A floating drug delivery system is a type of gastro retentive dosage form able to prolong gastric retention to obtain sufficient drug bioavailability. Floating systems are

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classified by two distinctly different technologies, depending on the mechanism of buoyancy: effervescent and non-effervescent systems (2, 6, 7). Effervescent floating dosage forms, which are matrix systems, are prepared with swellable polymers such as HPMC or chitosan and with an effervescent mixture of citric acid and sodium bicarbonate as a gas-generating agent (8, 9). Non-effervescent systems are prepared with gel-forming, highly swellable hydrocolloids and polymers. Floating chambers may also be added to the formulations to provide floating (2, 10). In this study, effervescent floating dosage forms were studied.

Polymer properties and type play an important role in the pattern and rate of drug release and floating behaviors in the floating system. Özdemir *et al*. (11) developed a floating bilayer tablet containing furosemide using HPMC as the rate-controlling polymeric excipient. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in the stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of conventional tablets. Baumgartner *et al*. (5) developed a matrix-floating tablet incorporating a high dose of freely soluble drug. The formulation containing 54.7 % of the drug, HPMC K4 M, Avicel pH 101, and a gas-generating agent gave the best results. It took 30 seconds to become buoyant. *In vivo* experiments with fasted beagle dogs revealed prolonged gastric residence time.

The objective of the present study was to develop a new floating two-layer tablet formulation that has a bulk density lower than that of gastric fluids and remains buoyant in the stomach. To achieve this objective, the contribution of several formulation variables on the drug release rate and floating properties of the gastric floating drug delivery system were examined. Acetylsalicylic acid (ASA), which has been widely utilized for treatment of cardiovascular disorders for its antithrombotic effect, was used as the model drug in this formulation.

EXPERIMENTAL

Materials

Acetylsalicylic acid (Bayer, Germany), hydroxypropyl methylcellulose of high viscosity (HPMC, 4000 cP) (Fluka, Switzerland), hydroxypropyl methylcellulose of low viscosity (HPMC, 100 cP) (Sigma, USA), sodium carboxymethylcellulose (NaCMC, medium viscosity) (Sigma), chitosan of different molecular mass [low, medium and high (LMW, MMW, HMW), degree of deacetylation of min. 75 %] (Aldrich, Germany), Di-Pac® (Amstar Corporation, USA), citric acid monohydrate (Aklar Chemistry, Turkey) and sodium bicarbonate (Aklar Chemistry) were used in the study. All other chemicals used were of reagent grade.

Methods

Preparation of floating two-layer tablets. – Formulations were prepared as two-layered tablets. One of the layers contained an effervescent mixture of citric acid and sodium bicarbonate as a gas-generating agent and HPMC 4000 as a matrix material to retain the air bubbles produced in the tablets. The other layer provided modified release of the

drug and comprised 100 mg ASA and various polymers such as HPMC 100, NaCMC or chitosan of different molecular mass as a retarding agent, and Di-Pac® as a direct tableting agent. The tablet formulations are shown in Table I. The components of each layer were blended homogeneously for 15 min in a mortar. Preparation of the two-layer tablet had two steps. At the beginning, the floating layer was placed in the die cavity and preparatory pressing was applied. Thereafter, the release layer was added and the final tablets were compressed using a single tableting hand press with a 12-mm flat-faced punch.

Floating behavior of tablets. – *In vitro* floating behavior of the tablets was tested using the paddle method (USP 24 apparatus II) containing 900 mL of simulated gastric fluid (12) (SGF) without enzyme, pH 1.2, with paddle rotation of 50 rpm at 37 ± 0.5 °C. The following parameters were determined: the time needed to float on the surface (floating lag time) and floating duration.

