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EFFECT OF EXCIPIENTS AND PROCESS VARIABLES OVER GASTRO RETENTIVE ANTIHYPERTENSIVE DOSAGE FORM

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ABSTRACT

The objective of this study was to formulate an oral floating tablet of Captopril using the hydrophilic polymer hydroxy propyl methyl cellulose (HPMC) and Carbopol 934P gas generating agent Calcium Carbonate and citric acid using direct compression method. The prepared tablets were evaluated in terms of their physical characteristics, in vitro release, buoyancy, buoyancy lag-time and swelling index. The results of all the pre and post compression tests of all formulations batches were found to be sympathetic. The in-vitro % drug release was found to be in range of 79.99 to 97.23 % at the end of 24 hrs. From the in-vitro dissolution study it was observed that tablet of batch F6 showed highest percentage cumulative drug release due to combination of HPMC K100M, HPMC K15M and carbopol selected as optimized batch. Optimized batch was further evaluated for the effect of dissolution apparatus USP type I and type II and hardness of tablet. The USP Type I apparatus suppresses the three dimensional drug releases from the matrix tablet. The tablet having higher hardness affects the floating lag time and also retards the drug release from the matrix.The n value obtained from the korsemeyer-peppas equation indicates tablet of batch F6 shows rather first order release mechanism.

Keywords: Floating Tablet, Hardness, HPMC, Carbopol 934P, Dissolution Apparatus.

INTRODUCTION

In the last three decades various attempts have been made to develop a novel and efficient gastro retentive dosage forms which can retain in the stomach for an extended period of time in a predetermined manner. This can be achieved by improving scientific and technological advancement to overcome physiological problems like pH of the stomach, motility and gastric emptying time by altering physiological and formulation variables. Many approaches are utilized in the development of gastric retention drug delivery systems viz., floating systems, swelling, expanding, high density, super porous hydro gels, bioadhesive, modified shape systems, ion exchange resin and by the simultaneous administration of pharmacological agents that delay gastric emptying. By utilizing one of these techniques it is possible to deliver drugs that have narrow absorption window [1,2].

From the formulation and technological point of view, the floating drug delivery system (FDDS) is considerably easy and logical approach in the development of GRDF. Floating drug delivery system float on the gastric fluid only when it has density less than that of gastric fluids, i.e. <1g/cm^3. Usually, floating formulations are prepared from hydrophilic matrices that either have a density lower than one or their density drops below one after immersion in the gastric fluids owing to swelling. More sophisticated devices are developed later and involved the use of various film coating techniques, incorporation of a floating chamber that is filled with harmless gas, or a liquid that gasifies at body temperature. These systems are often called hydro-dynamically balanced system (HBS) as they can maintain low density and keep floating even after hydrating. This system provides several advantages as prolonged gastric retention of drugs, improves bioavailability, reduces drug wastage and improves solubility for drugs that are less soluble in alkaline pH environment and provides local drug delivery

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to the stomach and proximal small intestine [3, 4].

The objective of present study was to develop Gastro retentive formulation, which releases drug in the stomach and upper part of gastrointestinal tract (GIT) and form an enhanced opportunity of absorption in the stomach and upper GIT rather than the lower portion of GIT. Captopril is soluble in acidic environment of the stomach. In the intestine, where neutral to slightly alkaline pH condition prevail; captopril is unstable, which adversely affect the absorption in the lower section of the intestine [5]. Captopril shows maximum oxidative stability at pH below 4.0. There is a need for system that resides in the stomach over a relatively long period of time and releases the active compound there in sustained manner [6]. This necessitated the design and development of sustained release Gastro retentive drug delivery system for Captopril using suitable polymers.

MATERIALS AND METHODS

Materials

Captopril was obtained as kind gift sample by Micro Laboratories, Bangalore, India. HPMC-K15M, HPMC-K100M and Carbopol 934P were obtained asgift sample by Colorcon Asia Pvt. Ltd., Goa, India. All other materials and solvents used were of analytical grade.

