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Formulation and Evaluation of Metoprolol Succinate Floating Tablets using Peanut Hust Powder as Natural Polymer

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Abstract : A sustained release system for Metoprolol succinate designed to increase its residence time in the stomach without contact with the tablets was achieved through the preparation of floating tablets by the direct compression method. In the present study attempt has been made to develop sustained released drug delivery system by formulating the floating tablets of Metoprolol Succinate using peanut husk powder as a natural polymer (cellulose 35.7%, hemicelluloses 18.7%, lignin 30.2%) which is biodegradable, biocompatible, nontoxic, economically cheap cost, devoid of adverse and side effects and easily availability. Metoprolol succinate [MS] ((+)-1-(isopropyl amino)-3-[p-(2-methoxyethyl)]-2-propanol succinate) is a β1- selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. Hence the drug has relatively short half-life about 4-6hrs, in the normal course of therapy multiple administration is required every 4-6hrs. The 9 batches of floating tablets (MF1 to MF9) were formulated by direct compression method using different ratio of polymers like peanut husk power, HPMC and carbopol. The formulated tablets were evaluated by means of different parameters like shape and density of tablet, hardness, friability, weight variation, drug content uniformity, *Invitro* buoyancy, swelling Index, *Invitro* dissolution studies. The formulation MF6 has better sustained release when compared other formulations, it release the drug of about 31.32% at the 1sthr and almost 60% release at the end of 8hrs, hence we conclude that the combination of peanut husk powder, HPMC and carbopol shows better Gastric retention time which sustains the release of the dosage form.
Keywords : Metoprolol Succinate, Floating tablets, Peanut Husk Powder, Natural Polymer.

Introduction:

Metoprolol succinate is a beta selected adrenoceptor blocking agent, for oral administration in the treatment of hypertension, angina pectoris and heart failure. It has a half-life of 3 to 7 hours. When dose is missing it may causes nocturnal attack, so attention was made to develop the extended release tablets of metoprolol succinate by utilizing hydroxyl propyl methyl cellulose K100M, Carbopol and Peanut Husk Powder.

To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of Metaprolol is desirable. The drug is freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. The most commonly used method of modulating the drug release is to include it in a matrix system [1].

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The purpose of controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible. In other words, they are able to exert a control on the drug release rate and duration. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery system because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance [1]. T

he need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. Prolonging the gastric residence of a dosage form may be of therapeutic value. Amongst the methods available to achieve this, floating dosage forms show considerable promise [2]. The basic idea behind the development of such a system is to maintain a constant level of drug in the blood plasma in spite of the fact that the drug does not undergo disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood [2].

Several approaches are used for the formulation of gastroretentive systems such as mucoadhesion, flotation, sedimentation, expansion and modified shape systems. Both single-unit systems (tablets or capsules) and multiple unit systems (Multiparticulates systems) have been reported in the literature. Among these, FDDS offer the most effective and rational protection against early and random gastric emptying compared to the other methods proposed for prolonging the gastric residence time (GRT) of solid dosage forms.

Extended-release dosage forms with prolonged residence time in the stomach are also highly desirable for drugs that are locally active in the stomach and those are unstable in the intestinal or colonic environment or which have low solubility at higher pH values. FDDS has a lower density than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [2].

Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. Effervescent floating dosage forms prepared with the help of swellable polymers such as methylcellulose and various effervescent compounds such as sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms [2].

The objective of present work was to develop gastro retentive formulation using peanut husk powder as a natural polymer which releases drug in the stomach and upper gastrointestinal (GI) tract, and form an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract [2].

Materials and Methods:

Metoprolol succinate, HPMC K100 M, Carbopol, Sodium Carbonate, Magnesium stearate and talcwere obtained from Madras Pharmaceuticals, Chennai. All reagents and solvents used were of analytical grade satisfying pharmacopeial standards

Preparation of gastro retentive floating tablets

Floating tablets contains were prepared by direct compression technique using variable concentrations of HPMC-K100 M, Peanut Husk Powder, Carbopol, Sodium Carbonate and talc with sodium bicarbonate. Different tablets formulations were prepared by direct compression technique. All the powders were passed through 100 mesh sieve. Required quantity of drug, and low-density polymer were mixed thoroughly. Talc and magnesium stearate were finally added as glident and lubricant respectively. The blend was directly compressed (9mm diameter punches) using tablet compression machine. Each tablet contained 100mg of Metoprolol succinate and other pharmaceutical ingredients as listed in table no 1 in each section.