In vitro *drug release.* – Dissolution experiments were used to evaluate the *in vitro* drug release of the tablets. These studies were carried out using the paddle method at a paddle speed of 50 rpm in 900 mL of SGF at 37 ± 0.5 °C for 8 h. At predetermined time intervals, a sample was withdrawn from the dissolution vessel. To maintain a constant volume, fresh SGF was added to the dissolution vessel after each withdrawal. The amount of drug released was assayed with a UV-visible spectrophotometer (Shimadzu UV-1202, Japan) at a wavelength of 247 nm. Each *in vitro* release study was performed in triplicate. The data obtained from the dissolution tests were analyzed statistically using the simple analysis of variance (one-way ANOVA) or independent-sample *t*-test.

Table I. Formulation of floating tablets containing ASA

Composition (mg)	Formulation code												
Release layer	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
ASA	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMC 100 cP	50	50	50	50	30	90	50	–	–	–	–	–	–
NaCMC	–	–	–	–	–	–	–	50	–	–	–	–	–
Chitosan (LMW)	–	–	–	–	–	–	–	–	50	–	–	75	–
Chitosan (MMW)	–	–	–	–	–	–	–	–	–	50	–	–	75
Chitosan (HMW)	–	–	–	–	–	–	–	–	–	–	50	–	–
Di-Pac®	20	20	20	20	20	20	20	20	20	20	20	20	20
ASA (%)	58.8	58.8	58.8	58.8	66.7	47.6	58.8	58.8	58.8	58.8	58.8	51.3	51.3
Floating layer													
HPMC 4000 cP	250	250	250	250	250	250	125	250	250	250	250	250	250
Sodium bicarbonate	17	34	51	68	34	34	34	34	34	34	34	34	34
Citric acid monohydrate	14	28	42	56	28	28	28	28	28	28	28	28	28
Total mass	281	312	343	374	312	312	187	312	312	312	312	312	312

Kinetic assessment of dissolution data. – The dissolution rate data obtained were evaluated for compatibility with the kinetics of zero order, Higuchi equation (13) (Eq. 1), Korsmeyer-Peppas (14) (*Eq. 2*) and Peppas-Sahlin (15) (*Eq. 3*) equation:

$$\frac{M_t}{M_\infty} = k\,t^{1/2} \tag{1}$$

$$\frac{M_t}{M_\infty} = k^1\,t^n \tag{2}$$

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{3}$$

where M_t/M_∞ is the fraction of drug released after time t relative to the amount of drug released at infinite time, k and k^1 are kinetic constants characteristic of the drug/ polymer system, n is the release exponent that depends on the release mechanism and the shape of the matrix tested, k_1 and k_2 are the kinetic constants for the diffusional and relaxation drug dissolution, respectively, m is the purely Fickian diffusion exponent for a device of any geometrical shape that exhibits controlled release.

RESULTS AND DISCUSSION

Characterization of floating two-layer tablets

Two-layer tablet formulations were successfully prepared using a direct compression method. Physical properties of the tablets are shown in Table II. The thickness of all tablet batches ranged from 3.7 ± 0.1 to 4.4 ± 0.1 mm and the diameter of all tablets was 12 mm. The mass of the tablets ranged from 355.5 ± 0.5 to 543.5 ± 0.6 mg due to the differences in formulation design. Drug content was found to be consistent and uniform in all tablet formulations.

Floating two-layer tablet formulations were prepared using an effervescent approach. The first layer provided the floatation, accomplished by incorporating a gas-forming agent dispersed into HPMC 4000 as a swellable hydrophilic matrix to retain the air bubbles. HPMC 4000 was also chosen as a low-density hydrocolloid system. On contact, the simulated gastric medium reacted with the effervescent mixture in the floating layer of the two-layer tablet. It was observed that the gas generated was trapped in and protected by the gel formed HPMC.