Methods

Formulation of Captopril Floating Tablet

Floating hydrophilic matrix tablets were prepared by direct compression technique using different polymers with varying concentration of selected different excipients.All the ingredients except citric acid, Calcium Carbonate, magnesium stearate, and aerosil were passed through mesh No.40. Calcium Carbonate and citric acid were passed through mesh no.100.All the ingredients were blended uniformly. Magnesium stearate and aerosil was added in above blend and further mixed for additional 2-3 minutes. The tablets were directly compressed by using flat punch on a rotary punching machine as Shown in Table No.1.

Evaluation of Precompression Parameter of Powder Blend

The flow properties of granules were characterized in terms of angle of repose, Carr index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated [7-10].

Evaluation of Captopril Floating Tablet

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

Dimensions Measurement

Diameter and thickness of tablet was measured by using digital Vernier caliper. For each batch ten tablets were tested.

Hardness

Hardness was measured by using VK 200 Tablet hardness tester. For each batch ten tablets were tested.

Friability

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again.

Buoyancy Property

One tablet from each formulation batch was placed in USP type II dissolution apparatus containing 900 ml of 0.1 N HCl using paddle at a rotational speed of 50 rpm[11,12]. The temperature of medium was maintained at $37^0 \pm 2^0$ C. The time taken for tablet to emerge on surface of medium and the duration of time by which the tablet constantly remain on surface of medium was noted.

Swelling Study (Water Uptake Study)

For each formulation batch, one tablet was weighed and placed in a USP type II (paddle) dissolution apparatus containing 900 ml of enzyme free SGF with the paddle speed of 50 rpm. After predetermined time interval the tablet was removed from apparatus, blotted to remove excess water, and weighed on analytical balance. The increase in the wet mass represents the medium uptake (swelling index)[13-15].

The % weight gain by the tablet was calculated by the formula**,**

Swelling Index (S.I.) = $\{(W_t-W_o)/W_o\} \times 100$

Where, S.I. = swelling index

W_t = weight of tablet at time t

W_o = weight of tablet before immersion

Dissolution Study

Nine hundred ml of enzyme free SGF was filled in a dissolution vessel and the temperature of the medium were set at $37^0 \pm 2^0$ C. One tablet was placed in each dissolution vessel and the rotational speed of paddle was set at 50 rpm. The 10 ml of sample was withdrawn at predetermined time interval for 24 hours and same volume of fresh medium was replaced. The 5 ml from withdrawn sample was diluted to 10 ml in volumetric flask and filtered through 0.45µ membrane filter. The resultant samples were analyzed for drug content against enzyme free SGF as a blank at λ_{Max} of 205.0 nm using double beam UV visible spectrophotometer. The content of drug was calculated using the following expression. The % cumulative drug release was calculated [16].

Kinetic Modeling for Drug Release

Analysis of drug release from swellable matrices must be performed with a flexible model that can identify the contribution to overall kinetics The dissolution profile of optimized batch (F6) was fitted to various models such as zero-orderHiguchi, Korsmeyer andPeppasto ascertain the kinetic modeling of drugrelease[17-19].

Effect of Hardness on Floating Lag Time and Drug Release

The tablets of batch F6 were compressed at two different compression pressures to get hardness of 60 N and 80 N. The tablets were evaluated for determination of Floating lag time as well as drug release. The method adopted and remaining parameters were same as described in dissolution study[20].

Effect of Type I (Basket) Apparatus on Drug Release

For the study, the drug release study of tablet of batch F6 was carried out using Type I (Basket) Apparatus. The method adopted and remaining parameters were same as described in dissolution study [21].

Infrared Spectra Analysis

IR has been the method of choice to probe the nature and extent of interactions in polymer blends. The premise of using an IR to study polymer blends is that the mixing of the two components at molecular level will cause changes in oscillating dipoles of the molecules. This will manifest itself as changes in frequency and bandwidth of interacting group, in the spectrum. If the drug and polymer interact then functional groups in FTIR spectra will show band shifts and broadening compared to the spectra of pure drug. The potassium bromide disc containing drug, polymer and their physical mixture were prepared to record the spectrum in the range of 4000 - 400 cm^{-1} by using FTIR Spectrophotometer[22, 23].

