Formulation Development and Evaluation of Gastroretentive Floating Tablet of Captopril Using Natural and Synthetic Polymer with Comparision of Polymer Efficacy

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***Abstract*: The aim of the present work was to develop gastro-retentive floating tablets of Captopril investigate the effects of both natural and synthetic polymers retardant on *in-vitro* release. Captopril is an antihypertensive drug with an oral bioavailability of only 50% because of its poor absorption from lower gastrointestinal tract. The floating tablets of Captopril were prepared to increase the gastric retention, extend the drug release, improve the bioavailability of the drug, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. The gastro-retentive floating tablets of Captopril were formulated using natural and synthetic polymers as Chitosan, Hydroxy propyl methyl cellulose. Carbopol, and Lactose with a solution of PVP K-30 (Poly vinyl pyrrolidone) isopropyl alcohol and citric acid were used in different concentration as a channeling and chelating agent to obtain best optimized formulation. The presence of lactose in matrices containing HPMC increased the release rate of captopril.**
The prepared tablets were assessed for the quality control tests, for example, weight variation, hardness, friability, thickness, drug content, *in vitro* buoyancy studies and *in vitro* dissolution.
The *in vitro* release investigation of the tablets was performed in 0.1 N HCl as a dissolution media. The results of the present study clearly indicate the floating tablet of Captopril formulated by using synthetic polymer showed better release, less toxic effects & better anti-hypertensive activity.

***Keywords*: Bioavailability; Gastro-retentive; Dissolution; Formulation; Gastrointestinal tract GIT; Hydroxy propyl methyl cellulose etc.**

1. Introduction:

The oral bioavailability of several drugs is limited by their unfavorable physicochemical characteristics or absorption in the precise part of the gastrointestinal tract (GIT). **[1].**Extended gastric retention improves both bioavailability and the solubility for drugs that are less soluble in a high pH environment and correspondingly reduce the drug waste by remain in the gastric region**[2].**Various approaches have been encourage the gastric retention of an oral dosage form in the stomach, including Mucoadhesive / bioadhesive drug delivery system, Swelling and expanding drug delivery system, High density system, Modified shape system, Delayed gastric emptying system, Floating drug delivery system (FDDS)**[3,4,5].**
Captopril is a sulfahydryl containing angiotensin converting enzyme (ACE) inhibitor used in the treatment of hypertension, some kind of congestive heart failure and diabetic nephropathy. Chemical name of Captopril is 1-[(2S)-3-mercapto-2-methyl propionyl]-L-proline **[6]**. Molecular structure of Captopril is shown in figure below.

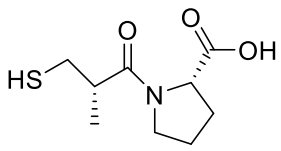

Figure 1: structure of Captopril

Captopril is freely soluble in water **[7]**. It has been accounted for, in any case, that the span of antihypertensive activity after a solitary oral absorption of captopril is just 6–8 h, so clinical use requires an everyday portion of 37.5–75 mg to be taken multiple time and modes of administration of Captopril is oral and its elimination half-life of 1.7 h. It is partly metabolized and partly excreted unchanged in urine **[8-10]**. Therefore, it is selected as a suitable drug for the design of a gastro-retentive floating drug delivery system (GFDDS) with a view to improve its oral bioavailability and to increase their retention time in the body.

Hydroxy propyl methyl cellulose (HPMC) is hydrophilic cellulose ether widely used as release retarding material. HPMC releases drug by diffusion mechanism **[11]**.The objective of the present study was to develop a gastro-retentive floating drug delivery system (GFDDS) of Captopril by using synthetic and natural polymers.

2. Material and Methods

2.1 Materials

Captopril was obtained as a complimentary sample from Drug Centre, Delhi India. HPMC, Carbopol, Sodium bicarbonate, Lactose, Magnesium Stearate, Xanthan gum, Chitosan and Citric acid was received from Zee Laboratories Pvt. Ltd. Poanta Sahib Distt. Sirmour HP, India. All the reagents and solvents used were of analytical grade.

2.2. Drug Excipients Compatibility Study

Compatibility studies were done to recognize the possible interactions between drug Captopril and excipients utilized in the formulation. Physical mixtures of drug and excipients in the proportion 1:1 were set up to study the compatibility. Drug polymer compatibility studies were completed utilizing FTIR spectroscopy. The IR Spectra's were recorded in the middle of 500–4000 cm^{-1}.

