International Journal of Pharmaceutical Development & Technology

e ISSN - 2248 - 910X

www.ijpdt.com

Print ISSN - 2248 - 9096

FORMULATION AND EVALUATION OF FLOATING MATRIX TABLETS OF RAMIPRIL USING PEANUT HUSK POWDER

Chandra Sekhara Rao G*, Ramadevi K, Soujanya V, Prasad Ch

Department of Pharmaceutical Technology, Yalamarty Pharmacy College, Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

Gastroretentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Floating drug delivery system is one of the several techniques currently used to formulate a successful gastroretentive drug delivery system. The aim of this study was to develop non effervescent floating matrix tablets of ramipril using peanut husk powder. Formulations were prepared by direct compression method and evaluated for buoyancy behavior, drug content, and *in vitro* drug release. Use of HPMC K100M in the formulations enhanced the floating duration and dimensional stability. The optimized formulation followed Higuchi kinetics. It can be concluded that peanut husk powder can be a promising low density material in the formulation of gastroretentive floating drug delivery systems in combination with synthetic polymer HPMC K100M.

Keywords: Floating drug delivery system, Non effervescent, Peanut husk powder, Ramipril.

INTRODUCTION

Gastroretentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drug [1-3]. Several techniques are currently used to formulate a successful gastroretentive drug delivery system such as floating drug delivery systems, bioadhesive systems, high density systems and magnetic systems. Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. While the system is floating on the gastric contents the drug is released slowly at a desired rate from the system. Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are: Effervescent System and Non-Effervescent System. Effervescent systems include use of gas generating agents, carbonates and other organic acid present in the formulation to produce carbon dioxide gas, thus reducing the density of system and making it float on the gastric fluid. The non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as chitosan and carbopol [4,5].

The aim of this study was to develop non effervescent floating matrix tablets of ramipril using natural peanut husk powder as a light weight floating materials. A wide variety of plants are being used for their medicinal value since a long time. In addition, plants can also be very good source of excipients for different formulation strategies. Adjuvants of natural sources are preferred over synthetic materials due to their nontoxicity, low cost, ease of availability and chemically inert. Peanuts [6] are widely used to produce cooking oil and routinely used as food material. Neither the nuts nor the husk showed any toxic effects.

Ramipril IP [7,8] was selected as the model drug for this study. It has been widely used for the treatment of hypertension and congestive heart failure. The biological half life of ramipril is 2-4 hr which requires a dose of 1.5 – 20 mg to be taken three times a day. The extent of absorption of ramipril is 50 – 60% mainly in the stomach but the absorption is reduced in presence of food. The above reasons make ramipril a suitable drug for sustained release floating matrix tablets.

MATERIALS AND METHODS

Ramipril IP was obtained as gift sample from Aurobindo Pharma Private Ltd., Hyderabad. Peanut husk

Corresponding Author :- **Dr. G. Chandra Sekhara Rao** Email:- gonuguntac@yahoo.co.in

powder was collected from seeds of Arachis hypogea in Srikakulam. Hydroxy Propyl Methyl Cellulose (HPMC) K100M and Micro Crystalline Cellulose (MCC) PH 102 were obtained as gift samples from Hetero Pharma Private Ltd. Lactose was purchased from Hetero Pharma Private Ltd. Magnesium stearate was purchased from Qualikems, New Delhi. Talc was purchased from Kemphasol, Bombay. All other chemicals were of analytical grade.

Preparation of Peanut husk powder

The seeds of peanuts were collected from the fields of Kinjangi village, Srikakulam district. These seeds were dried in an oven at 40^{O}C for three hours and the surface layer was removed from the seeds by crushing them with hands. The husk was milled into fine powder by using mixer grinder. The obtained Peanut Husk Powder (PHP) was passed through sieve no. 100 and the fine powder was stored in a dessicator for further use.