Table no 1:- Composition of Each tablet

Ingredients	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
Metoprolol Succinate	100	100	100	100	100	100	100	100	100
Peanut Husk powder	35	35	-	35	60	60	155	-	-
HPMC E50	120	-	120	60	60	35	-	155	-
Carbopol	-	120	35	60	35	60	-	-	155
Sodium bicarbonate	25	25	25	25	25	25	25	25	25
Magnesium Stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10

Evaluation of tablets

Compatibility studies:

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used.

Pre Compression Parameters

Angle of repose, bulk density, tapped density, Carr's(compressibility) index and hausner's ratio are determined to find out the flow property of granules during formulation.

A)Angle of repose:

In order to determine the flow property, the Angle of repose was determined. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane.

$\Theta = \tan^{-1} (h/r)$
Where,
h = height
r = radius
Θ = angle of repose

Procedure:

- An accurately weighed sample was taken.
- A funnel was fixed in the stand in such a way that the tip of the funnel was at the height of 6 cm from the surface.
- The sample was passed through the funnel slowly to form a heap.
- The height and the circumference of the powder heap formed were measured.
- The radius was measured and the angle of repose was determined using the above formula. This was repeated five times for a sample.

B) Compressibility index (Carr's indices):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material.

$$C_I = 100 \frac{(V_O - V_f)}{V}$$

C) Determination of bulk density and tapped density:

A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

The bulk density, and tapped density were calculated using the following formulas

Bulk density = W / V_O
Tapped density = W / V_f
Where,
W = weight of the powder
V_O = initial volume
V_f = final volume

D) Hausner's ratio: Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post Compression Parameters

Thickness

The thickness of the tablets was determined by using vernier calipers. Five tablets were used, and average values were calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a Sartorius electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Friability Test

The friability of tablets were determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by –

$\%F = 100 (1-W_0/W)$

% Friability of tablets less than 1% are considered acceptable. ⇨

Drug Content:

Chromatographic conditions:

Column	:	250 mm x 4.6 mm, 5µ
Detector	:	222 nm
Flow	:	1.2 ml/minute
Injection volume	:	20 µl
Temperature	:	Ambient

Diluent:. Mix Acetonitrile: Phosphate buffer (0.05M phosphate buffer of pH 3.0) in the ratio of 350:650

Mobile phase: Filtered and degassed mixture of Acetonitrile: Phosphate buffer (0.05M phosphate buffer of pH 3.0) in the ratio of 350:650

Standard preparation: Weighed accurately about 0.100g of Metoprolol Succinate working standard into a 100ml volumetric flask, added 70ml of diluent, shaked and sonicated to dissolve the content, made up the volume with diluent. Pipetted out 5ml of resulting solution to 100ml volumetric flask made up with diluent.Filtered through 0.45 micron membrane filter.Collected the filtrate after discarding the few ml of the filtrate.

Assay preparation: Weighed 20 tablets, triturate to a fine powder. Weighed accurately about 0.300g powdered tablets (equivalent to 0.100g of Metoprolol Succinate) in to a 100ml volumetric flask. Added 70ml of diluent sonicated for 30minutes, and made up the volume with diluent, pipetted out 5ml of filtrate to 100ml with diluent. Filtered the solution through 0.45micron membrane filter.Collected the filtrate after discarding the first few ml of the filtrate.

Procedure: Separately injected equal volumes (about 20 µl) of the standard preparation and the assay preparation into the chromatograph, recorded the chromatograms, and measured the responses for the Metoprolol Succinate peak.

In Vitro dissolution studies

The release rate of valsartan from floating tablets was determined using *The United States Pharmacopoeia* (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 75 rpm A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 8 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 222 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

In vitro buoyancy studies

The in vitro buoyancy was determined by floating lag time method described by Dave B.S.The tablets were placed in 250 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Results and Discussion:

Compatability Studies:

In the present study, it has been observed that there is no chemical interaction between Metoprolol Succinate and the polymers used.

