

Formulation and evaluation of effervescent floating tablets of tizanidine hydrochloride

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Tizanidine hydrochloride is an orally administered prokinetic agent that facilitates or restores motility throughout the length of the gastrointestinal tract. The objective of the present investigation was to develop effervescent floating matrix tablets of tizanidine hydrochloride for prolongation of gastric residence time in order to overcome its low bioavailability (34–40 %) and short biological half life (4.2 h). Tablets were prepared by the direct compression method, using different viscosity grades of hydroxypropyl methylcellulose (HPMC K4M, K15M and K100M). Tablets were evaluated for various physical parameters and floating properties. Further, tablets were studied for *in vitro* drug release characteristics in 12 hours. Drug release from effervescent floating matrix tablets was sustained over 12 h with buoyant properties. DSC study revealed that there is no drug excipient interaction. Based on the release kinetics, all formulations best fitted the Higuchi, first-order model and non-Fickian as the mechanism of drug release. Optimized formulation (F9) was selected based on the similarity factor (f_2) (74.2), dissolution efficiency at 2, 6 and 8 h, and t_{50} (5.4 h) and was used in radiographic studies by incorporating BaSO₄. *In vivo* X-ray studies in human volunteers showed that the mean gastric residence time was 6.2 ± 0.2 h.

Keywords: tizanidine hydrochloride, gastroretentive drug delivery system, floating tablets, release kinetics

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Effective gastroretentive drug delivery systems (GRDDS) depend upon the factors such as the gastric emptying process, gastrointestinal transit time of the dosage form, drug release from the dosage form and the site of drug absorption. Rapid GI transit leads to incomplete drug release from the dosage form in the absorption zone. This led to the development of GRDDS. Several approaches cited in the literature (1–4) include muco-adhesion, swelling or expansion, modified shape systems, floatation, gastric emptying delaying devices (5) or simultaneous administration of gastric emptying delaying drugs.

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Among the various approaches, the floating drug delivery systems offer the most effective, simple and practical approach to achieve increased gastric residence time and sustained drug release compared to the other methods (4). Based on the mechanism of buoyancy, non-effervescent and effervescent technologies have been utilized in the development of floating drug delivery systems (FDDS). Non-effervescent systems commonly use gel-forming or highly swellable cellulose type hydrocolloids. Effervescent systems utilize swellable polymers and inclusion of gas generating agents, *i.e.*, sodium bicarbonate and citric or tartaric acid (6).

Tizanidine hydrochloride is an orally administered prokinetic agent that facilitates or restores motility throughout the length of the gastrointestinal tract. Tizanidine is least absorbed from the lower part of the gastrointestinal tract and better absorbed from the stomach. The main limitations of the therapeutic effectiveness of tizanidine hydrochloride is its low bioavailability (30–40 %), short biological half life (4.2 h) and the fact that it undergoes first pass metabolism. Thus, tizanidine hydrochloride is a candidate for the development of GRDDS. In the present study, the details of formulation development and evaluation of effervescent floating tablets of tizanidine hydrochloride are described.

EXPERIMENTAL

Materials

Tizanidine hydrochloride was a gift sample from Symed Lab Ltd., India. Hydroxypropyl methylcelluloses (HPMC K4M, K15M, and K100M) were gift samples from Danmed Pharmaceuticals, India. Microcrystalline cellulose was obtained from Aurabindo Laboratories, India. Sodium bicarbonate and magnesium stearate were purchased from S.D. Fine-Chem. Ltd., India. All other chemicals used were of analytical grade.

Methods

Development of tablets. – Tizanidine hydrochloride tablets were prepared using different viscosity K-grade HPMC polymers such as K4M (4000 cps), K15M (15,000 cps) and K100M (1,00,000 cps). Preliminary formulations (F1-F4) were studied to optimize the effervescent concentration. Then, floating tablets were prepared with an optimized concentration of effervescent composition. All formulation ingredients were sifted through a 420- μ m aperture size sieve to get uniform size particles. The mixture was placed in a polyethylene bag and further mixed for 5 to 10 minutes to ensure a homogeneous mass. Then, the powder was lubricated with magnesium stearate and talc and compressed on a 16-station rotary tablet punching machine (Cadmach, India) using 8-mm standard flat-face punches. Formulated tablets were round and flat with an average diameter of 8.1 ± 0.2 mm and a thickness of 3.36 ± 0.2 mm. Quantitative composition of tizanidine hydrochloride floating matrix tablets is shown in Table I.