Preparation of Non effervescent floating matrix tablets

The powder mixture containing drug, HPMC, MCC, lactose, peanut husk powder, magnesium stearate and talc were passed through sieve no 40 and blended thoroughly in a mortar. Quantities of 250 mg of the mixture were weighed and compressed with 9 mm flat punches using a single punch tablet machine (Grover Manual). The different formulae were given in Table 1.

EVALUATION OF PEANUT HUSK POWDER

Infrared Spectra Analysis

Infrared spectra of ramipril, peanut husk powder, and physical mixture of ramipril and peanut husk powder were obtained on Fourier Transform Infrared spectrophotometer (Bruker FTIR Pus 6.5 version) using KBr dispersion method.

Scanning Electron Microscopy and X-ray Microanalysis

The particles of peanut husk powder were mounted on double side carbon tape and coated with a thin gold layer. The surface topography was analyzed with a scanning electron microscope (SEM JEON – JLN 660). The obtained images were also utilised for size analysis using the computer. The chemical composition was obtained by Energy Dispersive Spectroscopy (EDS) by obtaining an X-ray spectrum.

EVALUATION OF PRE-COMPRESSION POWDER BLEND

Bulk Density and Tapped Density

A suitable amount of powder from each formulation was poured into 20ml measuring cylinder and the initial volume (V_0) was measured. Then the measuring cylinder was set into Bulk Density Apparatus (ElectroLab). The density apparatus was set for 100 taps and after that the final volume (V_f) was measured and the operation was continued till two consecutive readings are same. Bulk density and tapped density were calculated using the formula [9].

Bulk Density (D_b) = Weight of the powder/ Initial volume (V_0)

Tapped Density (D_t) = Weight of the powder/ Final volume (V_f)

Compressibility Index and Hausner Ratio

The *Compressibility index* and *Hausner ratio* are the measures of the propensity of a powder to be compressed. The compressibility index [10] and Hausner ratio were calculated using measured values for bulk density (D_b) and tapped density (D_t) as follows:

Compressibility index (%) = $\frac{D_t - D_b}{D_b} \times 100$

Hausner ratio = $\frac{D_t}{D_b}$

Angle of repose

The flow characteristics were evaluated by determining angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. Angle of repose was calculated using the equation [11].

$$\tan\theta = h/r$$

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where h = height of pile

r = radius of the base of the pile

θ = angle of repose

Evaluation of Tablets

The prepared Ramipril floating tablets were evaluated for thickness, hardness, friability, uniformity of weight. The thickness of tablets was measured by vernier calipers. Hardness of tablets was tested using Monsanto hardness tester. Friability of tablets was determined by using Friability test apparatus. Uniformity of weight was determined by taking 20 tablets randomly from each batch. These tablets were individually weighed using an analytical balance (Shimadzu AY 220). The average weight and standard deviation were calculated and the results were reported.

Drug content

Weight of the powdered tablet material equivalent to 10 mg of ramipril was taken and transferred into 100 ml volumetric flask. Then 30 ml of 0.1N HCL was added slowly, mixed properly and the volume was made upto 100 ml with 0.1N HCL. The above solution was filtered and 10 ml of filtrate was taken into 100 ml volumetric flask and made upto final volume with 0.1N HCL and the drug content was estimated by measuring the absorbance at λ_{max} 209 nm using a spectrophotometer.

***In Vitro* Buoyancy Test**

The prepared tablets were subjected to *in vitro* buoyancy test by placing them in 250 ml beaker containing 200 ml of 0.1 N HCl (pH 1.2, temp. 37±0.5 ^{O}C). The time between introduction of the dosage form and its buoyancy in the medium and the floating durations of tablets was noted for the determination of lag time and total buoyancy time by visual observation. The Time taken for dosage form to emerge on surface of medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time the dosage form remained buoyant is called Total Floating Time (TFT)

Dissolution Protocol

In Vitro dissolution study was carried out using USP Type II dissolution apparatus (ElectroLab) using 500 ml of 0.1 N HCl (pH 1.2) for 12 hours. The temperature of the dissolution medium was kept at 37± 0.5^{O}C and the paddle was set at 50 rpm. 5 ml of sample solution was withdrawn at specified intervals of time. The absorbance of the withdrawn samples was measured at λ_{max} 209 nm using UV visible spectrophotometer. The concentration was determined from the standard curve of Ramipril prepared in 0.1N HCl (pH 1.2) at λ_{max} 209 nm.