Stability Study

The batch F6 was selected as an optimum batch and the stability study was carried out at accelerated condition of 40°C/75 % RH$\pm$ 2% condition for a period of two months in hermetically sealed condition.Ten tablets were individually wrapped using aluminum foil and packed in amber color screw cap bottle and put at above specified condition in incubator for 3 months. After each month tablet sample was analyzed for the *in vitro* drug release study. The method adopted and remaining parameters were same as described in dissolution study [24].

RESULT AND DISCUSSION

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From results (Fig.1-2), it was concluded that there was no interference in the functional group as the principle peaks of the Captopril were found to be unaltered in the drug polymer physical mixture.

The physical parameters of drug as well as excipients concluded that these were considerably good to formulate the tablet using direct compression technique. Results were given in Table No.2

From the results of floating lag time it was found that as the concentration of gas generating agent increases the floating lag time get shortens. As the concentration of gas generating agent ($NaHCO_3$ and Citric acid) was increased the floating lag time get shortened (F9) and at the same time floating ability get increased. Another aspect of result of these studies clears that the level as well as viscosity of the polymer had a great impact over the floating lag time and total floating time, as the level and viscosity of the polymer was reduced the floating lag time get shorten. It was also observed that total floating time was greater when the viscosity of the polymer used was greater. Results were given in Table No.3

Swelling Study

The higher swelling index was found for tablet with combination of HPMC K15M, K100M and Carbopol. Whereas highest swelling index was observed with tablets of batch F3 containing Carbopol alone as a polymer. This indicates a linear relationship between swelling and viscosity of polymer. Results of the swelling study also revealed that concentration of gas generating agent ($CaCO_3$ and Citric acid) had a profound effect over the swelling and erosion process. In case of tablets of batch F8, the swelling index was observed to be the highest and lowest with the tablet of batch F9. This might be due to the fact that citric acid in particular concentration acts as disintegrating agent and leads to erosion phenomenon more dominant over swelling, while the decreased concentration of citric acid flavors the swelling process. These findings were well supported by the Patel and co-worker, reported that citric acid in particular concentration acts as disintegrating agent and ultimately favors the erosion. Fillers were found to have significant influence over the swelling and erosion properties of the tablets. The water soluble filler (Lactose) has the tendency to leach out from the tablet when comes in contact with water. While with water insoluble filler MCC, swelling phenomenon was found to be dominating over the erosion (F5), which might be due to the tendency of the MCC to form tight gel barrier around the hydrophilic matrix compared to that formed with lactose.

***In -Vitro* Release Study**

From the results of in vitro release study, (Fig 4) it was observed that the tablet of batch F6 gave highest % cumulative drug release which might be due to the presence of HPMC K100M, K15M and Carbopol 934P than that in F1, F2, and F3 (less than 80%), while with the

tablet of batch F9 there was observed a drug release at a rapid rate than that observed with F6 but it fails (F9) to maintain the matrix integrity up to 24 hrs. (Tablet burst at 22nd hr.). The most probable fact behind these observations with tablet of batch F9 was the excess of citric acid concentration. The in vitro drug release study was further carried out to study the influence of type of filler over the drug release, it was cleared that water-soluble fillers (F7) have release rate enhancing effects whereas water insoluble fillers MCC (F5) have release retardant effect. Further batch F6 was evaluated for the influence of the combination of the hydrophilic and hydrophobic fillers over the drug release; intermediate release pattern was observed due to leaching action of Lactose compared to that observed with F5 and F7.In vitro drug release study was carried out over the tablet of batch F8 and F9 to study the effect of citric acid over the drug release. it was found that tablets of batch F9 showed the highest % cumulative drug release at the end of 22nd hr. but it failed to maintain its integrity for the 24 hrs (it get burst after 22 hrs). This might be due to the presence of high amount of citric acid. Whereas the tablet of batch F8 showed retarded drug release due to the decreased concentration of citric acid.