Physical characterization of compressed tablets

Compressed tablets were characterized for mass and thickness variation. Mass variation (20 tablets) was carried out using a digital balance (Shimadzu, Japan) and thick-

Table I. Composition of tizanidine hydrochloride effervescent floating tablets

| Formulation | Tizanidine HCl (mg) | HPMC K4M (mg) | HPMC K15M (mg) | HPMC K100M (mg) | Sodium bicarbonate (mg) | MCC (mg) | Magnesium stearate (mg) | Talc (mg) | Total mass (mg) |
|-------------|---------------------|---------------|----------------|-----------------|-------------------------|----------|-------------------------|-----------|-----------------|
| F1 | 10 | – | 70 | – | 18 | 76 | 2 | 4 | 180 |
| F2 | 10 | – | 70 | – | 27 | 67 | 2 | 4 | 180 |
| F3 | 10 | – | 70 | – | 36 | 58 | 2 | 4 | 180 |
| F4 | 10 | – | 70 | – | 45 | 49 | 2 | 4 | 180 |
| F5 | 10 | 40 | – | – | 36 | 88 | 2 | 4 | 180 |
| F6 | 10 | 60 | – | – | 36 | 68 | 2 | 4 | 180 |
| F7 | 10 | 80 | – | – | 36 | 48 | 2 | 4 | 180 |
| F8 | 10 | – | 30 | – | 36 | 98 | 2 | 4 | 180 |
| F9 | 10 | – | 40 | – | 36 | 88 | 2 | 4 | 180 |
| F10 | 10 | – | 60 | – | 36 | 68 | 2 | 4 | 180 |
| F11 | 10 | – | 80 | – | 36 | 48 | 2 | 4 | 180 |
| F12 | 10 | – | – | 40 | 36 | 88 | 2 | 4 | 180 |
| F13 | 10 | – | – | 60 | 36 | 68 | 2 | 4 | 180 |
| F14 | 10 | – | – | 80 | 36 | 48 | 2 | 4 | 180 |

HPMC – hydroxypropyl methylcellulose, MCC – microcrystalline cellulose

ness (10 tablets) was measured with a digital screw gauge micrometer (Digimatic micrometer Series 293, Mitutoyo, Japan). Crushing strength (6 tablets) was measured with a Monsanto tester (Campbell Electronics, India), and friability (10 tablets) was determined (Roche type friabilator, Germany).

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to the average mass of one tablet was added in 100 mL of 0.1 mol L⁻¹ HCl, followed by sonicating for 2 h. The drug content was estimated by recording absorbance at 319 nm using a UV-Visible spectrophotometer (Elico-161, India).

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al.* (7). The tablet was placed in a 100-mL beaker containing 0.1 mol L⁻¹ HCl. The time required for the tablet to rise to the surface for floating was defined as the floating lag time and total duration of time the tablet remained buoyant was defined as total floating time (TFT).

In vitro drug release studies

The release of tizanidine hydrochloride from floating matrix tablets (3 tablets) was studied using a USP 28 (8) type II (paddle) dissolution apparatus (Electro Lab, India). The dissolution test was performed using 900 mL 0.1 mol L⁻¹ HCl maintained at 37 ± 0.5 °C

and a rotation speed of 50 rpm. Aliquots of 5 mL were collected at predetermined time intervals, filtered through a 0.45- μ m membrane filter and replenished with an equivalent volume of fresh dissolution medium. Drug content in the samples was determined at 319 nm after suitable dilutions.

In vivo X-ray studies

The *in vivo* X-ray studies were approved by the Institutional Human Ethical Committee of KLR Pharmacy College (New Paloncha, A. P., India). The study was performed on 3 healthy male human volunteers, weighing between 55 and 70 kg and in an age group of 25 ± 2 years. Before participation in these studies, a written consent was obtained from the volunteers and an expert radiologist and a physician supervised these studies. F9 was modified by adding 20 mg of X-ray grade barium sulfate (10 mg of drug and 10 mg of microcrystalline cellulose were replaced). After overnight fasting, the volunteers were fed low calorie food and the tablet was given to every subject with 200 mL water. After one hour of tablet ingestion, a glass of water was given to the subject. Gastric radiography was done after 1, 2, 4 and 6 h. The mean gastric residence time was calculated.