Drug Release Kinetics

To analyze the drug release kinetics and mechanism, the data obtained were fitted into zero order, first order, Higuchi model and Korsmeyer's models [12,13]. The criteria for selecting the most appropriate model were selected on the basis of correlation coefficient values.

RESULTS

Table 1. Composition of Floating Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Ramipril	20	20	20	20	20	20	20	20
PHP	10	10	15	15	15	20	20	20
HPMC K100M	10 (4%)	20 (8%)	20 (8%)	25 (10%)	28(11.2%)	30 (12%)	30 (12%)	30 (12%)
MCC PH 102	200	80	80	80	80	80	40	-
Lactose	-	110	105	110	97	95	130	170
Talc	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5
Total	250	250	250	250	250	250	250	250

Table 2. Pre-compression Parameters of Tablets

Formulation	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner ratio
F1	37.89	0.89	0.92	9.63	1.25
F2	36.86	0.85	0.89	11.59	1.32
F3	37.82	0.76	0.78	10.52	1.49
F4	35.53	0.71	0.83	9.89	1.22
F5	34.82	0.80	0.85	11.53	1.29
F6	34.89	0.88	0.89	9.85	1.22
F7	37.58	0.85	0.89	11.32	1.49
F8	36.52	0.83	0.88	11.49	1.45

Table 3. Post-compression Parameters of Tablets

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	2.8±0.02	3.5±0.5	0.34	249.68±4.9	98.91±2.8
F2	2.8±0.02	3.5±0.5	0.38	242.42±2.5	98.46±3.2
F3	2.8±0.02	3.6±0.5	0.25	240.51±2.1	97.41±2.1
F4	2.8±0.02	3.8±0.5	0.28	243.69±5.0	97.97±2.6
F5	2.8±0.02	3.5±0.5	0.34	239.42±3.6	96.54±2.6
F6	2.8±0.02	3.8±0.5	0.39	240.36±2.9	96.33±2.5
F7	2.8±0.02	3.5±0.5	0.49	240.29±4.2	96.54±1.8
F8	2.8±0.02	2.8±0.5	0.41	248.58±4.9	98.77±2

●All readings are average ± SD

Table 4. Floating Properties of Formulations

Formulation	Floating lag time (seconds)	Total floating time (hours)
F1	110	3
F2	105	>12
F3	85	>12
F4	75	>12
F5	64	>12
F6	40	>12
F7	42	>12
F8	37	>12

Table 5. Cumulative Percentage Drug Released of F1 - F4

Time (hr)	F1	F2	F3	F4
1	78.52±0.28	22.24±0.14	25.12±0.31	20.25±0.23
2	92.35±0.14	29.32±0.11	35.14±0.17	31.52±0.18
3	100	32.12±0.30	44.21±0.19	43.85±0.54
4	100	37.63±0.1	52.31±0.14	47.82±0.20
5	100	42.10±0.28	59.48±0.25	51.75±0.27
6	100	48.45±0.15	62.10±0.41	58.92±0.12
7	100	51.43±0.25	69.75±0.13	63.68±0.23
8	100	56.55±0.31	74.96±0.27	69.25±0.14
9	100	65.29±0.27	79.21±0.17	72.39±0.16
10	100	72.35±0.12	82.12±0.22	75.29±0.18
11	100	85.69±0.29	89.17±0.13	78.93±0.14
12	100	90.25±0.17	96.29±0.36	80.29±0.25

