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Formulation and characterization of gastroretentive drug delivery system of losartan potassium

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ABSTRACT

Floating matrix tablets of losartan potassium were developed with an aim to prolong its gastric residence time and increase the bioavailability of drug. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The tablets were prepared by wet granulation technique, using polymers Methocel K15 and Methocel K100 in combination with other standard excipients. Sodium bicarbonate was incorporated as gas generating agent. The effects of sodium bicarbonate and polymers on drug release profile and floating properties were investigated. It was found that viscosity of Methocel K15 and Methocel K100 along with sodium bicarbonate had significant impact on the release and floating properties of the delivery system. The decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer with high viscosity Methocel K100 was shown to be beneficial than low viscosity polymer Methocel K15 in improving the floating properties of gastric floating drug delivery system (GFDDS). The observed difference in the drug release and floating properties of GFDDS could be attributed to the difference in the basic properties of two polymers, Methocel K15 and Methocel K100 due to their water uptake potential and functional group substitution. The release mechanism were explored and described with zero-order, first-order and Korsmeyer-Peppas equations. The drug release profiles and buoyancy of the floating tablets were stable when stored at 40°C/75% RH for 6 months.

***Key Words*:** Floating tablets, methocel, flow property, buoyancy, dissolution, stability study.

INTRODUCTION

Drug biodisponibility is a crucial fact in therapeutic effectiveness. One of the essential factors is the residence time of the drug at the absorption site. Over the last two decades, numerous gastroretentive dosage forms have been designed to prolong gastric residence time. They may be broadly classified into: high-density (sinking) systems, low-density (floating) systems, expandable systems, superporous hydrogel systems, mucoadhesive systems and magnetic systems. They enable oral therapy by drugs with a narrow absorption window in the upper part of the gastrointestinal tract or drugs with a poor stability in the colon. Furthermore, the drug can act locally within the stomach and prolonged intimate contact with the absorbing membrane increases efficacy (Gro *et al.*, 1984; Moes *et al.*, 1993; Deshpande *et al.*, 1996).

Oral delivery of drugs is by far the most preferable route of drug delivery. However, this route has several physiological problems, including an unpredictable gastric emptying rate, a brief gastro intestinal transit time and the existence of an absorption window in the upper small intestine for several drugs (Agyilirah *et al.*, 1991). Unpredictable gastric residence time of a controlled release dosage form leads to interest in targeting and retaining the dosage form in the stomach for a prolonged period of time (Ali *et al.*, 2007). Drug absorption from the gastro intestinal tract is a complex procedure subject to many variables. It is widely acknowledged that the extent of gastro intestinal tract drug absorption

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Table 1: Composition of floating tablets of losartan potassium.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Losartan potassium	50	50	50	50	50	50	50	50
Methocel K15	80	100	80	100	-	-	-	-
Methocel K100	-	-	-	-	80	100	80	100
Sodium bicarbonate	30	30	40	40	30	30	40	40
Citric acid	15	15	15	15	15	15	15	15
PVP K30	50	50	50	50	50	50	50	50
Lactose	35	15	25	05	35	15	25	05
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Weight of tablets	280	280	280	280	280	280	280	280

is related to contact time with the small intestine mucosa (Arora *et al.*, 2005).

Drugs that have narrow absorption window in the gastro intestinal tract will have poor absorption window. For these drugs gastrointestinal drug delivery offer the advantage in prolonging the gastric emptying time (Arza *et al.*, 2009). Gastro retentive controlled release systems are widely used for controlled drug administration. These systems are attractive approaches from an economic as well as process development point of view (Pablo *et al.*, 2008). The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of gastrointestinal tract (Jaimini *et al.*, 2007).

Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients (Chandel et al, 2012). Various approaches that have been reported in the literature for the formulation of gastroretentive systems: mucoadhesion, (Ponchel *et al.*, 1998; Lanerts *et al.*, 1990) flotation, (Deshpande *et al.*1997) sedimentation, (Rednick *et al.*, 1970; Davis *et al.*,1986) expansion (Urguhart *et al.*, 1994; Mamajel *et al.*, 1980) and modified shape systems (Fix *et al.*, 1993; Kedzierewicz *et al.*, 1999). Both single unit systems and multiple unit systems have been reported in the literature (Bechgaard *et al.*, 1978). Floating drug delivery systems also called hydrodynamic balanced system is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug (Bardonnet *et al.*, 2006). This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine, drugs acting locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid (Rouge *et al.*, 1996; Umamaheshwari *et al.*, 2003).

Losartan potassium is a potent, highly specific angiotensin II type 1(AT 1) receptor antagonist with antihypertensive activity. It is readily absorbed from the gastro intestinal tract with oral bioavailability of about 33% and a plasma half-life ranging from 1.5 to 2.5 hour (Goldsmith *et al.*, 1978). Floating matrix tablets of losartan potassium were developed to prolong gastric residence time, leading to an increase in drug bioavailability.

MATERIALS AND METHODS

Losartan potassium was provided as a kind gift from Cadila Pharma, Ahemdabad, India. Methocel K15 and Methocel K100 were received as a gift sample from Colorcon Asia Pvt. Ltd. Mumbai, India. Polyvinyl pyrrolidine K30 (PVP K30), lactose and talc were purchased from E Merck (India) Ltd, Mumbai. Magnesium stearate, sodium bicarbonate and citric acid were purchased from SD Fine Chem. Ltd. Mumbai, India. All other ingredients used were of laboratory grade.

Preparation of the losartan potassium floating tablets

All the ingredients (except glidents and lubricant) as shown in Table 1 were weighed separately, mixed thoroughly in poly bag for 10 minutes to enusure uniform mixing and the mixture was passed through sieve no.60. Granulation was done with a solution of calculated quantity of PVP K30 in sufficient isopropyl alcohol. The wet mass was passed through sieve no. 12, and dried at 45-55°C for 2 hours. The dried granules were sized by sieve no. 18 and mixed with magnesium stearate and talc. The blend thus obtained was compressed (8 mm diameter, flat punches) using a single station compression machine (Cadmach, Ahmedabad, India).

Flow properties of granules

Angle of repose was determined using fixed funnel method. A glass funnel is held in place with a clamp on a ring support over a glass plate. Approximately 1gm of power is transferred in to funnel keeping the orifice of the funnel blocked by the thumb. When the powder is emptied from funnel, the angle of the heap to the horizontal plane is measured.

Granules were poured gently through a glass funnel in to a graduated cylinder cut exactly to 10 ml mark. Excess granules were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (ϱb) and tapped density (ϱt) were calculated. Hausner ratio (H_R) and Carr index (I_C) were calculated according to the equations given below (Sinha *et al.*, 2005):

$$H_R = \frac{\rho_t}{\rho_b}$$

$$I_c = (\rho_t - \rho_b)$$

Post compressional studies of the prepared floating tablets

The prepared tablets were tested as per standard procedure for weight variation (n=20), thickness (n=20), hardness (n=6), friability and drug content. Thickness of the tablets was measured by digital micrometer; hardness of tablet was determined by using tablet hardness tester (EH-01, Electrolab, Mumbai); friability test was conducted using Roche friabilator (I.P., 1996; Banker *et al.*, 1987; Rosa *et al.*, 1994).

For estimation of drug content, ten tablets were randomly selected and powdered. A quantity of powder equivalent to 50 mg of losartan potassium was accurately weighed and transferred into a volumetric flask and dissolved in 100 ml of 0.1N hydrochloric acid (HCl). The flask was shaken on a flask shaker for 24 h and the solution was filtered through 0.45µ membrane. 1 ml of the above solution was transferred to a volumetric flask and diluted suitably with 0.1N HCl. The absorbance of resulting solution was measured at 254 nm using UV/visible spectrophotometer.