Ideally, the floating system should float a few minutes after contact with the gastric fluid to prevent the dosage forms transiting into the small intestine (7, 16). Therefore, the floating layer formulations were optimized to obtain the shortest lag time and to prolong the gastro retention time. We prepared F1, F2, F3, F4 and F7 coded formulations, which included different concentrations of sodium bicarbonate and citric acid as

gas-generating agents and HPMC 4000 in the floating section, without changing the release layer. When the concentration of the effervescent mixture increased in the floating layer, the tablets were found to exhibit short floating lag time due to faster and higher CO_2 generation. However, tablet integrity decreased with a larger amount of effervescent mixture in the floating layer. Moreover, the formulations containing lower effervescent mixture did not float because of the lower efficiency of the gas forming agent.

By using HPMC 4000, significant and stable, persistent buoyancy was obtained. Reduction of the concentration of HPMC 4000 in the floating layer reduced the floating lag time, but decreased tablet integrity due to the lack of HPMC 4000 to restrain the gas--bubbles. Therefore, the amount of the effervescent mixture was chosen for the shortest possible lag time and floating duration of up to 8 h. The optimized floating layer formulation, coded as F2, had a floating lag time of 2.8 min, good matrix integrity and floating duration of more than 8 h (Table II). It is well known that the compression force strongly effects the lag time of floating (11, 17). Two different F2 formulations were pressed at pressures of 16 and 32 MPa. However, the F2 formulation produced at 16 was found to have better floating behavior. When the compression force was increased from 16 to 32 MPa, it was observed that the onset of floating increased from 3 to 18 min. The tablets compressed at a lower pressure retained a higher trapped air concentration, which resulted in decreasing the agglomerate density and allowing floating of the tablets. On the other hand, the tablets compressed at higher pressure were found to be less porous with high density preventing the tablets to float. Thus, a compression force of 16 MPa was adopted in the pressing of all tablet formulations. The final floating two-layer tablet formulations were prepared, containing the optimized floating layer and the release layer comprising ASA, Di-Pac® and various polymers. Di-Pac® was used in these formulations as a direct tableting agent in the drug-loading layer to compress the tablets more easily. It was also reported that hydrophilic substances such as Di-Pac® enhanced the water uptake of matrix tablets (11).

In vitro *drug release*

Before the dissolution test of formulations, the dissolution profile of pure ASA was determined in a simulated gastric environment. It was seen that the dissolution rate of the drug was quite fast and more than 80 % of the drug released within 15 min (Fig. 1). Design of the release layer may require different types and amounts of polymers to obtain floating tablets with desirable properties. The polymer properties used in this layer are an important factor in modifying the drug release. Therefore, the effect of several polymers such as HPMC 100, NaCMC and chitosan on the release profiles of the drug from the tablets was examined. All polymers were used as matrix-gel forming agents that hydrate and form a gelatinous barrier. As shown in Figs 1a and b, they exhibited substantial decrease in the drug release rate.

The F8 coded tablet formulation containing NaCMC in the drug-loaded layer quickly gelled and lost shape. Floatation began within 4.2 min upon contact with the gastric medium and floated for 4 h, but then the drug-loaded section separated from the floating section. The release profiles appear to be bi-phasic with an initial burst effect followed by a polymer-controlled slower release in the second phase (Fig. 1a). However, NaCMC as a polymer in the release layer produced inadequate drug release where the release

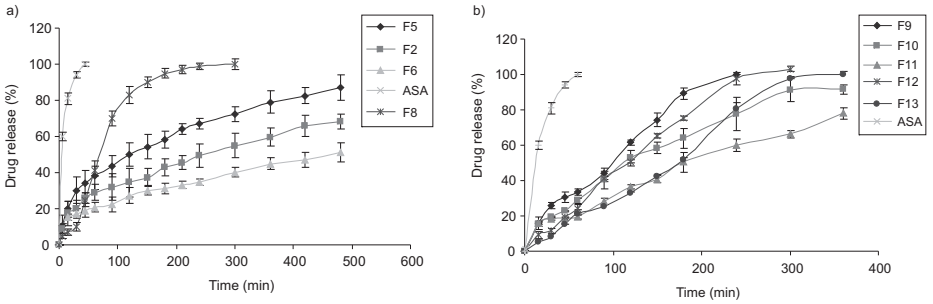

Fig. 1. Release profiles of ASA from the two-layer floating tablets using: a) NaCMC and HPMC 100, b) chitosan with different properties (mean ± SD, n = 3).

could not be controlled for a long time, possibly because of the poor strength of the matrix. Approximately 80 % of the drug from the tablet was released within 2 h.