Table No 2 :- Precompressional Evaluation of Metoprolol Succinate Powder Blend

S.No	Formulation	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's ratio
1	MF1	24°65'±0.24	0.312±0.36	0.415±0.28	19.23±0.18	1.21±0.42
2	MF2	23°67'±0.21	0.314±0.35	0.416±0.29	18.25±0.19	1.19±0.45
3	MF3	26°58'±0.25	0.316±0.37	0.419±0.30	19.27±0.21	1.20±0.47
4	MF4	25°74'±0.24	0.318±0.34	0.413±0.27	17.21±0.23	1.23±0.41
5	MF5	27°55'±0.26	0.317±0.40	0.420±0.25	20.28±0.15	1.21±0.43
6	MF6	23°49'±0.28	0.320±0.36	0.423±0.28	19.30±0.17	1.18±0.45
7	MF7	28°62'±0.30	0.324±0.41	0.417±0.31	18.31±0.19	1.19±0.42
8	MF8	23°57'±0.29	0.319±0.38	0.415±0.26	17.29±0.20	1.21±0.45
9	MF9	24°69'±0.27	0.315±0.36	0.418±0.27	18.26±0.18	1.20±0.41

Table No 3 :-Post Compressional Evaluation of Metoprolol Succinate floating tablets

S.No	Formulations	Thickness (mm)	Diameter (Cm)	Hardness (Kg/cm^2)	Friability (%)	Weight (mg)	Drug Content (%)
1	MF1	4.030±0.15	13.58±0.43	2.6±0.44	0.3±0.59	300.98±0.23	99.43±0.24
2	MF2	4.032±0.34	13.54±0.37	3.2±0.26	0.4±0.36	300.21±0.41	99.24±0.34
3	MF3	4.025±0.37	13.50±0.11	3.2±0.34	0.4±0.41	301.25±0.13	100.04±0.44
4	MF4	4.032±0.28	13.58±0.64	2.8±0.49	0.3±0.74	300.88±0.42	98.32±0.26
5	MF5	4.034±0.96	13.60±0.37	3.0±0.33	0.5±0.11	300.79±0.55	100.02±0.25
6	MF6	4.030±0.73	13.54±0.25	3.0±0.24	0.3±0.24	300.22±0.97	100.29±0.37
7	MF7	4.025±0.37	13.50±0.19	3.8±0.77	0.2±0.36	301.09±0.28	99.86±0.19
8	MF8	4.027±0.16	13.52±0.73	3.4±0.29	0.4±0.47	300.69±0.63	98.94±0.34
9	MF9	4.032±0.55	13.58±0.37	3.6±0.551	0.3±0.67	300.58±0.57	99.72±0.55

Hardness test:-

The measured hardness of tablets of each batch ranged between 2.6 to 3.8kg/cm^2 (Table 3).This ensures good handling characteristics of all batches.

Friability Test:-

The values of friability test were tabulated in Table 3.The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Weight Variation Test:-

The percentage weight variations for all formulations were tabulated in Table no 3. All the formulated (MF1 to MF9) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Drug Content Uniformity:-

The percentage of drug content for MF1 to MF9 was found to be between 98.94% and 100.29% of Metoprolol succinate, it complies with official specifications. The results were shown in Table 3.

In vitro Buoyancy Study:-

On immersion in 0.1N HCl solution pH (1.2) at 37^0C, the tablets floated, and remained buoyant without disintegration. Table 7.8 shows the results of Buoyancy study shows Buoyancy character of prepared tablet.

From the results it can be concluded that the batch containing only HPMC polymer showed good Buoyancy lag time (BLT) and Total floating time (TFT). Formulation containing showed good BLT of 45 sec, while the formulation containing peanut powder, drumstick powder (alone) did not float more than 1.5 hrs. This may be due to the nature of polymer and gas generating agent, which were kept constant in the present study. But the different combination of different natural and synthetic polymers gives the greater floating time more than 24 hrs also. The gas generated cannot be entrapped inside the gelatinous layer, and it escapes leading to variation in BLT and TFT.

