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Formulation and *In Vitro* Evaluation of Floating Tablets of Losartan Potassium

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Abstract

Drugs that have narrow absorption window in the gastrointestinal tract (GIT) will have poor absorption. For these drugs, gastroretentive drug delivery systems offer the advantage in prolonging the gastric emptying time. Losartan potassium is prescribed to treat hypertension. Intragastric buoyant sustained-release tablets were prepared in this investigation by wet granulation method using hydrophilic polymer (Methocel), effervescent substance (sodium bicarbonate, citric acid) and drug (losartan potassium). Floating tablets of losartan potassium were evaluated for physico-chemical characteristics, floating lag time, total duration of floating and *in vitro* drug release. The addition of gel forming polymer Methocel K15, Methocel K100 with gas generating agent sodium bicarbonate was essential to achieve *in vitro* buoyancy. Stable and persistent buoyancy was achieved by trapping the gas in the gel formed by the hydration of high-viscosity Methocel. The drug release mechanism from floating tablets was found to be non-Fickian (i.e. anomalous diffusion) according to Korsmeyer-Peppas equation. This study showed that there was potential for intragastric floating tablets to remain in the stomach for a longer period of time with sustained drug release.

Keyword: Gastroretentive drug delivery system, Floating tablets, Buoyancy, Losartan potassium.

INTRODUCTION

Oral sustained release dosage forms deliver the drug for longer period and help in producing the therapeutic effect for 24 h for those drugs which are having low plasma half life [1]. Drugs that have narrow absorption window in the gastro intestinal tract (GIT) will have poor absorption[2,3]. For these drugs, gastroretentive drug delivery systems (GRDDSs) have been developed. Oral sustained release dosage form with prolonged residence time in the stomach helps in absorption of the drugs which are less soluble or unstable in the alkaline pH and those which are absorbed from the upper gastrointestinal tract. Gastroretentive dosage systems (GRDDSs) help in maintenance of constant therapeutic levels for prolonged periods, increases therapeutic efficacy and thereby reduce the total dose of administration. Floating drug delivery system (FDDS) has less density (<1.004 g/cm^3) than gastric fluid, so they remain buoyant in gastric fluid and show sustained drug release [4].

It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastro re-tentive properties would enable an extended absorption phase of these drugs. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage forms for these drugs[5]. The need for gastroretentive dosage forms has led to extensive efforts in both academia and industry towards the development of such drug delivery systems[6]. These efforts resulted in gastroretentive (GR) dosage forms that were designed in large part based on the following approaches[7]: (a) low density form of the dosage forms that causes buoyancy above gastric fluid[8]; (b) high density dosage forms that is retained

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in the bottom of the stomach; (c) bioadhesion to stomach mucosa[9]; (d) slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients[10]; (e) expansion by swelling or unfolding to a large size which limits emptying of the dosage forms through the pyloric sphincter.

Sustained or controlled-release drug delivery systems can provide several advantages over conventional dosage forms including reduced frequency of administration, the strength of the required dose, and the number and/or severity of side effects, whilst increasing the drug effectiveness, improving patient compliance and providing a constant, prolonged, and uniform therapeutic effect[11]. Among the many approaches widely used for designing oral controlled release dosage forms, hydrophilic matrix tablets offer precise modulation of drug release as a result of hydration of the constituent polymer(s), flexibility to obtain desired drug release profiles, cost effectiveness and broad Food and Drug Administration (FDA) acceptability[12].

Losartan potassium, or 2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2-(1H-tetrazol-5-yl) biphenyl-4-yl) methyl] imidazole potassium is a potent, highly specific angiotensin II type 1 (AT1) receptor antagonist with anti-hypertensive activity. Losartan potassium is used in treatment of hypertension due to mainly blockade of AT_1 receptors. Losartan is used to treat high blood pressure and to help protect the kidneys from damage due to diabetes. It is also used to lower the risk of strokes in patients with high blood pressure and an enlarged heart. The main limitation of low therapeutic effectiveness is due to narrow therapeutic index, poor bioavailability (25-35%), and short biological half life (1.5-2h)[13, 14]. To increase therapeutic efficacy, reduce frequency of administration and for better patient compliance sustained release floating tablets of losartan potassium were prepared by using hydrophilic polymer hydroxyl propyl methyl cellulose (Methocel K15 and Methocel K100). Hence, FDDS of losartan potassium was developed in order to improve its oral bioavailability.