2.3. Preparation of Tablets

Floating tablets containing Captopril were prepared by conventional wet granulation method using varying concentrations of retardants (HPMC) with sodium bicarbonate. Ingredients except glidants and lubricant were thoroughly mixed and passed through 60 mesh sieves. Granulation was done with a solution of calculated quantity of PVP K30 in sufficient isopropyl alcohol. Firstly, wet mass of ingredients was prepared then passed through 12 mesh sieves and dried at 50 °C for 2 h. The dried granules were lubricated with magnesium stearate and talc. The final granules compressed into tablets having 200mg using tablets punch machine. The compositions of all formulations prepared by using synthetic and natural polymer are given in Table 1 and Table 2.

Table1. Formulation of Tablets using synthetic polymers

Sr. No.	**Formulation code**	**Captopril (mg)**	HPMC K15M (mg)	Na_2CO_3 (mg)	Carbopol(mg)	Lactose (mg)	Mag. stearate (mg)	Citric acid (mg)	Total wt. (mg)
1	F1	50	40	30	20	30	20	10	200mg
2	F2	50	40	30	35	20	20	10	200mg
3	F3	50	32	30	25	31	20	12	200mg
4	F4	50	30	33	28	25	20	14	200mg
5	F5	50	34	32	14	28	16	15	200mg

Table2. Formulation of tablet using natural polymers

S.no	**Formulation code**	**Captopril (mg)**	**Chitosan (mg)**	**Na_2CO_3 (mg)**	**Xanthan gum (mg)**	**Lactose (mg)**	**Mag. sterate (mg)**	**Citric acid** (mg)	**Total wt. (mg)**
1	F1	50	40	31	20	29	20	10	200mg
2	F2	50	42	30	33	20	20	10	200mg
3	F3	50	32	30	25	31	20	12	200mg
4	F4	50	30	33	28	25	20	14	200mg
5	F5	50	34	32	25	28	16	15	200mg

2.4. Evaluation of Tablet Properties

2.4.1.1 Determination of Pre-compression Parameters

The pre-formulating studies including Bulk density, tapped density, Hausner's ratio, and Angle of repose were performed of the powder **[12]**.

2.4.1.2. Organoleptic evaluation of pure drug

Organoleptic characters like colour, odour, and taste of drug were observed and recorded using descriptive terminology **[13]**.

2.4.2. Determination of Post compression Parameters.

2.4.2.1. Hardness Test.

Monsanto hardness tester was used for the determination of hardness or tablet crushing strength of tablets **[19]**.

2.4.2.2. Friability.

Friability of the tablets was determined using Roche's Friabilator. Pre-weighed sample of tablets was placed in the friabilator and operated for 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed**.** The tablets that loose less than 1% weight were considered to be compliant **[20]**.

The % friability was calculated by using this formula:

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

Where, W_0 is weight of the tablets before the test and W is the weight of the tablet after the test.

2.4.2.3. Weight Variation

Twenty tablets were selected randomly from the lot and average weight was determined **[21].** Then individual tablets were weighed and was compared with average weight.

2.4.2.4. Thickness

The individual crown-to crown thickness of 10 tablets was determined using slide caliper for each batch.

2.4.2.5. Drug Content (Assay)

Ten tablets were finely powdered, amounts of the powde requivalent to 50mg of Captopril were accurately weighed and transferred to a 100mL of volumetric flask. The flask was filled with 0.1N HCl (pH 1.2 buffers) solution and mixed all together. The solution was made up to volume 100 mL and filtered. Dilute 1mL of the resulting solution to 100 mL with 0.1 N HCl. The absorbance of the resulting solution was measured by Shimadzu UV visible spectrophotometer. The linearity equation got from calibration curve was used for estimation of Captopril in the tablet formulations **[26]**.

2.4.2.6. *In Vitro* Buoyancy Studies.

Floating time was determined by using I.P. tablet dissolution apparatus. Tablets were placed in the apparatus, containing 900 ml of 0.1N HCL, temperature maintained at 37±0.5°C and rotation of peddles set at 50rpm. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the time period up to which the tablet remained buoyant is determined as total floating time (TFT) **[27]**.