Table No4 :-Buouancy studies of Metoprolol Succinate Floating tablets

S.No	Formulations	Floating Lag time	Floating time
1	MF1	3±0.21	13.50±0.34
2	MF2	8±0.32	12.00±0.16
3	MF3	5±0.44	19.00±0.44
4	MF4	4±0.25	14.00±0.35
5	MF5	16±0.36	13.00±0.47

6	MF6	12±0.74	13.50±0.38
7	MF7	14±0.58	15.00±0.55
8	MF8	9±0.59	14.00±0.68
9	MF9	15±0.19	18.30±0.49

In-vitro Dissolution Study

All the Nine formulation of prepared floating tablets of Metoprolol succinate were subjected to invitro release studies these studies were carried out using dissolution apparatus, 0.1N HCL (PH 1.2)

The release data obtained for formulations MF1 to MF9 wereshows the plot of cumulative % drug released as a function of time for different formulations. The invitro release of all nine batches of floating tablets showed the release with an initial effect. In the first hour % drug released were 23.38, 21.18, 22.94, 36.18, 31.32, 26.91, 14.12, 27.35 and 18.97 For MF1, MF2, MF3, MF4, MF5, MF6, MF7, MF8 and MF9 respectively.

From the in-vitro dissolution data it was found that formulation MF1, MF2, MF3, MF4, MF5, MF6, MF7, MF8 and MF9 released more than 60% of drug before 8 hrs of the study indicating that the polymer amount is not sufficient to control the drug release. While MF2, MF3, MF6, MF7 and MF9 containing all polymers released more than 60% of drug within 8 hr. It concludes MF6 had better controlled release than the other formulation.

Table no 5 :-Standard calibration curve of Metoprolol succinate

Concentration(µg/ml)	**Absorbance**
0	0
1	0.0401
2	0.0852
3	0.1237
4	0.1621
5	0.1979
6	0.2361
7	0.2721
8	0.3223
9	0.3624
10	0.4081
Slope value(b) =	**0.0401**
R^2 Value =	**0.99945**

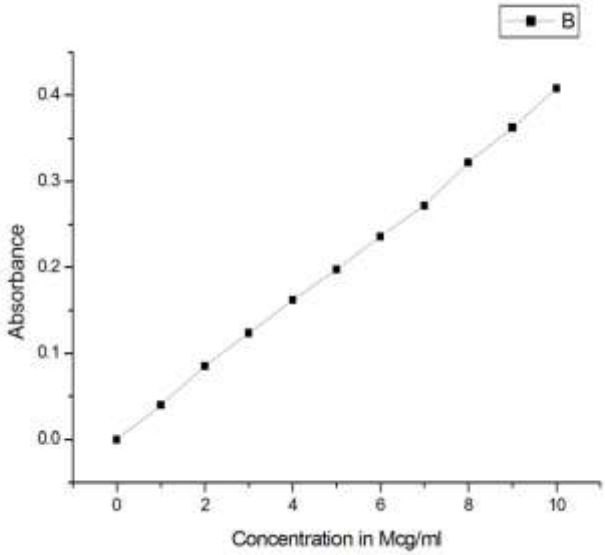

Figure no1:- Standard Calibration Curve of Metoprolol Succinate

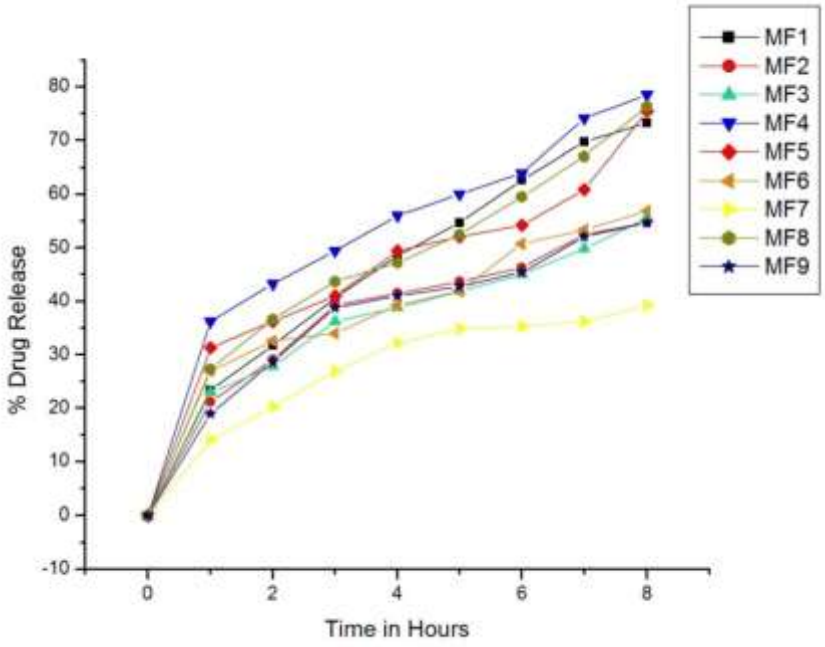

Figure No 2 :- Dissolution of Metoprolol Succinate floating tablets Batches MF1 to MF9