MATERIALS

Losartan potassium was provided as a gift sample 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 analytical grade.

METHODS

Preparation of Losartan Potassium Floating Tablets

Floating tablets of losartan potassium were prepared by wet granulation method. 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^{o}C for 2 hours until the LOD becomes less than 2%. The dried granules were sized by sieve no. 18 and mixed with magnesium stearate and talc. The blend thus obtained was compressed using a single station compression machine (Cadmach, Ahmedabad, India).

Flow Properties of Granules

Angle of repose (θ) was determined by using a funnel whose tip was fixed at a constant height (h) of 2.0 cm from the horizontal surface. The granules were passed separately through the funnel until the tip of the conical pile touches the tip of the funnel. The radius of the base of the conical pile is measured as r (cm). It was calculated with the formula:

$$\theta = \tan^{-1} (h/r)$$

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	100	120	100	120	-	-	-	-
Methocel K100	-	-	-	-	100	120	100	120
Sodium bicarbonate	50	50	60	60	50	50	60	60
Citric acid	15	15	15	15	15	15	15	15
PVP K30	50	50	50	50	50	50	50	50
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Lactose	35	15	25	05	35	15	25	05

The previously weighed granules were collected into a graduated measuring cylinder and the initial (or bulk) volume was noted. It was placed in the tapped density tester USP (Electrolab, Mumbai, India) and subjected to constant tapping at a rate of 100 drops/min. It was recorded as the final tapped volume. Carr's index and Hausner's ratio were calculated with the following formulae[16]:

$$\% \text{ Carrs index} = \frac{\text{Tapped density - Poured Density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Poured Density}}$$

Physico-chemical Characterization of Floating Tablets

The prepared floating tablets were evaluated for thickness using digital micrometer (cm), uniformity of weight using 20 tablets, hardness using tablet hardness tester (EH-01, Electrolab, Mumbai, India), friability using Roche type friabilator (Electrolab, Mumbai, India) and drug content by spectrophotometric method.

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100 ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45 μ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 254 nm using 0.1 N hydrochloric acid as blank.

In Vitro Buoyancy Study

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form constantly remain on surface of medium is called the total floating time (TFT). The tablets were placed in a beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time[17].

Dissolution Study

The release rate of losartan potassium from floating tablets was determined using

United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method; Veego Scientific, Mumbai, India). The dissolution test was performed using 900 ml of 0.1 N hydrochloric acid, at 37±0.5°C and 75 rpm. A sample (5ml) 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 hydrochloric acid. Absorbance of these solutions was measured at 254 nm using UV/Vis double-beam spectrophotometer (UV 1700, Shimadzu, Japan). Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Stability Study

To determine the stability study the floating tablets of losartan potassium were packed in glass bottle and stored at 40±2°C and 75%±5% RH for a period of six months as per the ICH guidelines. The tablets were withdrawn after a period of 0, 30 and 180 days and evaluated for hardness, friability, content uniformity, *in vitro* floating behaviour and dissolution study[18]. 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

Gastroretentive tablets of losartan potassium were developed to increase the gastric retention time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug up to 24 h. The floating tablets were made using gel-forming polymers, Methocel K15 and Methocel K100. They are known to be beneficial in improving the buoyancy characteristics and drug release characteristics. When a combination of gas entrapping as well as controlled-release system was there, the use of disintegrating agent was important which does not quickly break the matrix and allows slow disintegration of the swollen matrix. PVP K30 in an optimized concentration was employed for such unique disintegrating agent. The talc and magnesium stearate were employed for their glidant and lubricant property. The prepared floating tablets were evaluated for thickness, weight variation, hardness, friability, drug content, *in vitro* buoyancy studies and dissolution studies.