F2, F5 and F6 formulations containing different concentrations of HPMC 100 in the drug-loaded layer had the floating lag time below 5.3 min (Table II). The flotation and floating lag time did not change significantly by increasing the amount of polymer in the drug release layer. All tablets had to float on the dissolution medium for more than 12 h. Fig. 1a shows the dissolution profiles of ASA from the prepared tablets containing HPMC 100 at various concentrations. The data indicates that the presence of HPMC 100

Table II. Physicochemical characterization of ASA floating tablets

Formulation code	ASA (%)[a]	Mass (mg)[b]	ASA conc. uniformity[b]	Thickness (mm)[b]	Tablet integrity at pH 1.2	Floating lag time (s)[c]	Floating duration (h)[c]
F1	22.2	449.1 ± 0.7	99.3 ± 1.7	3.8 ± 0.1	Eroded	–	–
F2	20.8	479.3 ± 0.5	97.2 ± 0.8	4.2 ± 0.1	Good	2.8 ± 0.1	> 12
F3	19.5	511.7 ± 0.9	99.3 ± 0.9	4.1 ± 0.1	Eroded	–	–
F4	18.4	543.5 ± 0.6	101.2 ± 0.4	4.2 ± 0.1	Eroded	–	–
F5	21.6	462.3 ± 0.4	99.8 ± 1.7	3.4 ± 0.1	Good	2.7 ± 0.8	> 12
F6	19.2	532.4 ± 0.6	100.1 ± 1.1	4.3 ± 0.1	Good	5.3 ± 1.7	> 12
F7	28.0	355.5 ± 0.5	99.9 ± 1.4	2.8 ± 0.1	Eroded	0.5 ± 0.01	–
F8	20.8	481.5 ± 0.5	99.2 ± 0.6	3.5 ± 0.1	Eroded after 4 h	4.2 ± 0.9	4
F9	20.8	480.4 ± 0.4	100.2 ± 1.9	3.8 ± 0.1	Good	9.7 ± 2.0	> 12
F10	20.8	484.6 ± 0.5	99.3 ± 1.7	3.7 ± 0.7	Good	11.3 ± 1.2	> 12
F11	20.8	475.2 ± 0.6	101.5 ± 1.0	3.8 ± 0.1	Good	9.7 ± 1.7	> 12
F12	19.7	505.3 ± 0.5	99.1 ± 0.8	4.2 ± 0.1	Good	9.0 ± 1.9	> 12
F13	19.7	509.6 ± 0.5	100.9 ± 1.2	4.1 ± 0.1	Good	10.0 ± 1.5	> 12

[a] Concentration of ASA in the whole tablet.
Mean ± SD: [b] n = 6, [c] n = 3.

Table III. Kinetic assessment of release data obtained from two-layer floating tablet formulations prepared using HPMC 100, NaCMC and chitosan

Kinetic model	Rate constant (unit)	Formulation								
		F2	F5	F6	F8	F9	F10	F11	F12	F13
Zero-order	k_0 (mg min^{-1})	0.125	0.159	0.086	0.388	0.412	0.231	0.198	0.362	0.299
	R^2	0.914	0.872	0.903	0.847	0.975	0.939	0.969	0.973	0.983
Higuchi	k (min$^{-1/2}$)	3.189	4.245	2.360	6.367	5.831	4.797	3.686	5.214	4.392
	R^2	0.998	0.996	0.995	0.966	0.980	0.993	0.988	0.959	0.930
Korsmeyer-Peppas	K (min^{-n})	0.048	0.478	0.031	0.009	1.502	0.002	1.564	0.007	0.004
	R^2	0.989	0.972	0.990	0.930	0.970	0.969	0.930	0.961	0.987
	n	0.423	0.307	0.541	0.884	0.600	0.624	0.550	0.878	0.925