Drug release kinetics

The rate and mechanism of drug release was analyzed by fitting the dissolution data into several mathematical models, zero-order, first-order, Higuchi and Peppas (9–12).

Dissolution profiles were compared with the similarity factor using the theoretical release profile as a reference (13). Similarity factor (f_2) (14) is a logarithmic, reciprocal square root transformation to the sum of squared errors. If f_2 value is between 50 and 100, the two dissolution profiles are considered to be similar. From the dissolution profiles of each formulation, the dissolution efficiency (DE) (15) at 2, 6 and 8 h and t_{50} was determined.

Differential scanning calorimetry (DSC)

The physicochemical compatibilities of the drug and excipients used were tested by performing DSC analyses of pure drug and optimized formulation (F9). DSC curves of the samples were obtained with a differential scanning calorimeter (DSC 6, Perkin Elmer, USA). 2–4 mg of sample was placed in an aluminum pan and then crimped with an aluminum cover. Heating and cooling rates were 10 and 250 $^{\circ}\text{C min}^{-1}$, respectively. All measurements were performed over 50–350 $^{\circ}\text{C}$ under a nitrogen purge at 50 mL min^{-1} .

RESULTS AND DISCUSSION

Physical characterization of tablets

Physical characteristics of the formulated matrix are shown in Table II. To avoid processing variables, all batches were produced under similar conditions. The mean hardness of the tablets was $3.2 \pm 0.6 \text{ kg cm}^{-2}$, average mass variation was $182 \pm 4 \text{ mg}$, mean thickness was $3.2 \pm 0.4 \text{ mm}$ and friability ranged from 0.5 to 0.7 % (m/m) ($0.6 \pm 0.2 \%$). The content uniformity of the tablets was $98.9 \pm 2.3 \%$.

In vitro buoyancy

For determination of optimum *in vitro* buoyancy and floating lag time, formulations (F1-F4) were prepared with different concentrations of sodium bicarbonate (10, 15, 20, and 25 %). Whitehead *et al.* (16) had demonstrated good correlation between *in vitro* and *in vivo* buoyancy of floating dosage forms. Their results showed that increasing concentration of sodium bicarbonate decreased the floating lag time. At 20 % sodium bicarbonate concentration tablets remained rigid and buoyant for 12 h with a lag time of 125 to 140 seconds, whereas the tablets with 25 % NaHCO₃ showed shorter lag time and the tablet integrity was lost during the study after 6 to 8 h (results not shown). In this study, penetration of water into tablets with low viscosity HPMC K4M was slow, causing delayed gel formation and subsequent increase in the floating lag time and decreased total floating duration (< 8 h) compared to the tablets prepared with K15M and K100M. F9 showed the best floating lag time of 120 ± 5 s. With the exception of formulations F5 to F7, all the formulated tablets were buoyant for more than 12 h.

Drug excipient interactions

Fig. 2 represents the DSC curves of pure drug and optimized formulation (F9). A sharp endothermic peak was observed at 290.1 °C, indicating the melting point of tizanidine hydrochloride. In the DSC thermogram of optimized formulation, the peak was observed at 284.7 °C. This finding clearly indicates there was no interaction between the drug and excipients used in the formulation.

In vitro dissolution studies

By using pharmacokinetic parameters of tizanidine hydrochloride, the theoretical drug release for a 12-h dosage form was calculated. An effective drug plasma concentration