●All readings are average ± SD

Table 6. Cumulative Percentage Drug Released of F6 - F8

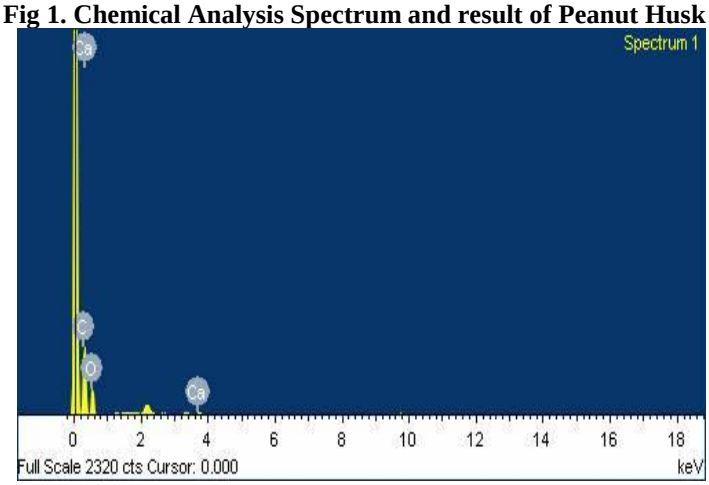
Time (hr)	F5	F6	F7	F8
1	19.25±0.28	18.69±0.22	18.59±0.25	19.55±0.11
2	23.27±0.27	29.23±0.76	22.53±0.15	22.29±0.38
3	28.52±0.24	32.51±0.25	25.54±0.23	29.53±0.12
4	32.39±0.25	38.26±0.14	29.62±0.24	34.64±0.39
5	39.60±0.19	40.75±0.18	33.32±0.21	38.52±0.50
6	45.79±0.26	44.29±0.19	39.62±0.22	42.63±0.29
7	49.25±0.29	48.28±0.42	45.29±0.27	45.85±0.11
8	52.53±0.16	50.26±0.25	49.60±0.35	48.59±0.12
9	59.65±0.23	52.94±0.37	52.15±0.18	52.65±0.29
10	68.23±0.18	58.81±0.11	56.42±0.14	55.38±0.16
11	71.26±0.29	62.52±0.22	61.28±0.22	58.68±0.18
12	75.29±0.13	68.63±0.19	64.29±0.15	63.19±0.22

●All reading are average ± SD

Table 7. Correlation coefficient values in the analysis of release data

Formulation	Zero order	First order	Higuchi model	Korsmeyer peppas model
F1	0.721	0.824	0.604	0.652
F2	0.492	0.889	0.934	0.938
F3	0.898	0.993	0.996	0.997
F4	0.830	0.854	0.995	0.989
F5	0.911	0.972	0.966	0.965
F6	0.877	0.967	0.989	0.986
F7	0.821	0.986	0.976	0.957
F8	0.812	0.983	0.995	0.983

Fig 1. Chemical Analysis Spectrum and result of Peanut Husk Powder



Element	Weight %	Atomic %	Compound %	Formula
C K	26.64	32.91	97.61	CO2
Ca K	1.71	0.63	2.39	CaO
O	71.65	66.46		
Totals	100.00			