2.4.2.7. *In-Vitro* Dissolution Studies

In vitro dissolution studies of all the fabricated tablets and the pure drug was carried out USP paddle method at 50 rpm in 900 ml of Phosphate Buffer pH 5.8, maintained at 37 $\pm$ 0.5 °C. 5 ml of aliquots withdrawn at specified intervals and for filtration passed through whatmann filter paper. The dissolution was carried out for 12 hours. The absorbance of the samples at different time intervals were carried out using UV - visible spectrophotometer at λ_{max} of 243 nm **[28]**.

2.4.2.7. Disintegration test

Disintegration time was determined using the disintegration apparatus USP. In 0.1N HCl for 2 h and then in phosphate buffer pH 6 maintaining the temperature at 37 ± 2°C. Put in distilled water for five minutes to dissolve the coat. Then put in simulated gastric fluid (0.1N HCL) for one hour. Then put in simulated intestinal fluid for two hours. If one or two tablets fail to disintegrate, repeat

this test on another 12 tablets. So, 16 tablets from 18 should completely disintegrate. If more than two fail to disintegrate the patch must be rejected **[29]**.

3 RESULTS AND DISCUSSION

3.1 Drug-Excipients Compatibility Studies: The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. It does not show any well defined interaction between Captopril and excipients. This indicates that the drug is compatible with the excipients. The spectra for pure drug, drug-excipients mixture are shown in Figures 1,2,3,4 respectively.

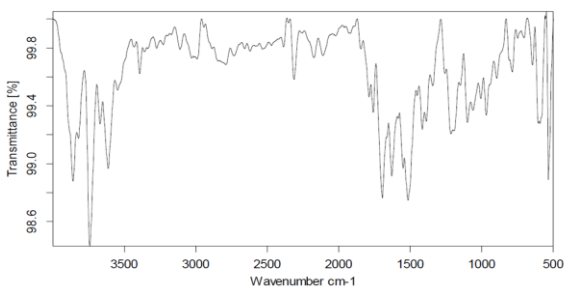

Fig:1 FTIR of captopril

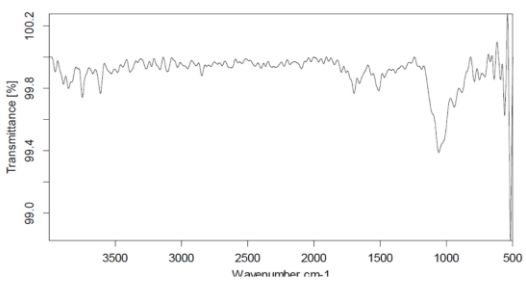

Fig :2 FTIR of captopril with polymer HPMC

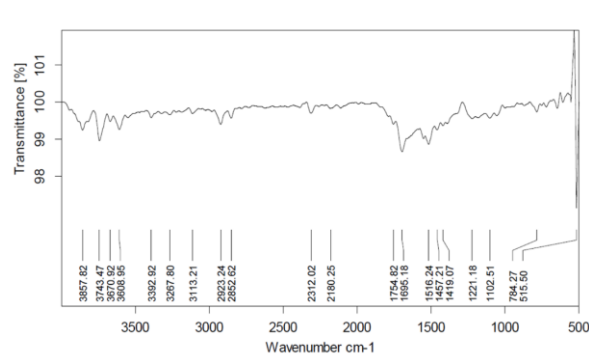

Fig:3 FTIR study of Captopril with Carbopol

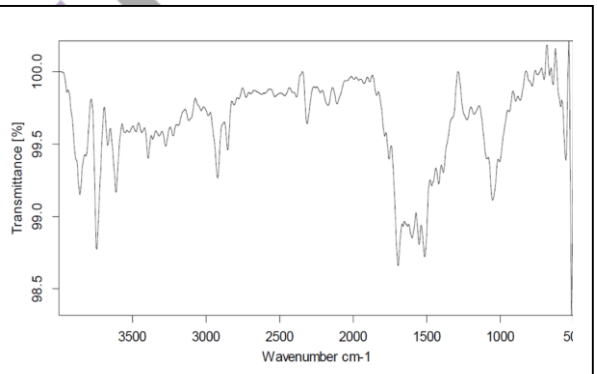

Fig: 4 FTIR study of Captopril +Xantham gum+ Chitosan

3.2. Pre - Compression Parameters*:* Results of the precompression parameters performed on the blend for batch F1 to F5 for both synthetic and natural polymer are tabulated in Table 2 and 3. The bulk density and the tapped density for all the formulations by using synthetic and natural polymer varied from 0.40 to 0.59 g/mL and 0.49 to 0.65 g/mL, respectively. Carr's index lies within the range of 8.21.2 to 18.14% in case of both synthetic and natural polymer. All formulations show good compressibility. Hausner ratio was found to be in the range of 1.05 to 1.26. Angle of repose of all the formulations was found to be less than 30^0, which indicates a good flow property of the powders.