Table II. In vitro release kinetics of tizanidine hydrochloride effervescent floating tablets

| Formulation | R ² | | | n |
|-------------|----------------|------------|---------|------|
| | First-order | Zero-order | Higuchi | |
| F5 | 0.972 | 0.928 | 0.945 | 0.58 |
| F6 | 0.978 | 0.954 | 0.988 | 0.64 |
| F7 | 0.968 | 0.928 | 0.942 | 0.68 |
| F8 | 0.958 | 0.885 | 0.948 | 0.62 |
| F9 | 0.988 | 0.919 | 0.922 | 0.74 |
| F10 | 0.977 | 0.932 | 0.962 | 0.56 |
| F11 | 0.969 | 0.948 | 0.906 | 0.63 |
| F12 | 0.948 | 0.926 | 0.923 | 0.67 |
| F13 | 0.969 | 0.894 | 0.926 | 0.64 |
| F14 | 0.962 | 0.868 | 0.936 | 0.59 |

R² – coefficient of determination, n – release exponent of Korsmeyer-Peppas

was maintained when the sustained release formulation released the required quantity of drug with predetermined kinetics. To achieve this, floating tablets should be formulated so that they release the drug in a predetermined and reproducible manner. The release of tizanidine hydrochloride from effervescent floating tablets was analyzed by plotting the cumulative percent drug release against time. The *in vitro* drug release studies revealed that formulations F5, F6 and F7 (Fig. 1a) containing 22, 33 and 44 % HPMC K4M, respectively, were able to sustain the drug release for 4, 6 and 8 h, respectively. Floating lag time was 435 seconds; total buoyancy was 6 to 8 h and tablet integrity was poor for HPMC K4M formulations. Drug release profiles of formulations F8 to F11 containing 16.6, 22, 33 and 44 % HPMC K15 M, respectively, are shown in Fig. 1b. For F8, 98 % of the drug was released after 10 hours. 95, 86 and 81 % of drug was released from formulations F9, F10 and F11, respectively, after 12 h. Formulation F8 underwent swelling and erosion, resulting in faster drug release. In F9, 22 % of HPMC K15M was sufficient to sustain the drug release for 12 h. On increasing the quantity of HPMC K15M up to 44 %, the release of the drug was too slow and only 81 % of the drug was released. It was observed that when the polymer concentration was increased, the drug release rate decreased. Formulation F9 matched the theoretical release profile and floating lag time of 120 s; for these reasons, F9 was considered the best among all the formulations.

Drug release profiles of formulations F12-F14, composed of HPMC K100M, are shown in Fig. 1c. The percentage of drug released from these formulations was 91, 83 and 76 %, respectively, after 12 h. This variation was considered to be due to different polymer concentrations. Release of the drug was faster with lower viscosity grades of HPMC (K4M) due to lower gel strength, less entanglement and smaller diffusion path

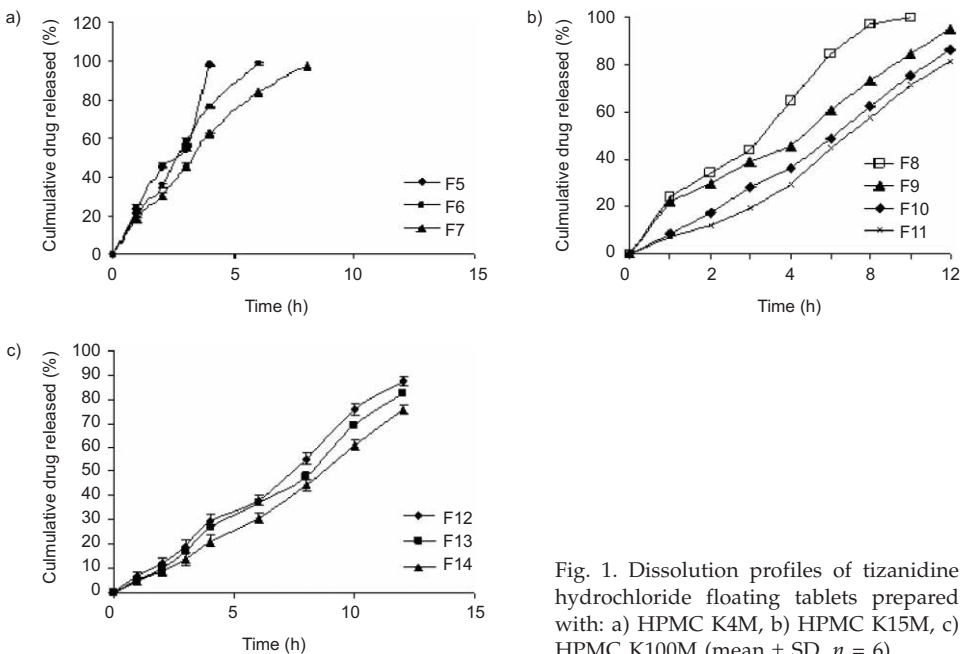


Fig. 1. Dissolution profiles of tizanidine hydrochloride floating tablets prepared with: a) HPMC K4M, b) HPMC K15M, c) HPMC K100M (mean \pm SD, $n = 6$).