***In vitro* buoyancy study**

The *in vitro* buoyancy was determined as per the method described by Rosa *et al.* The test was performed by placing each of the tablets in a 250 ml beaker, containing 200 ml of 0.1N HCl with Tween 20 (0.02% w/v), pH 1.2, maintained at 37±0.5°C. The time between introduction of the dosage form and its buoyancy on the 0.1N HCl (lag time) and the time during which the dosage form remains buoyant (total buoyancy time) were determined visually (Rosa *et al.*, 1994).

***In vitro* dissolution study**

The release rate of losartan potassium from floating tablets was determined using *United States Pharmacopeia (USP)* 24 Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at 37±0.5°C and 75 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 254 nm using a UV/Vis double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Stability study

To assess the drug and formulation stability, stability studies were done according to International Conference on Harmonisation (ICH) guidelines. The floating tablets were stored at 40±2°C/75±5% relative humidity (RH) in closed high-density polyethylene bottles for a period of 6 months. Tablets were analyzed at specified time intervals for the drug content, *in vitro* dissolution and buoyancy behaviour. The differences in parameters from floating tablets were evaluated using unpaired t-test. In t-test, a probability value of $p < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Flow properties of granules

The granules prepared for the formulation of floating tablets were evaluated for angle of repose, Carr's index and Hausner ratio. Angle of repose ranged from 24.34 to 27.36 with Methocel K15 and 22.63 to 28.29 with Methocel K100, Hausner ratio ranged from 1.12 to 1.24 with Methocel K15 and 1.12 to 1.21 with Methocel K100, Carr's index ranged between 11.79 to 14.53 with Methocel K15 and 13.55 to 15.36 with Methocel K100. These results indicate good flow property of the granules.

Table 2: Physico-chemical characterization of floating tablets of losartan potassium.

Code	Thickness (mm)	Average Weight (mg)	Hardness (kg/cm²)	Friability (%)	Drug Content (mg/tablet)	Floating Lag time (s)	Total Floating Time (h)
F1	4.38±0.001	279±1.25	4.75±0.000	0.642 ±0.000	49.570±0.035	56.0±0.14	8.00±0.09
F2	4.40± 0.005	277±2.07	4.50±0.001	0.451±0.001	49.757±0.015	67.5±1.13	9.30±0.06
F3	4.39±0.008	279±1.18	5.25±0.002	0.672±0.001	49.991 ±0.025	42.5±1.06	7.30±0.08
F4	4.38±0.005	278±2.05	4.50±0.002	0.730±0.000	49.970±0.045	59.0±0.21	8.50±0.04
F5	4.40±0.003	277±1.32	4.75±0.001	0.582±0.000	49.247±0.045	89.6±0.32	11.50±0.07
F6	4.38±0.002	279±1.20	4.25±0.001	0.704±0.001	49.190±0.068	80.4±0.50	14.20±0.04
F7	4.40±0.001	278±3.07	5.25±0.002	0.455±0.000	49.835±0.045	52.8±0.15	10.50±0.02
F8	4.39±0.003	279±2.18	4.75±0.000	0.681±0.000	49.139±0.047	48.0±1.11	13.20±0.37

Physicochemical characterization of floating tablets of losartan potassium

The purpose of this study was to investigate the influence of sodium bicarbonate on the physico-chemical properties of sustained release floating tablets containing Methocel K15 or Methocel K100. The resulting formulations produced tablets with acceptable physical properties (Table 2). The thickness of floating losartan potassium tablets was ranged from 4.38 to 4.40 mm. The weight variation data of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value. All tablets prepared in this study meet the pharmacopeial requirements for weight variation tolerance; coefficient of variance was less than 1%. The hardness was found to be between 4.25 to 5.25 kg/cm² indicating satisfactory mechanical strength. Tablet friability was measured using friability testing equipment which evaluates tablet integrity during shipping and handling. The friability was below 1% which is an indication of good mechanical resistance of the tablets. Tablet friability results will show the integrity of the tablet to withstand mechanical stress during shipping and handling. Uniformity of tablet thickness and drug content ensures the individual dose consistency and reproducibility. The drug content varied between 98.63% to 99.82% in all tablet batches with low standard deviation indicating content uniformity of the prepared batches. Consistency in achieving tablet weight was indication of providing adequate dose to the patients.