Flow Properties of Granules

The granules for the formulation of floating tablets were evaluated for angle of repose, Carr's index and Hausner's ratio. Angle of repose was in the range of 22.21º to 29.66º with granules containing Methocel K 15 and 22.63º to 29.88º with granules containing Methocel K 100, Hausner's ratio was found to be between 1.11 to 1.25 with granules of different formulations. Carr's index was in the range of 11.27 to 16.37 with granules containing Methocel K 15 and 11.70 to17.70 with granules containing Methocel K 100. These values indicate that the prepared granules exhibited good flow properties.

Physico-chemical Characterization of Floating Tablets

The floating losartan potassium tablets were off-white, smooth, and flat shaped in appearance. The results of physico-chemical characterizations are shown in Table 2. The thickness of floating tablets was in the range of 4.15 to 4.85 mm. The weight of the tablets for different formulations was found to be between 317 to 319 mg with low standard deviation values, indicating uniformity of weight. The hardness for different formulations was found to be between 4.25 to 5.35 kg/cm^2 indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug

content varied between 49.00 to 49.85 mg in different formulations with low coefficient of variation (C.V. < 1.0%), indicating content uniformity in the prepared batches.

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

Code	Thickness (mm)	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%) (mg/tablet)	Drug Content	Floating Lag time (s)	Total Floating Time (h)
F1	4.20±0.000	319±0.401	5.35±0.005	0.631±0.001	49.41±0.072	40.5±0.53	7.40±0.09
F2	4.45±0.003	318±0.870	4.50±0.002	0.450±0.001	49.00±0.058	55.7±0.19	8.30±0.41
F3	4.85±0.002	319±2.011	4.75±0.003	0.734±0.002	49.85±0.038	38.0±0.28	6.10±0.34
F4	4.15±0.001	318±0.705	5.25±0.002	0.630±0.001	49.24±0.062	48.0±0.40	7.20±0.20
F5	4.35±0.000	318±2.650	4.25±0.004	0.405±0.001	49.74±0.055	55.6±0.53	12.30±0.06
F6	4.80±0.002	319±2.301	4.50±0.006	0.652±0.002	49.24±0.075	66.5±0.19	14.05±0.08
F7	4.25±0.001	317±1.450	5.25±0.008	0.581±0.003	49.62±0.045	58.7±0.28	11.35±0.07
F8	4.30±0.001	319±1.400	4.50±0.003	0.479±0.000	49.52±0.060	70.3±0.37	10.40±0.35

Floating Behaviour of Losartan Potassium Floating Tablets

All the floating tablet formulations were prepared by effervescent approach. Sodium bicarbonate induced carbon dioxide generation. The *in vitro* buoyancy of floating tablets was induced by sodium bicarbonate and anhydrous citric acid in presence of dissolution medium (0.1 N hydrochloric acid) in optimized ratio without compromising the matrix integrity with the possible shortest bouncy lag time and buoyancy duration of up to 14 h. It was observed that the gas generated was trapped in the tablet and was protected within the gel formed by hydration of polymers, thus decreasing the density of the tablet below 1, and the tablet became buoyant. Methocel K100 or Methocel K15 in the formulations was used to obtain a stickier gel to prevent the air bubble from rupture. By using this type of HPMC, stable and persistent buoyancy was achieved. The tablet swelled radially and axially during *in vitro* buoyancy studies.

The floating tablets containing Methocel K15 exhibited buoyancy lag time of 38.0 to 55.7s and floated till 9 h, while the floating tablets containing Methocel K100 exhibited buoyancy lag time of 55.6 to 70.3 s and floated till 14 h. These results shows that the formulation containing higher amount of sodium bicarbonate has less floating lag time and less total buoyancy while the formulation contain higher percentage of polymer. Methocel K100 showed greater buoyancy as compared to Methocel K15. 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. Tablet hardness was also found to be a factor with regard to the buoyancy of the tablets.