length compared to higher viscosity grades of HPMCs. In all the formulations, polymer concentration greatly affected the release of the drug. The drug release rate was inversely proportional to the polymer concentration present in the matrix.

Drug release kinetics

The results of kinetic models for tizanidine hydrochloride release from floating matrix tablets are shown in Table II. The coefficient of determination (R^2) was used as indicator of the best fitting for each of the models considered. The results revealed that all formulations of floating matrix tablets fitted best the Higuchi (9) and first-order models (10). To explore the mechanism of drug release, the results of *in vitro* data were fitted into the Korsmeyer and Peppas equation ($M_t / M_\infty = kt^n$, where M_t / M_∞ is the fraction of

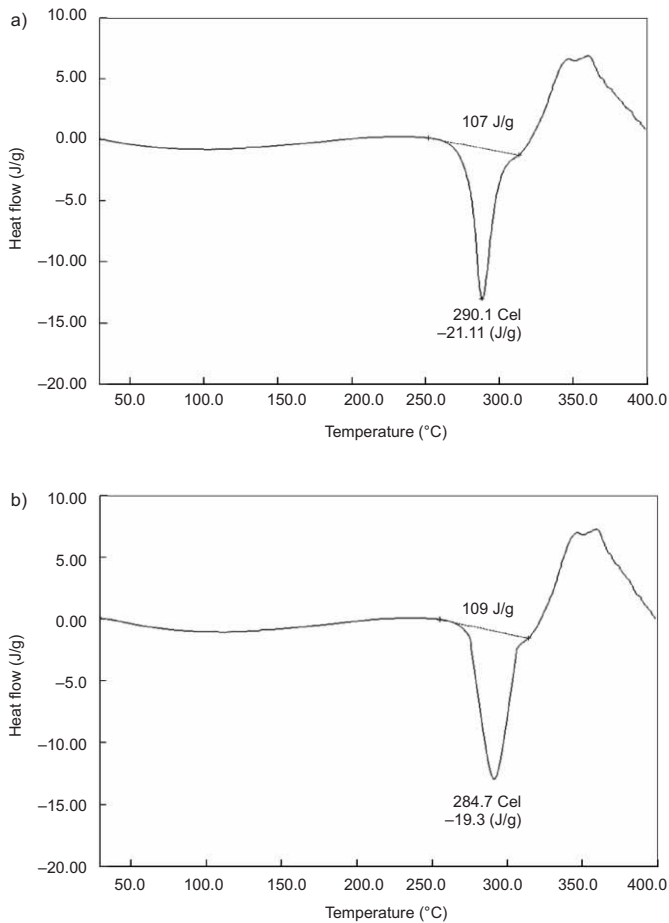


Fig. 2. DSC curves of: a) tizanidine hydrochloride, b) optimized formulation (F9).

drug released at infinite time, k is the kinetic constant and n is the diffusional exponent indicative of the mechanism of drug release) (11, 12) characterizing the transport mechanism. The value of n was 0.54–0.78, indicating release governed by the non-Fickian diffusion mechanism.

The optimized formulation was selected based on the similarity factor (f_2) (14) value, dissolution efficiency (15) at 2, 6 and 8 h, and t_{50} value (Table III). The similarity factor (f_2) of F9, when compared with the theoretical release profile, was found to be 74.2, which was higher than for other formulations. The other independent model parameters such as dissolution efficiency and t_{50} revealed that the drug release profile from formulation F9 was similar to the theoretical release profile.