***In vitro* buoyancy study**

Effervescent floating drug delivery was used to achieve *in vitro* buoyancy. Floating tablets prepared using polymers Methocel K15 and Methocel K100 exhibit sufficient swelling to provide *in vitro* buoyancy. Sodium bicarbonate and citric acid was added as a gas generating agent. Sodium bicarbonate induced CO_2 generation in the presence of dissolution medium (0.1N HCl). The gas generated is trapped and protected within the gel formed by hydration of polymer, thus decreasing the density of the tablet (Eyjolfsson *et al.,* 2000). The *in vitro* buoyancy of floating tablets was induced by sodium bicarbonate and citric acid without compromising the matrix integrity with the possible shortest bouncy lag time and buoyancy duration of up to 14h.

All the batches of tablets were found to exhibit short floating lag times due to presence of sodium bicarbonate and citric acid. Decrease in the sodium bicarbonate level increased the floating lag time and tablets were found to float for longer duration. The tablets with Methocel K100 were found to float for longer duration as compared with formulation containing Methocel K15. The tablets with high viscosity grade Methocel K100 floated for longer duration as compared with formulations containing low viscosity grade Methocel K15. As shown in the Table 3 that the formulations containing Methocel K15 shows total floating time from 7.30 h to 9.30 h while Methocel K100 showed 10.50 to 14.20 h. This indicates that the viscosity of the gel forming polymer Methocel influenced the *in vitro* buoyancy. Reduction in Methocel level in the formulations shortened the total floating time. With reference to buoyancy studies results it can be concluded that the batch containing Methocel K100 polymers showed satisfactory total floating time when compared to batches containing Methocel K15. In the present study, it was observed that the erosion rate of the matrices decreased with increase in polymer viscosity.

Table 3: Fit of various kinetics models for floating drug delivery systems of losartan potassium.

Code	Zero-order		First-order		Korsmeyer-Peppas	
	K (mg/h)	R^2	K (h^1)	R^2	n	R^2
F1	6.0278	0.9628	2.0024	0.9754	0.7930	0.9824
F2	4.8455	0.9896	2.0204	0.9681	0.7116	0.9958
F3	9.750	0.9702	1.9872	0.9584	0.7678	0.9982
F4	13.824	0.9562	1.9741	0.9397	0.7894	0.9794
F5	8.9429	0.9723	1.9968	0.9586	0.7985	0.9869
F6	10.824	0.9740	1.9994	0.9485	0.7892	0.9877
F7	12.879	0.9782	1.9791	0.9547	0.7343	0.9964
F8	12.571	0.9701	2.0014	0.9677	0.7507	0.9853

***In vitro* dissolution study**

The release of losartan potassium from floating tablets were determined by using six station dissolution test apparatus 2 (USP, 2004) in 0.1N hydrochloric acid. The dissolution data of all batches was fitted to zero-order, first-order, Korsemeyer-Peppas model to ascertain drug release mechanism.

Since the pH of the stomach is elevated under fed condition (~3.5), therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bi- carbonate more over citric acid has an establishing effect on losartan potassium formulation. The effect of two different grades of Methocel in the tablets with sodium bi- carbonate on the release profile was studied (Dave *et al.*, 2004).