Fig 2. Scanning Electron Microscopy image of Peanut Husk Powder

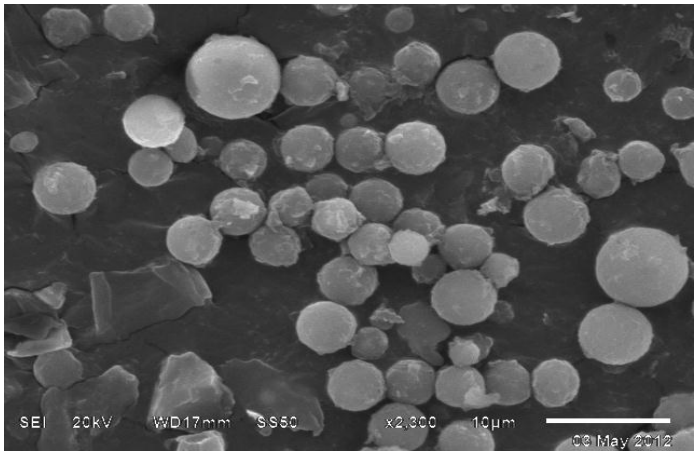


Fig 3. Size Analysis of Peanut Husk Powder

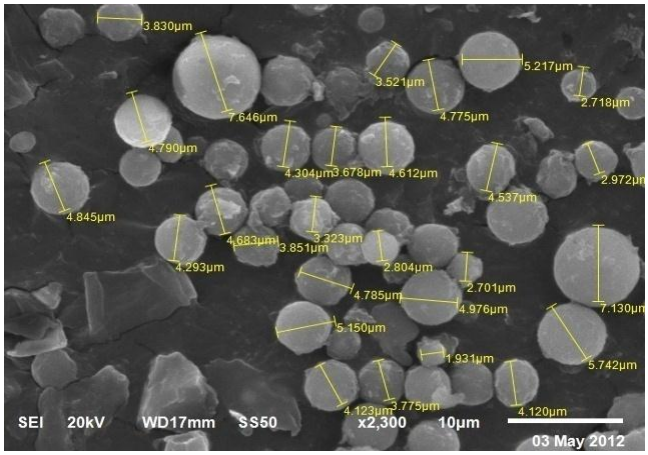


Fig 4. FTIR of Ramipril

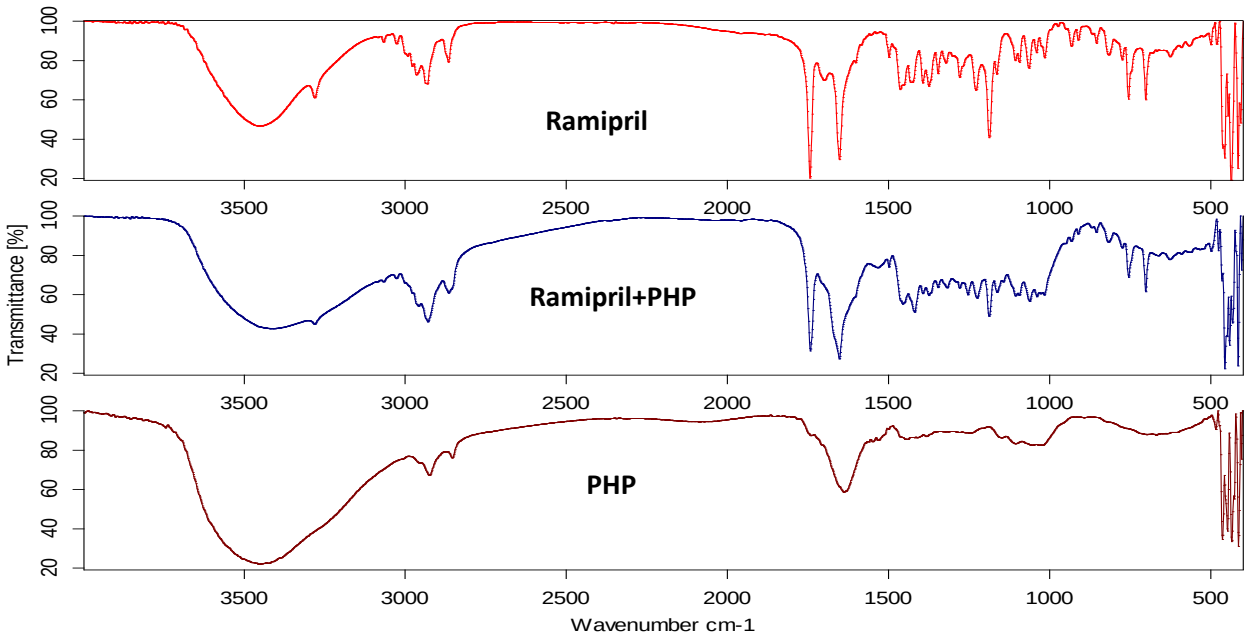


Fig 5. Plot of Cumulative % Drug Released Vs Time

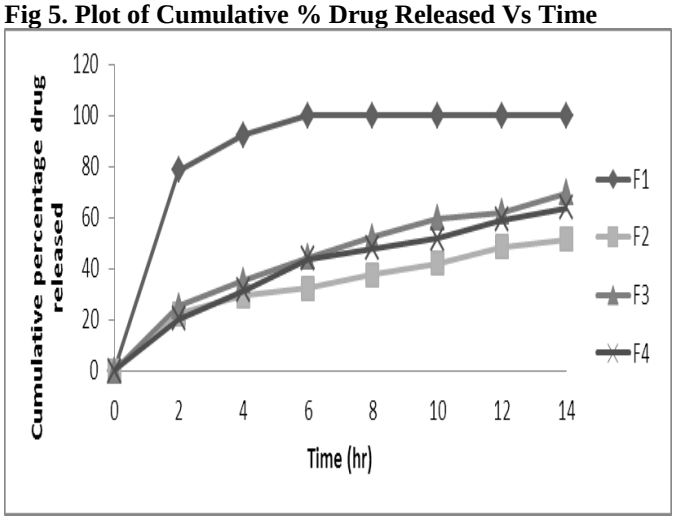
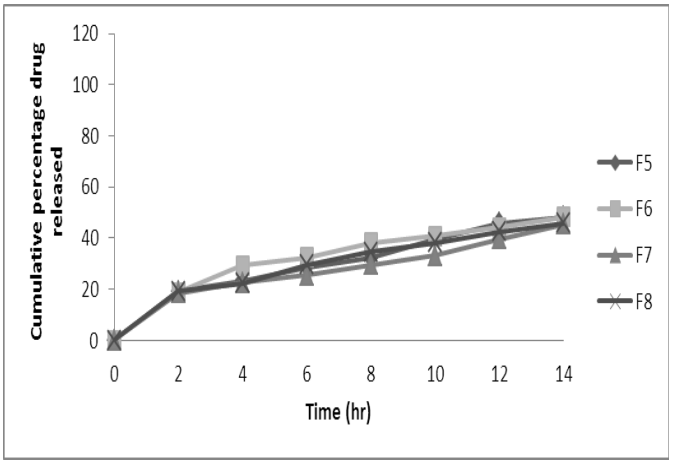


Fig 6. Plot of Cumulative % Drug Released Vs Time of F5 - F8



DISCUSSION

Peanut Husk Powder

A fine and characteristic flavoured powder with light brown colour was obtained after milling the husk of peanuts of the plant *Arachis hypogea*. The peanut husk powder is a light weight material with a bulk density of 0.54 g/ml as determined in our laboratory. The powder possesses fair flow property as it showed an angle of repose value of 34.88. The chemical analysis spectrum (Figure 1) shows the presence of calcium and oxygen elements which showed energy emissions in the K series only. It does not show the presence of any heavy elements, as emissions from L and M were absent which can catalyse some chemical interaction with drug material. The SEM photos (Figure 2) show the spherical structure of PHP particles. The absence of dark shades on these spherical structures also indicates the non interacting nature of the powder. From the size analysis (Figure 3), it was observed that the particles are present in the size range of 1.23-7.58µm. These characterization studies and other qualities of pure PHP indicates the potential of the powder that can be used as pharmaceutical excipient.

FTIR

The FTIR spectra were given in Figures 4. In the ramipril spectrum absorption peaks were observed at 3281.03 cm^{-1} due to –NH and –OH stretching of acid peaks, 3457 cm^{-1} and 2978-2864 cm^{-1} due to –CH aliphatic, 3000-3100 cm^{-1} due to aromatic –CH stretching and 1742.34 cm^{-1} due to –C=O group. The infrared absorption spectrum of peanut husk powder showed peaks at 3455 cm^{-1} due to -NH stretching and 1638.30 cm^{-1} due to-OH stretching. The infrared absorption spectrum of physical mixture of ramipril and peanut husk powder showed all the characteristic peaks of ramipril. This information indicates that there were no possible interactions between the drug and peanut husk powder.