Effect of Hardness on Floating Lag Time and Drug Release

On increasing the hardness of tablets of batch F6 from 60 N. to 80 N. results in drastic increased in lag time which might be due to high compression resulting in reduction of porosity of the tablets and moreover, the compacted surface hydrocolloid particles on the surface of the tablet cannot hydrate rapidly when the tablets contacts the gastric fluids and as a results of this, the capability of the tablet to float is significantly reduced.From the results of the in vitro release study of the tablets with different hardness, it was observed **(**Table no. 4**)** that there was a drastic retardation of drug release fromthe tablet at high hardness i.e., 80 N.

Effect of Type I (Basket) Apparatus on Drug Release

From the results of the effect of dissolution apparatus study, **(**Table no. 4**)** it was cleared that, the dissolution profiles from the swellable floatable system are sensitive to their position in vessel and also to the hydrodynamic conditions. Use of type I apparatus for dissolution study to the swellable floatable delivery system appeared to inhibit the three dimensional swelling process of the dosage form and consequently suppressed the drug release from formulation.

[$t_{50\%}$ with USP Type II = 4.8 ± 0.33 Hrs; with Type I = 7.9 ± 0.52 Hrs;]

The statistical analysis of $t_{50\%}$ data indicated that there was a significant difference between USP Type II and Type I apparatus. The attributes to these findings might be due to the mechanical attrition; as the floatable system tends to adhere to the basket wall consistently. This resulted in significant slower release rate.

From the results of dissolution profile (Fig.5) of tablets put on stability studies it was concluded that the tablets batch F6 were stable for period of 2 month at 40^0±0.2C/ 75% RH±5% as there was not observed any significant change in dissolution profile of tablet over period of study

Dissolution data of the tablet of batch F6 was subjected to the treatment with different kinetic equations, which showed that release patterns are best fitted to the first order release equation and involves combination of polymer relaxation and consequently swelling. The n value obtained with the application of Korsmeyer and Peppas equation was found to be 0.5175. This value indicates a non-fickian release mechanism that may be attributed to swelling and dissolution of the polymeric matrix. Results were given in Table no. 5