R^2 = determination coefficient, n = release exponent

had a significant effect on the release of the delivery system. As expected, there is a clear difference in the ASA release pattern between the polymers in different concentrations ($p < 0.05$). A decrease in the release rate was observed with an increase in the amount of the polymer in the release layer. Similar results were reported by Colombo *et al*. (18), who reported that increased viscosity resulted in a corresponding decrease in the drug release rate. The effect of the polymer concentration is connected with increased viscosity and the length of the dissolution path through the matrix. For formulations F2, F5 and F6, drug release was 87 %, 68 % and 51 %, respectively, within 8 h. All formulations were able to keep their integrity during the dissolution test and therefore showed good control of the drug release, with slower release rate for a desired period of time. In addition, it was observed that adding the HPMC as a polymer to the release layer decreased the drug release rate and resulted in linearization of the drug release curves. The release rate constants obtained from Higuchi kinetics for tablets coded F5 (containing 66.7 % ASA), F2 (containing 58.8 % ASA) and F6 (containing 47.6 % ASA) were found to be 4.245, 3.189 and 2.360 min$^{-1/2}$ respectively (Table III); these values indicated that the drug release was enhanced with increasing the drug concentration. A linear correlation (R^2 = 0.972) was also found between these values.

In the release layer, different molecular mass chitosans (HMW, MMW, LMW chitosan) and concentrations of chitosan were used to optimize drug release and floating properties (Table I). None of the formulations containing chitosan showed a significant effect on the floating lag time and floatation period. All tablet formulations began floating approximately 10 min after immersion into the release medium and floated until the end of the dissolution test. It was also noted that the tablets remained intact during drug release. The release profiles of formulations coded F9, F10, F11, F12 and F13, prepared by using chitosan, are illustrated in Fig. 1b. When chitosan was added to the drug-loaded layer, the drug release rate decreased dramatically. Significant differences were observed between dissolution profiles ($p < 0.05$) of formulations prepared by using chitosan (F9-F13). The results showed that the molecular mass of chitosan played an important role in the design of the drug release layer. Comparing drug release rates among the dif-

ferent tablet formulations, it was evident that formulation F9, which contained LMW chitosan, exhibited the highest drug release rate. On the other hand, formulations F10 and F11, prepared with MMW and HMW chitosan, respectively, exhibited slower release rates. The slowest release rates were observed for formulations containing HMW chitosan, as a result of its high viscosity. As seen in Fig. 1b, the dissolution rate of the drug did not change effectively by increasing the chitosan concentration.

Kinetic assessment of dissolution data

Zero-order kinetics, Higuchi equation and Korsmeyer-Peppas and Peppas-Sahlin models were used to determine the drug release kinetics (13-15). Kinetic assessments of the dissolution data are shown in Tables III and IV. In all formulations containing NaCMC and HPMC 100 in the release layer, the Higuchi equation was found to be efficient in describing the kinetics of drug release, with drug release proportional to the square root of time, due to the hydrophilic structure of the matrix. It has been suggested that the erosion mechanism, in addition to diffusion, was influential on the release of active material. To explore the release pattern, results of the *in vitro* release data of the formulations were also fitted to the Korsmeyer-Peppas equation, which characterizes the transport mechanism based on the values of n (14). For the matrix tablet, when n takes the value of 0.45, it indicates diffusion-controlled drug release whill for the value 0.89, it indicates swelling-controlled release. Values of n between the two values can be regarded as indicators of anomalous transport (19). All formulations exhibited values close to 0.45, indicating that the drug release was governed by Fickian diffusion. However, increasing the polymer content increased the exponent n (Table III). This is attributed to an increasing restriction of drug release produced by increasing polymer viscosity. The formulations containing a low concentration of chitosan (LMW, MMW and HMW) fitted well to the Higuchi equation, indicating a diffusion mechanism. When the concentration of chitosan in the formulation was increased, n increased from 0.600 to 0.925, characterizing the anomalous transport release mechanism, and the release mechanism was close to zero-