Formulations

A total of eight formulations were designed and the tablets were prepared by direct compression method. The results of evaluation of powder blend were reported in Table no. 2. The Angle of repose values ranges from 34.82 to 37.89 which indicate passable flow property. The Compressibility index value ranges from 9.63 to 11.59 indicates good flow property. Hausner ratio values ranges from 1.25 to 1.75 which indicate fair to passable flow property.

The results of evaluation of tablets were reported in Table 3. The Drug content values ranges from 96.33±2.5 to 98.91±2.8. Hardness values ranges from 3.5±0.5 to 3.8±0.5 but hardness of F8 formulation was less i.e. 2.8±0.5. It might be due to more amount of PHP. Friability values ranges from 0.25 to 0.49. The % weight variation values were present in the range of 239.42±3.6 to 249.68±4.9.

Floating Behaviour

The results of i*n vitro* buoyancy study were reported in Table 4. Incorporation of the highly porous peanut husk powder in the matrix tablets provided densities (0.89 - 0.93 g/ml) that are lower than the density of the release medium (1 g/ml) [14]. From the initial trials, it was found that a minimum of 10% w/w PHP was required to achieve proper *in vitro* floating behaviour. As the proportion of PHP was increased from 10% to 20% the floating lag time was also decreased as shown in Table 4. Jeetendra [15] *et al* also reported similar results in the formulation of floating tablets employing light weight *Euryale ferox* seed powder. Although tablets of F1 floated within 110 sec, they lost the integrity and floating nature within 2 hrs. This might be due to low proportion of HPMC. In F3, F4 and F5 formulations, although the proportion of PHP was same, the floating lag time decreased respectively. It might be due to corresponding increase in the proportions of HPMC K100M which might form good swellable network for retaining the porous low density PHP powder. In formulations F6, F7 and

F8 the proportions of PHP and HPMC K100M were similar and the floating lag times were also found to be similar.

Dissolution Profiles

The effect of swellable retardant polymer HPMC K100M and diluents MCC PH102 and lactose on drug release were studied and the data was reported in Tables 5, 6 and Figures 5, 6. It was observed that as the proportion of HPMC K100M was increased from 4% to 12%, the drug release was decreased respectively. In case of F1, the total amount of drug was released within 3 hrs. It might be due to low proportion (4%) of the polymer and high proportion of the direct compression diluent MCC PH102. Hence in the next formulations, the proportion of HPMC K100M was increased (8%) and also the proportion of MCC PH102 was decreased and fixed at 32% that is 80 mg per tablet. The rest of the MCC was replaced by ordinary lactose. These modifications in the subsequent formulations were found to be satisfactory and achieved the sustained release rate of the drug. Percentage of the drug released over 12 hours time period was found to be 90% to 96%. Again as the proportion of the polymer HPMC K100M was increased to 10% in F4 lesser amount that is only 80% of the drug was released within 12 hrs. The subsequent formulations F5, F6, F7 and F8 also showed less amount of drug release that is 75%, 68%, 64% and 63% respectively within 12 hrs. The optimum concentration of HPMC K100M was found to be 8% in these formulations. HPMC K100M was the release retarding polymer and as its concentration was increased the release rate was decreased similar to the other reports [16.17]. In F8 formulation, MCC PH 102 was completely replaced by lactose and this modification did not show significant difference in dissolution profiles. However the hardness of F8 was found to be slightly less. As F3 formulation showed floating lag time of 85 seconds and 96% of drug release over 12 hours period, it was found to be the best formulation.