Fig. 1. FTIR of Captopril

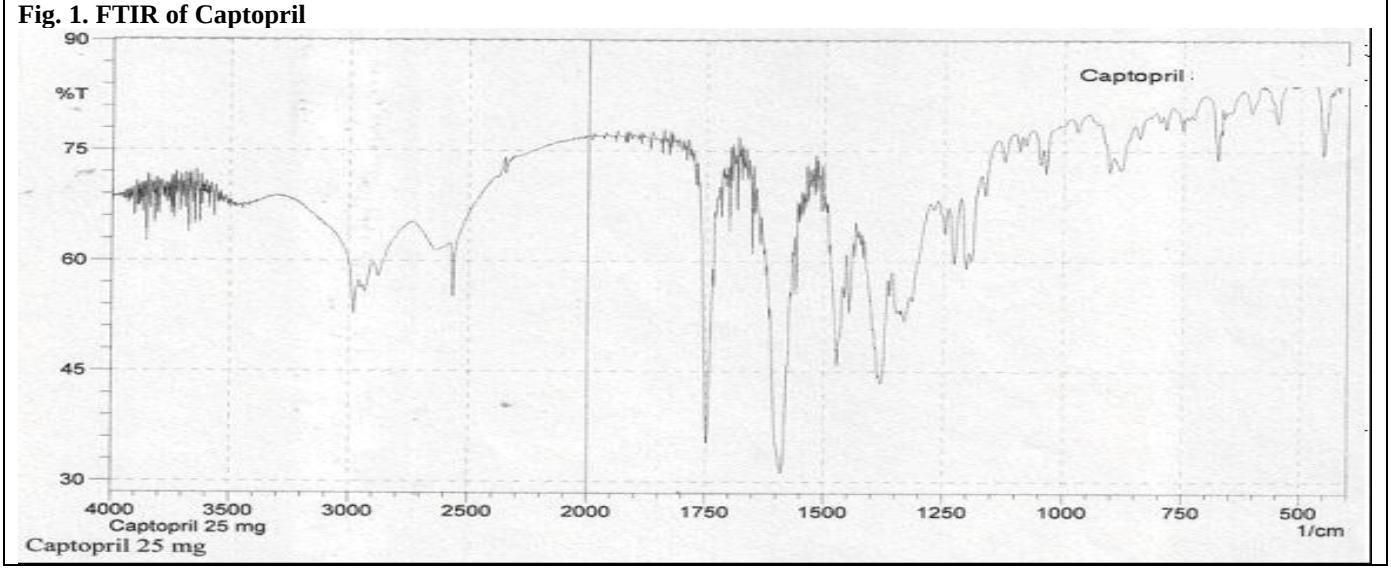

Fig. 2. FTIR of Physical Mixture of Drug and Polymers

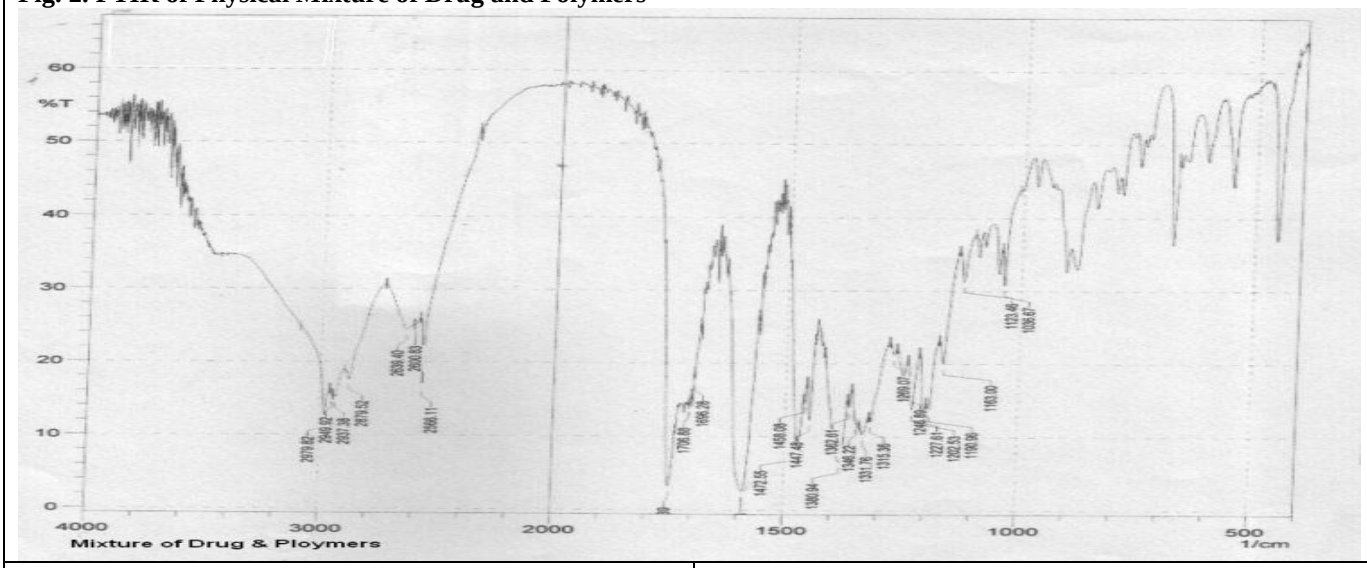

Fig. 3. Swelling Index of tablets of batch F1 to batch F9

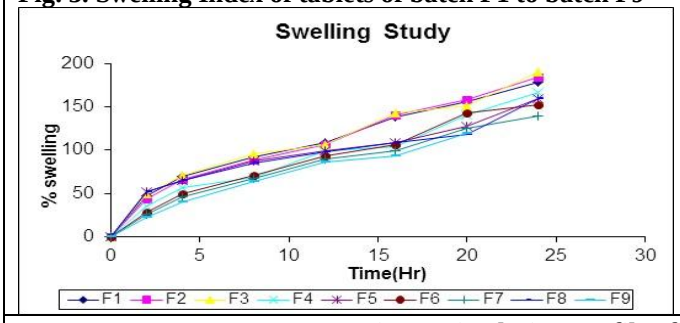

Fig. 4. Dissolution Profile of Tablets of Batch F1-F9.

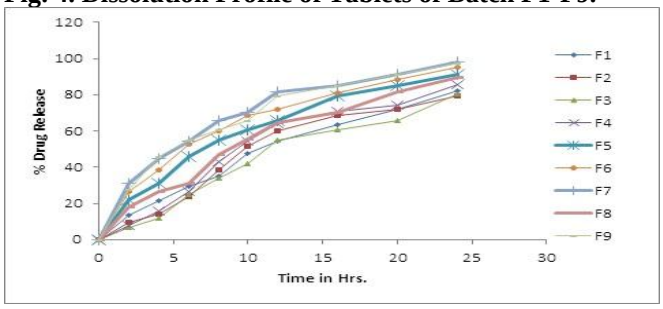

Fig. 5. Dissolution Profile of Batch F6 After Stability Study

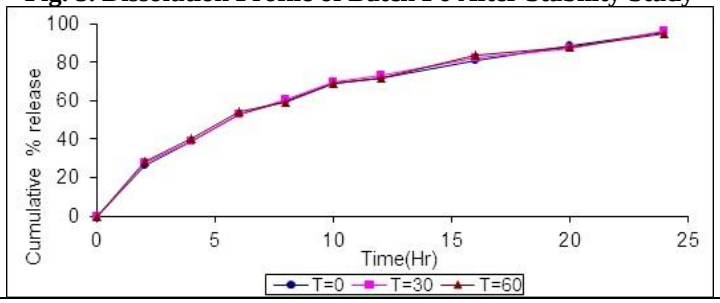

Table 1. Composition of Captopril Floating Tablet

Ingredients(mg)	Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Captopril	25	25	25	25	25	25	25	25	25
HPMCK15M	225	--	--	50	50	50	50	50	50
HPMCK100M	--	225	--	200	200	200	200	200	200
Carbopol 934P	--	--	225	50	50	50	50	50	50
Lactose	115	115	115	40	40	40	40	50	30