In vitro dissolution studies of all the formulation of floating tablets of losartan potassium were carried out in 0.1N HCl. The study was performed and cumulative drug release was calculated at predetermined time intervals (Figure 1). A significantly higher rate and extent of drug release was observed from the batches based on Methocel K100 as compared with Methocel K15. Varying the amount of Methocel K100 affect the amount of drug release. Drug release from Methocel K 15 was lesser due to difference in molecular weight of the two varieties of Methocel. Methocel K 100, being of high molecular weight, forms gel of higher viscosity compared to Methocel K 15. However, due to higher molecular weight, the polymers chain are bulkier in Methocel K100 leading to less flexibility and hence more time is required for polymer solvent interaction and polymer chain relaxation. Consequently, the polymer chain unwinding is delayed in case of Methocel K100 compared to Methocel K15, thereby leading to reduced gelling rate for former, as a result of which the effective diffusion rate of the drug through the matrix containing higher percentage of Methocel K100 is more prone to higher drug release.

It is evident from the *in vitro* release data that increase in sodium bicarbonate concentration increased the release rate and also reduced the floating time, probably due to of excess carbon dioxide, disturbing the monolithic tablets.

It was observed that the release of losartan potassium from such formulations increased on decreasing the proportion of Methocel in the formulation. Comparing the two different grades of Methocel, it was found that Methocel K100 pro-

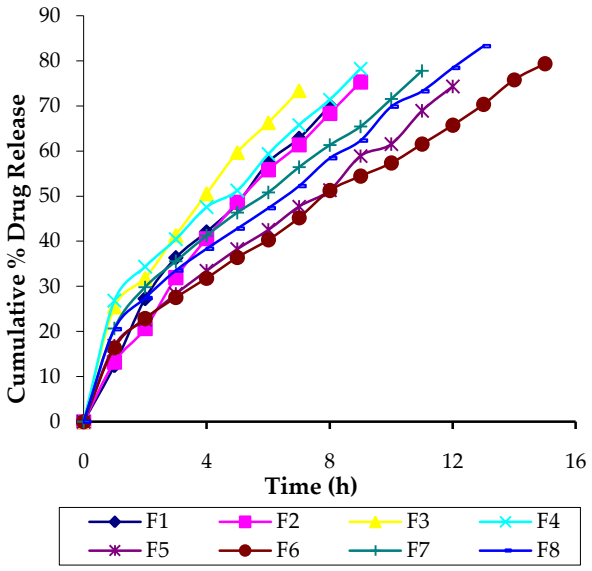

Figure 1: Comparison of drug release profiles of losartan potassium floating tablets prepared with polymers Methocel K15 and Methocel K100.

vided better release characteristics with total floating time of 14 h.

The coefficient of regression and release constant values for zero-order and first-order kinetics, Korsmeyer-Peppas equation were computed and are shown in Table 3. The 'n' value calculated from Korsmeyer-Peppas model were found to be between 0.7343 to 0.7678 indicating non-Fickian diffusion mechanism of drug release from floating tablets (Korsmeyer *et al.*, 1981). Varying the Methocel grade increased the *n* value that is indicative of the release mechanism from diffusion toward a relaxation and erosion controlled process. The presence of CO_2 bubbles produced after reaction of sodium bicarbonate with the acidic dissolution medium decreases the drug release rate. The matrix containing sodium bicarbonate indicates a little more contribution of relaxation and erosion to release mechanism.

Overall, the release mechanisms from these polymers can be explained as a result of rapid hydration of the polymers on the surface of the tablets, which results in a gel or a highly viscous solution surrounding the matrix that restrict water penetration in to the center. The net result is a reduction of the rate of drug release as a function of time. From this study, it can be concluded that the drug release predominantly follows non-Fickian diffusion. The dissolution data reveal sustained release of losartan potassium from the prepared floating tablets.