The drug release kinetics and mechanism were studied by fitting the data into various models. The R^2 values for each kinetic model i.e. zero order, first order and Higuchi and Korsmeyer peppas were shown in Table 7. The release kinetics of all the formulations followed first order kinetics except F1 and F4. Except F1 the drug release followed diffusion controlled mechanism as the R^2 values were close to one in Higuchi model. Based on the n value calculated by Korsemayer peppas model, the best formulations F3 (0.532) follows non fickian diffusion [18]. Among all the formulations the drug release in case of F1 is far deviating from the various kinetic models as seen from the R^2 values.

CONCLUSION

Peanut husk powder was found to be a promising low density material in the formulation of floating matrix tablets of Ramipril in combination with HPMC K100M. Use of HPMC K100M with peanut husk powder enhanced the floating duration and maintained the dimensional stability, which is an important requirement. The drug release was sustained properly up to 12 hrs. Based on this work it was found that non-effervescent type of floating drug delivery systems holds a lot of potential and comparable with effervescent systems. We can certainly explore this drug delivery with many other existing drugs. It is the responsibility of future scientists working in this area to effectively use the potential of this drug delivery system for the benefit of mankind.

ACKNOWLEDGEMENTS

The authors are grateful to Aurobindo Pharma Private Limited, Hyderabad, for providing gift sample of the drug. The authors are also grateful to the Chairman and the Principal of Yalamarty Pharmacy College for providing facilities to carry out the research work.

REFERENCES

1. Chien YW. Novel Drug Delivery Systems. Edn 2, Informa health care USA, New York, 2011, 164-69.
2. Robinson JR, Lee VHL. Controlled Drug Delivery. Edn 2, Informa health care USA, New York, 2011, 253-57.
3. Jain NK. Controlled and Novel Drug Delivery. Edn 1, CBS Publishers & Distributors, New Delhi, 2010, 5-7.
4. Klausner EA, Lavy E, Friedmon M, Hoffman A. Expandable gastroretentive dosage forms. *J Control Release*, 90, 2003, 143-62.
5. Brahma N. Singh, Kwon H. Kim. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J Control Release*, 63, 2000, 235-59.
6. Peanut. Available from: URL: http://en.wikipedia.org/wiki/Peanut
7. The Indian Pharmacopoeia. Vol. III, Controller of Publications, New Delhi, 2007, 1648-50.
8. Hardman JG, Limbird LE. Goodman and Gilman's The Pharmacological Basis of Therapeutics. Edn 10, Mc Graw-Hill Medical Publishing Division, 2001, 820-24.
9. Shah D, Shah Y, Rampradhan M. Development and evaluation of controlled release diltiazem microparticle using cross-linked poly (vinyl alcohol). *Drug Dev Ind Pharm*, 23(6), 1997, 567-74.
10. Aulton ME. Pharmaceutics the Design and Manufacture of Medicines. Edn 3, Elsevier Limited, 2007, 336-360.
11. Carter SJ. Cooper and Gunn's Tutorial Pharmacy. Edn 1, CBS Publishers and Distributors, New Delhi, 2005, 211-33.
12. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. *J Pharm Sci*, 52, 1963, 1145-49.

13. Korsmeyer RW, Gunny R, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. *Int J Pharmaceutics*, 15, 1983, 25-35.
14. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. *European Journal of Pharmaceutical Sciences*, 18, 2003, 37-45.
15. Jeetendra Singh N, Vandana J, Nikhil K. Development of non-effervescent floating matrix tablets based on *Euryale ferox* seeds. *Asian Journal of Pharmaceutics*, 2011, 93-9.
16. Radke RS, Deshmukh SB, Jagtap PS, et al. Design and evaluation of gastroretentive floating tablets of captopril. *IJPBS*, V1(2), 2010, 1-10.
17. Sameer S, Kalpana P, Pathak AK, Mishra A. Formualtion and evaluation of floating tablet of captopril. *International Journal of Pharm Tech Research*, 3(1), 2011, 333-41.
18. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics. Edn 2, Vallabh Prakashan, Delhi, 2009, 431-33.