Dissolution Study

In vitro dissolution studies of floating tablets of losartan potassium were carried out in 0.1 N HCl. The study was performed for 14 h, and cumulative drug release was calculated at hourly intervals. Hydrophillic matrices immersed in water swell and eventually dissolve. When they are placed in water swelling starts and the

tablet thickness increases. The polymer dissolves because of the chain disentanglement. As the polymers chain becomes more hydrated and the gel becomes more diluted, the disentanglement concentration may be reached and the polymer chain detach from a gellified matrix. Thus there is a sloe diminution of the matrix undergoes simultaneously swelling, dissolution, and diffusion in to the bulk medium, resulting in a reduction of strength and erosion of the matix. The addition of sodium bicarbonate generates an expansion of hydration volume of Methocel matrices, producing an important elongation. The addition of sodium bicarbonate reduces the matrix coherence, producing a strong axial elongation of HPMC matrices. An increase reduction of gel consistency can be expected after addition of increasing proportion of sodium bicarbonate; this reduction of gel consistency increases the matrix propensity for erosion. Moreover the produced gas bubbles are expected to contribute to the same effect as foreign matter in the matrix and because of their tendency to leave the matrix. Increasing proportion of sodium bicarbonate and with this an increasing evolution of carbon dioxide, generate an increasing expansion of the matrix. Citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate.

It was observed from the batches that the formulations containing Methocel K100 performed a significantly higher rate and extent of drug release as compared with Methocel K15. Drug release from Methocel K 15 was lesser due to difference in molecular weight of the two varities 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. These results are attributed to the intrinsic polymer properties, the barrier effect of CO_2 bubbles, and the matrix volume expansion produced after addition of sodium bicarbonate.

It was observed from the *in vitro* release data that as the proportion of Methocel in the formulation increased there was decrease in the drug release. Comparing the two different grades of Methocel, it was found that Methocel K100 provided better sustained release characteristics with total floating time of 14 h.

The drug release data obtained from *in vitro* dissolution studies were fitted to zero-order, first-order, and Korsmeyer-Peppas equations (Table 3). To confirm the exact mechanism of drug release, the data were fitted according to Korsmeyer–Peppas equation[19]:

$$\frac{Mt}{M\infty} = kt^n$$

Where $Mt/M\infty$ is fraction of drug released, k is kinetic constant, t is release time, and n is the diffusional exponent for drug release. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders, and discs regardless of the release mechanism. The value of "n" gives an indication of the release mechanism; when n=1, the release rate is independent of time (zero-order; case II transport), n=0.5 for Fickian diffusion, and when $0.5<n<1.0$, non-Fickian diffusion is implicated. Lastly, when $n>1.0$, super case II transport is apparent.

Table 3. Fit of various kinetics models for floating tablets of losartan potassium.

Code	Zero-order		First-order		Korsmeyer-Peppas	
	K_o (mg/h)	$R^2_1(h^1)$	K (mg/h)	$R^2_1(h^1)$	n (mg/h)	$R^2_1(h^1)$
F1	7.780	0.972	2.018	0.959	0.649	0.990
F2	4.856	0.952	2.053	0.920	0.749	0.989
F3	7.142	0.985	2.028	0.958	0.664	0.990
F4	8.858	0.963	2.038	0.953	0.609	0.997
F5	10.208	0.962	2.023	0.957	0.595	0.988
F6	13.686	0.966	2.013	0.949	0.517	0.983
F7	17.009	0.969	1.977	0.924	0.582	0.994
F8	14.486	0.971	1.993	0.943	0.592	0.996

From this study, it can be concluded that the drug release predominantly followed non-Fickian diffusion and it was controlled by both diffusion and erosion. The dissolution data reveal sustained release of losartan potassium from the prepared floating tablets.