Stability study

Floating tablets of formulation F6 were subjected to stability study at 40°C/75%RH. The results do not show any significant change ($p > 0.05$) in physical appearance, hardness, friability, content uniformity, buoyancy and dissolution behaviour of floating tablets in comparison with initial values. No visible changes in the appearance of the tablets were observed at the end of the storage period and there was no change in the drug content. For buoyancy testing, the stored tablets floated on the surface of media (0.1N HCl) for 14 hours. The losartan potassium release rate from the floating tablets showed no significant change during storage. Thus, it was found that the floating tablets of losartan potassium prepared with sodium bicarbonate and Methocel polymer were stable under these storage conditions for at least 6 months.

CONCLUSION

Gastrofloating tablets of losartan potassium were prepared by direct compression method. The tablets were prepared with acceptable hardness, consistent weight uniformity and low tablet friability. Tablets containing Methocel K100 showed satisfactory buoyancy charcteristics and longer floatation time. *In vitro* release data were fitted to various kinetic models and drug release predominantly follows non-Fickian diffusion. The reduction in drug release rate as polymer content or viscosity increased may be attributed to stronger gel formation. Overall, this study concludes that viscosity is a major factor affecting the drug release and floating properties of FDDS.

REFERENCES

Agyilirah, G.A., Green, M., Ducret, R. (1991). Evaluation of the gastric retention properties of a cross linked polymer coated tablets. Int. J. Pharm., Volume 75, Pages 241-247. [DOI]

Ali, A., Arora, S., Ahuja, A., Babbar, A.K., Sharma, R.K., Khar, R.K. (2007). Formulation and development of floating capsules of celecoxib: in vitro and in vivo evaluation. AAPS PharmSciTech., Volume 8, Issue 4, Pages E1-E7. [DOI]

Arora, S., Ali, A., Ahuja, A., Khar, R.K., Baboota, S. (2005). Floating drug delivery systems: a review. AAPS PharmSciTech., Volume 5, Issue 6, Pages E372-E390. [DOI]

Arza, K.A., Gonugunta, S.C., Veerareddy, R.P. (2009). Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin hydrochloride tablets. AAPS PharmSciTech., Volume 10, Issue 1, Pages 220-226. [DOI]

Banker, G.S., Anderson, N.R. (1987). The Theory and Practice of Industrial Pharmacy. (3rd ed., pp. 297-299). Bombay: Varghese Publishing House. [DOI]

Bardonnet, P.L., Faivre, V., Pugh, W.J., Piffaretti, J.C., Falson, F. (2006). Gastroretentive dosage forms: overview and special case of Helicobacter pylori. J. Controlled Release, Volume 111, Issue 1, Pages 1-18. [DOI]

Bechgaard, H., Ladefoged, K. (1978). Distribution of pellets in gastrointestinal tract. The influence on transit exerted by the density or diameter of pellets. J. Pharm. Pharmacol., Volume 30, Pages 690-692. [DOI]

Chandel, A., Chauhan K., Parashar B., Kumar H., Arora S. (2012). Floating drug delivery systems: A better approach, International Current Pharmaceutical Journal, Volume 1, Issue 5, Pages 110-118. [DOI]

Dave, Brijesh S., Amin, Avani F., Patel, Madhabhai M. (2004). Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. AAPS PharmSciTech., Volume 5, Issue 2, Pages 1-6. [DOI]

Davis, S.S., Stockwell, A.F., Taylor, M.J. (1986). The effect of density on the gasric emptying of single and multiple unit dosage forms. Pharm. Res., Volume 3, Pages 208-213.

Deshpande, A.A., Rhodes, C.T., Shah, N.H., Malick, A.W. (1996). Controlled release drug delivery systems for prolonged gastric residence: An overview. Drug Dev. Ind. Pharm., Volume 22, Issue 6, Pages 531- 539. [DOI]

Deshpande, A.A., Shah, N.H., Rhodes, C.T., Malick, W. (1997). Development of a novel controlled release system for gastric retention. Pharm. Res., Volume 14, Pages 815-819. [DOI]

Eyjolfsson, R. (2000). Ranitidine HCl: tablet film coating acidity and discoloration. Drug Dev. Ind. Pharm., Volume 26, Pages 693-694. [DOI]

Fix, J.A., Cargill, R., Engle, K. (1993). Controlled gastric emptying, III: GRT of a non disintegrating geometric shape in human volunteers. Pharm. Res., Volume 10, Pages 1087-1089.