Calcium Carbonate	40	40	40	40	40	40	40	40	40
Citric acid	30	30	30	30	30	30	30	30	40
PVP K30	10	10	10	10	10	10	10	10	10
Mag.Stearate	10	10	10	10	10	10	10	10	10
Avicel	5	5	5	5	5	5	5	5	5
Total weight	460	460	460	460	460	460	460	460	460

Table 2. Characterization of Formulation Blend of Each Batch

Batches	Parameters			
	Bulk density (g/ml)	Tap density (g/ml)	Compressibility Index	Hausner Ratio
F1	0.391±0.23	0.463±0.19	15.63±0.53	1.185±0.07
F2	0.431±0.19	0.521±0.21	17.24±0.45	1.208±0.06
F3	0.446±0.18	0.568±0.33	21.42±0.56	1.273±0.06
F4	0.373±0.20	0.446±0.25	16.42±0.43	1.196±0.05
F5	0.362±0.17	0.431±0.18	15.94±0.49	1.190±0.07
F6	0.352±0.15	0.417±0.22	15.49±0.44	1.183±0.06
F7	0.368±0.21	0.439±0.23	16.17±0.37	1.193±0.08
F8	0.357±0.18	0.424±0.17	15.71±0.47	1.186±0.09
F9	0.362±0.20	0.421±0.13	15.94±0.36	1.190±0.08