Table IV. Parameter estimates derived from Peppas-Sahlin equation to experimental data

Formulation code	k_1 (min^{-m})	k_2 (min^{-2m})	R^2
F2	0.203	2.2×10^{-4}	0.974
F5	0.430	9.7×10^{-4}	0.970
F6	0.143	1.7×10^{-4}	0.937
F8	0.206	1.4×10^{-2}	0.993
F9	0.277	9.2×10^{-4}	0.977
F10	0.650	1.5×10^{-3}	0.952
F11	0.182	1.1×10^{-4}	0.986
F12	0.367	3.9×10^{-4}	0.989
F13	0.305	2.3×10^{-4}	0.984

k_1 – kinetic constant for diffusional drug dissolution, k_2 – kinetic constant for relaxation drug dissolution; m – purely Fickian diffusion exponent for a device of any geometrical shape that exhibits controlled release

-order. According to the Peppas and Sahlin equation, the derived k_2 values that represent case-II transport (erosion mechanism) were found much lower than k_1 (Table IV). It was concluded that diffusion was the predominant mechanism of drug release in all formulations.

CONCLUSIONS

In this study, we developed a two-layer floating oral drug delivery system with desired release profiles and floating properties. Stable and persistent buoyancy was achieved by trapping the gas in the gel formed by the hydration of HPMC 4000. Gas formation was obtained from an effervescent mixture of sodium bicarbonate and citric acid. The release of the drug from the release layer prepared with various types of polymers revealed different behaviors. Tablets including HPMC 100 showed the slowest release pattern. The release rate could effectively be modified by using HPMC 100 and chitosan for a modified release of 8 h, following the Higuchi diffusion mechanism. The drug release patterns can be effectively adjusted by varying simple formulation parameters, such as the type and viscosity of matrix-forming polymers.

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S A Ž E T A K

Učinak formulacijskih parametara na oslobađanje lijeka i svojstva dvoslojnih tableta koje plutaju u želucu

CANAN HASÇIÇEK, GÜNSELI YÜKSEL-TILKAN, BERNA TÜRKMEN i NURTEN ÖZDEMIR

U radu su opisane plutajuće tablete acetilsalicilne kiseline za antikoagulacijsku upotrebu s produljenim zadržavanjem u želucu i većom bioraspoloživošću. Plutajući dio tih dvoslojnih tableta sadržavao je hidroksipropil metilcelulozu (HPMC) visoke viskoznosti i efervescentnu smjesu limunske kiseline i natrijevog hidrogenkarbonata. Drugi sloj sadržavao je ljekovitu tvar, sredstvo za izravno tabletiranje i različite vrste matriksnog polimera poput HPMC niske viskoznosti, natrijeve soli karboksimetilceluloze i kitozana. Tablete su pripravljene metodom izravne kompresije. Ispitivan je utjecaj formulacijskih varijabli na fizikokemijska i plutajuća svojstva, te oslobađanje ljekovite tvari. Plutajuća svojstva ovise o količini efervescentnih tvari i gelirajućeg polimera u plutajućem sloju. Promjenom vrste i viskoznosti polimera u matriksnom sloju s lijekom produljeno je oslobađanje ljekovite tvari na 8 sati. Iz svih formulacija ljekovita tvar oslobađala se difuzijom.

Ključne riječi: dvoslojne plutajuće tablete, zadržavanje u želucu, hidroksipropil metilceluloza, kitozan

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