Table III. Dissolution parameters, floating lag time and f_2 factor of tizanidine hydrochloride floating tablets

| Formulation | Floating lag time (s) ^a | t_{50} | Dissolution efficiency (%) ^a | | | f_2 factor |
|-------------|------------------------------------|----------|-----------------------------------------|--------------|--------------|--------------|
| | | | 2 h | 6 h | 8 h | |
| Theoretical | 450 ± 5 | 4.8 | 38.3 | 63.1 | 75.5 | |
| F5 | 435 ± 7 | 2.4 | 45.4 | ^b | – | 50.9 |
| F6 | 430 ± 5 | 2.8 | 35.4 | 98.4 | ^c | 54.6 |
| F7 | 126 ± 6 | 3.2 | 30.1 | 83.5 | 97.23 | 55.6 |
| F8 | 120 ± 1 | 3.1 | 34.2 | 84.6 | 97.1 | 58.2 |
| F9 | 130 ± 2 | 5.4 | 30.3 | 60.8 | 73.2 | 74.2 |
| F10 | 136 ± 4 | 6.2 | 17.8 | 48.7 | 62.2 | 64.2 |
| F11 | 128 ± 6 | 7.1 | 12.2 | 44.8 | 57.7 | 59.8 |
| F12 | 139 ± 7 | 7.6 | 11.9 | 38.5 | 55.9 | 66.4 |
| F13 | 140 ± 8 | 8.3 | 10.2 | 36.9 | 48.3 | 56.7 |
| F14 | 139 ± 4 | 8.6 | 9.12 | 21.3 | 44.2 | 55.2 |

^a Mean ± SD, $n = 3$.

^b 97.7 % drug released in 4 h.

^c 98.1 % drug released in 6 h.

In vivo X-ray studies

After ingestion of the floating tablets developed by using barium sulfate, the duration of the tablet in the stomach and upper part of the intestine was monitored by radiograms (Fig. 3). The change in the location of the tablet at different time points suggested that the tablet did not adhere to the gastric mucosa; the mean gastric residence time was 6.2 ± 0.2 h.



Fig. 3. X-ray radiographic images of abdomen 1 and 6 h after ingestion of BaSO₄-loaded optimized F9 effervescent floating tablet.

CONCLUSIONS

The present study was conducted to develop an effervescent floating drug delivery system using three grades of HPMC polymer, in different concentrations. Optimized formulation F9 showed an excellent buoyant ability and a suitable drug release pattern. This could be advantageous in terms of increased bioavailability of tizanidine hydrochloride. The developed gastroretentive drug delivery system provides advantages of ease of preparation and sustained drug release for 12 h.

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S A Ž E T A K

Priprava i vrednovanje šumećih plutajućih tableta tizanidin hidroklorida

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Tizanidin hidroklorid je prokinetički agens za peroralnu primjenu koji olakšava ili obnavlja mobilnost kroz gastrointestinalni trakt. Cilj rada bio je razvoj šumećih plutajućih matriksnih tableta tizanidin hidroklorida za produljeno zadržavanje u želucu u svrhu poboljšanja niske bioraspoloživosti (34–40 %) i produljenja vremena poluživota (4,2 h). Tablete su pripravljene metodom izravne kompresije, koristeći hidroksipropil metilcelulozu različite viskoznosti (HPMC K4M, K15M i K100M). Određeni su različiti fizikalni parametri. Oslobođanje ljekovite tvari *in vitro* bilo je polagano tijekom 12 sati, a tablete su imale svojstvo plutanja. Prema DSC ispitivanja nema interakcije s pomoćnim tvarima. Kinetička ispitivanja pokazuju da oslobođanje iz svih pripravaka slijedi Higuchijev model, kinetiku prvog reda i ne-Fickov zakon. Na temelju faktora sličnosti (f_2) (74,2), oslobođanja ljekovite tvari nakon 2, 6 i 8 h, te vremena poluživota t_{50} (5,4 h) izabrana je optimirana formulacija (F9) i upotrebljena u radiografičkim ispitivanjima koja uključuju BaSO₄. *In vivo* ispitivanja rendgenskim zrakama na dobrovoljcima pokazala su da je srednje vrijeme zadržavanja u želucu bilo $6,2 \pm 0,2$ h.

Ključne riječi: tizanidin hidroklorid, sustav za isporuku lijekova sa zadržavanjem u želucu, plutajuće tablete, kinetika oslobođanja

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