Table 3. Physical Properties of Tablets of Each Batch

Batch	Physical parameters							
	Weight (mg)	Diameter (mm)	Thickness (mm)	Friability (%)	Hardness (N)	Drug Content (%)	Floating Lag Time (sec.)	Total Floating Time (Hrs)
F1	347.5±0.95	10.1±0.01	5.05±0.08	0.3	60.0 ±2.83	99.2 ±0.66	38±1.06	>24
F2	347.1±0.83	10.2±0.02	4.98±0.02	0.5	65.0 ±2.12	99.06 ±1.03	40±1.66	>24
F3	350.2±1.09	10.1±0.01	5.08±0.05	0.4	62.0 ±2.02	100.21 ±1.52	35±1.12	>24
F4	425.5±1.21	11.0±0.01	4.44±0.04	0.43	61.0 ±2.53	101.2 ±0.87	33±1.18	>24
F5	498.8±1.72	12.1±0.01	4.23±0.02	0.51	62.3 ±2.21	99.65 ±0.69	50±1.45	> 24
F6	499.5±0.87	12.1±0.03	4.22±0.03	0.36	64.3 ±2.88	99.36 ±1.13	40±1.04	> 24
F7	500.1±1.08	12.1±0.02	4.23±0.05	0.38	63.5 ±2.06	100.2 ±0.84	30±1.27	> 24
F8	488.4±0.75	12.1±0.03	4.21±0.04	0.46	60.5 ±2.77	99.72 ±0.98	38±1.22	> 24
F9	518.3±0.86	12.1±0.01	4.25±0.03	0.48	63.0 ±3.27	98.99 ±1.31	25±1.21	> 24

Table 4. Effect of Dissolution Apparatus on Drug Release of Batch F6

Time (Hrs)	Dissolution Apparatus (% Release)*		Hardness (% Release)	
	Type I	Type II	60N	80 N
0	0	0	0	0
2	22.67 ±0.76	26.6±0.86	26.6±0.86	20.07±0.88
4	31.68 ±0.41	38.68±0.39	38.68±0.39	28.35±0.79
6	46.99 ±0.78	52.66±0.81	52.66±0.81	36.01±0.78
8	51.87 ±0.82	59.99±0.79	59.99±0.79	48.33±0.69
10	62.05 ±0.39	68.8±0.38	68.8±0.38	56.05±0.46
12	67.64 ±0.53	72.02±0.51	72.02±0.51	66.98±0.54
16	74.81 ±0.67	81.2±0.68	81.2±0.68	74.81±0.63
20	82.65 ±0.59	88.5±0.54	88.5±0.54	79.05±0.59
24	89.42 ±0.54	95.4±0.62	95.4±0.62	83.65±0.59

n=3

Table 5. Kinetic Data for Dissolution of Batch F6

Kinetic equation	R^2	Slope	Intercept
First order	0.6699	0.0502	1.0881
Higuchi square root of time	0.9858	0.0496	-0.0272
Korse-Meyer Peppas	0.9916	0.5175	1.2861

CONCLUSION

Result of water uptake study cleared that, tablets of batch F1 to F9 shows linear increase in swelling. From the in-vitro dissolution study it was concluded that tablet of batch F6 showed highest percentage cumulative drug release due to combination of HPMC K100M, HPMC K15M and Carbopol 934P while the tablet of batch F9 rapid drug release (due to excess of citric acid) than tablet of batch F6 but it fails to maintain the matrix integrity up to 24 hrs. From the overall observation of different

evaluation studies tablet of batch F6 was selected as an optimized batch. The n value obtained from the korsemeyer-peppas equation indicates tablet of batch F6 shows rather first order release mechanism. It was concluded that type of filler has significant effect on drug release from the drug delivery system. The USP Type I apparatus suppresses the three dimensional drug releases from the matrix tablet. The tablet of higher hardness affects the floating lag time and also retards the drug release from the matrix.

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