Stability Study

The prepared floating tablets were subjected to stability study. The tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for a period of 6 months. 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. Thus, it was found that the floating tablets of losartan potassium tablets were stable under these storage conditions.

CONCLUSION

This study discusses the preparation and evaluation of gastroretentive tablets of losartan potassium. The effervescent based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel forming polymer Methocel and gas generating agent sodium bicarbonate was essential to achieve *in vitro* buoyancy. Stable and persistent buoyancy was achieved by trapping the gas in the gel formed by the hydration of high-viscosity Methocel. Tablets containing Methocel K100 showed satisfactory buoyancy characteristics and longer floatation time. The drug release from the tablets depends upon the nature of gel matrix. It was observed that polymer swelling play an important role in drug release from the floating tablets. Hence it can be concluded that the effervescent based floating drug delivery is a promising approach to achieve buoyancy.

REFERENCES

1. Arza AK, Gonugunta Rao CS, Veerareddy PR. Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin hydrochloride tablets. *AAPS Pharm Sci Tech* 2009; 10: 220-6.
2. Baumgartner S, Kristl J, Vrecer F, *et al*. Optimisation of floating matrix tablets and evaluation of their gastric residence time. *Int J Pharm* 2000; 195: 125-35.
3. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery *via* gastric retention. *J Control Rel* 2000; 63: 235-59.

4. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low-density foam powder: effects of formulation and processing parameters on drug release. *Eur J Pharm Sci* 2003; 181: 37- 45.
5. Hoffman A, Stepensky D. Pharmaco-dynamic aspects of modes of drug administration for optimization of drug therapy. *Crit Rev Ther Drug Carrier Syst* 1999; 16: 571- 639.
6. Deshpande A A, Rhodes CT, Shah NH, *et al*. Controlled-release drug delivery systems for prolonged gastric residence: an overview. *Drug Dev Ind Pharm* 1996; 22: 531-9.
7. Hwang SJ, Park H, Park K. Gastric retentive drug delivery systems. *Crit Rev Ther Drug Carrier Syst* 1998; 15: 243-84.
8. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery *via* gastric retention. *J Control Rel* 2000; 63: 235-59.
9. Moes A J. Gastroretentive dosage forms. *Crit Rev Ther Drug Carrier Syst* 1993; 10: 143-95.
10. Klausner EA, Lavy E, Friedman M, *et al*. Expandable gastroretentive dosage forms. *J Control Rel* 2003; 90: 143-62.
11. Zaghloul AA, Vaithiyalingam SR, Faltinek J, *et al*. Response surface methodology to obtain naproxen controlled release tablets from its microspheres with Eudragit L 100-55. *J Microencapsul* 2001; 18: 651-62.
12. Heng PW, Chan LW, Easterbrook MG. Investigation of the influence of mean HPMC particle size on the release of aspirin from swellable hydrophilic matrix tablets. *J Control Rel* 2001; 76: 39-49.
13. Rang HP, Dale MM, Ritter JK, *et al*. Rang and Dale Text book of pharmacology 5 ed. London: Churchill Livingstone, 2004: 385.
14. Tripathi KD. Essential of medical pharmacology, 6 ed. New Delhi: Jaypee Brothers Medical Publishers, 2010: 88-92.
15. Carstensen JT, Chan PC. Flow rates and repose angles of wet processed granulations. *J Pharm Sci* 1977; 66: 1235-8.
16. Wells J. Pharmaceutical preformulation: the physico-chemical properties of drug substances. In: Aulton ME (eds). The science of dosage form design, London: Churchill Livingstone, 2000: 133.
17. Tanwar YS, Rana AC, Jaimini M. Formulation and evaluation of famotidine floating tablets. *Curr Drug Deliv* 2006; 4: 51-5.
18. URL: www.ich.org (accessed Jan 2013).
19. Korsmeyer RW, Peppas NA. Effect of the morphology of hydrophilic polymeric matrices on the diffusion and release of water soluble drugs. *J Membr Sci* 1981; 9: 211-27.