Conclusion:

It was concluded that the metoprolol succinate floating tablets can be formulated using Peanut Husk Powder with good release profile for a prolonged period of time up to 12 hours. It could decrease the frequency of dose administration, prevent nocturnal attack and improves patient compliance. Further in vivo studied are required to correlate in vitro release data.

Reference:

1. Gothi GD, Porish BN, Patel TD, Prajapati ST, Patel DM, Patel CN. Study of design and development of sustained release tablets of metoprolol succinate. Journal Global PharmaTechnol, 2(2), 2010, 69-74.

2. Rao BP, Kottan NA, Snehith VS, Ramesh C. Development of Gastro retentive drug delivery system of cephalexin by using factorial design. ARS Pharmaceutical, 50, 2009, 8-24.
3. Srivastava A.K, Wadhwa S, Ridhurkar D, Mishra, B., "Oral sustained delivery of atenolol from floating matrix tablets-formulation and in vitro evaluation", Drug Dev. Ind. Pharm., 2005, 31(4), 367-74.
4. Dave, B.S., Smin, A.F., Patel, M.M., "Gastroretentive drug delivery system of Ranitidine hydrochloride: Formulation and in vitro evaluation", AAPS Pharm. Sci. Tech., 2004, 5, e34.
5. Streubel, A., Siepmann, J., Bodmeier, R., "Floating matrix tablets based on low density foam powder: effect of formulation and processing parameters on drug release", Eur. J. Pharm. Sci., 2003, 18(1), 37-45.
6. Li, S., Lin, S., Daggy, B.P., Mirchandani, H.L., Chien, T.W., "Effect of formulation variables on the floating properties of gastric floating drug delivery system", Drug Dev. Ind. Pharm., 2002, 28, 783-793.
7. Wei, Z., Yu, Z, "Design and evaluation of a two-layer floating tablet for gastric retention using cisapride as a model drug", Drug Dev. Ind. Pharm., 2001, 27(5), 469-74.
8. Li, S., Lin, S., Chien, T.W., Daggy, B.P., Mirchandani, H.L., "Statistical optimization of gastric floating system for oral controlled delivery of calcium", AAPS Pharm. Sci. Tech., 2001, 2 (1), e1.
9. Nur, A.O., Zhang, J.S., "Captopril floating and/or bioadhesive tablets: design and release kinetics", Drug Dev. Ind. Pharm., 2000, 26, 965-969.
10. Baumgartner, S., Kristel, J., Vreer, F., Vodopivec, P., Zorko, B., "Optimization of floating matrix tablets and evaluation of their gastric residence time", Int. J. Pharm., 2000, 195(1-2), 125-135.
11. Ozdemir, N., Ordu, S., Ozkan, Y., "Studies of floating dosage forms of furosemide: in vitro and in vivo evaluation of bilayer tablet formulation", Drug Dev. Ind. Pharm. 2000, 26(8), 57-866.
12. Wu, W., Zhou, Q., Zhang, H.B., Ma, G.D., Fu, C.D., "Studies on Nimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric resident time", Yao. Xue. Xue. Bao., 1997, 32 (10), 786-790.
13. Kondivanitha, Mohanvarma, Alluriramesh, "Formulation and *in-vitro* evaluation of floating tablets of hydralazine hydrochloride", Int. J. Pharm., 2012, pp 51-58.
14. N arunkumar1, C Rani , "Formulation and *in vitro* evaluation of oral floating tablets of atorvastatin calcium", Int. J. Pharm., *2008, 492-495.*
15. C.P.Jain1 and P.S. Naruka ," Formulation and evaluation of fast dissolving tablets of valsartan", Int. J. Pharm., 2009., 219-226
16. L. P. Hingmire, D. M. Sakarkar "Formulation and evaluation of valsartan sr tablets using hydrophilic and hydrophobic polymer" , Int. J. Pharm 2013, 252-260.

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