Goldsmith, J.A., Randall, N., Ross, S.D. (1978). On methods of expressing dissolution rate data. J. Pharm. Pharmacol., Volume 30, Pages 347-349. [DOI]

Gro, R. Ning, Heun, G. (1984). Oral dosage forms with controlled gastrointestinal transit. Drug Dev. Ind. Pharm., Volume 10, Pages 527- 539.

Indian Pharmacopoeia. (1996). Government of India, Ministry of Health and Family Welfare (pp. 734-736). Ghaziabad: The Indian Pharmacopoeia Commission.

Jaimini, M., Rana, A.C., Tanwar, Y.S. (2007). Formulation and evaluation of famotidine floating tablets. Curr. Drug Delivery, Volume 4, Issue 1, Pages 51-55. [DOI]

Kedzierewicz, F., Thouvenot, P., Lemut, J., Etinine, A., Hoffonan, M., Maincence P. (1999). Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. J. Controlled Release. Volume 58, Pages 195-205. [DOI]

Korsmeyer, R.W., Peppas, N.A. (1981). Effect of the morphology of hydrophilic polymeric matrices on the diffusion and release of water soluble drugs. J. Membr. Sci., Volume 9, Pages 211-227. [DOI]

Lanerts, V.M., Gurny, R. (1990). Bioadhesive drug delivery systems (pp. 1-14). Boca Raton: CRC Press.

Mamajek, R.C., Moyer, E.S. (1980). Drug dispensing device and method. US Patent 4207890.

Moes, A.J. (1993).Gastroretentive dosage forms. Crit. Rev. Ther. Drug Carrier Syst., Volume 10, Issue 2, Pages 143-195.

Pablo, E., Alejandra, H., Leopoldo, V. (2008). Effect of sodium bicarbonate on the properties of metronidazole floating matrix tablets. Drug Dev. Ind. Pharm., Volume 34, Pages 171-180. [DOI] PMid:18302036

Ponchel, G., Irache, J.M. (1998). Specific and non specific bioadhesive particulate system for oral delivery to the G.I. tract. Adv. Drug Delivery Rev., Volume 34, Pages 191-219. [DOI]

Rednick, A.B., Tucker, S.J. (1970). Sustained release bolus for animal husbandry. US Patent 3507952.

Rosa, M., Zia, H., Rhodes, T. (1994). Dosing and testing in vitro of a bioadhesive and floating drug delivery system for oral application. Int. J. Pharm., Volume 105, Pages 65-70. [DOI]

Rouge, N., Buri, P., Doelkar, E. (1996). Drug absorption sites in the gastrointestinal tract and dosage for site specific delivery. Int. J. Pharm., Volume 136, Pages 117-139. [DOI]

Sinha, V.R., Agrawal, M.K., Kumria, R. (2005). Influence of formulation and excipient variables on the pellet properties prepared by extrusion spheronization. Curr. Drug Delivery, Volume 2, Issue 1, Pages 1-8. [DOI]

Umamaheshwari, R.B., Jain, S., Bhadra, D., Jain N.K. (2003). Floating microspheres bearing acetohyxamic acid for the treatment of Helicobacter pylori. J. Pharm. Pharmacol., Volume 55, Pages 607-613. [DOI] PMid:14738585

United States Pharmacopoeia (USP 27, NF 22). (2004), (pp. 1529). Rock Ville, MD: United States Pharmacopoeial Convention Inc.

Urguhart, J., Theeuwes, F. (1994). Drug delivery system comprising a reservoir containing a plurality of tiny pills. US Patent 4434153.