Table 3: Characters of blend on various parameters (F1-F5) of synthetic polymers

Material	Angle of repose (Degree)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr index	Hausner ratio	FLT {sec}
F1	26.2	0.40	0.49	15.57	1.05	44
F2	21.29	0.45	0.53	11.54	1.14	46
F3	31.05	0.42	0.52	17.53	1.24	30
F4	24.55	0.51	0.62	8.21	1.10	55
F5	29.38	0.44	0.52	16.12	1.22	61

Table 4: Characters of blend on various parameters (F1-F5) of natural polymers

Material	Angle of repose (Degree)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr index	Hausner ratio	FLT {sec}
F1	29.84	0.45	0.52	16.51	1.09	42
F2	25.03	0.47	0.57	14.50	1.19	44
F3	32.88	0.46	0.55	18.23	1.26	42
F4	26.17	0.59	0.65	10.25	1.15	31
F5	32.64	0.50	0.58	18.14	1.25	55

3.3. Post compression Parameters: The tablets formulated by using both synthetic and natural polymer were subjected for post compression evaluation such as thickness, hardness, weight variation, friability, drug content, *in vitro* buoyancy studies and *in vitro* dissolution studies. Tablet thickness (n = 3) was almost uniform in all the formulations and values for tablets ranged from 2.97 to 3.97mm.The hardness of all formulations was in the range of 5 to 7 kg/cm^2, indicating satisfactory mechanical strength. The weights of tablets ranged from 203 to 209 mg. All the tablets passed weight variation test. The friability values ranged from 0.10 to 0.15%. The percent drug content of the tablets was found to be in between 91 to 99%. In the disintegration test, the disintegration test of different formulation it was observed that disintegration time of captopril ranged from 23 to 28 min. in 0.1N HCl. Table 5 and table 6 shows the results of physicochemical characters of Captopril tablets by using synthetic and natural polymer.

3.4 *In Vitro* Buoyancy Studies. *In vitro* buoyancy of the tablets from each formulation F1 to F5 by using both synthetic and natural polymer was evaluated and the results are mentioned in Table 5 and 6,where the highest and lowest floating lag time (FLT) were observed >9 to>12 with the formulations.

Table 5: Characters of tablet on various parameters (F1-F5) of synthetic polymer

Formulation Code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)	Total floating duration (h)	Disintegration time (min.)
F1	3.21	5.5	203 ± 0.5	0.10	98.63%	>9	25
F2	2.97	5.7	207 ± 0.5	0.12	97.21%	>10	28
F3	3.51	5.9	209 ± 0.5	0.14	99.09%	>12	23
F4	3.19	6.0	207 ± 0.5	0.11	96.99%	>12	27
F5	3.47	5.4	206 ± 0.5	0.13	98.47%	>11	24

Table 6: Characters of tablet on various parameters (F1-F5) of natural polymer

Formulation Code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)	Total floating duration (h)	Disintegration time (min.)
F1	3.11	5.2	202 ± 0.5	0.12	96.31%	>11	29
F2	3.97	5.9	205± 0.5	0.14	92.22%	>9	25
F3	3.46	5.1	207 ± 0.5	0.13	97.06%	>10	27
F4	3.55	6.5	204± 0.5	0.10	96.91%	>8	26
F5	3.77	5.8	209 ± 0.5	0.15	91.41%	>9	24

3.5 *In Vitro* Dissolution Studies.

The *in vitro* drug release profiles for the formulations F1–F5 formulated by both natural and synthetic were depicted in Tables 7 and 8. The plot of cumulative percentage drug release versus time (hrs) for formulations were plotted and depicted in Figures 5 and 6 respectively. *In vitro* release the release study in vitro aqueous Floating tablet of Captopril time period 12 The synthetic polymer higher concentration (f-5) showed faster release 89.25% in 12 hrs. and the formulation of natural polymer f4 higher polymer concentration showed faster release 82.23 % in 12 hrs.

Formulations which are using synthetic polymers turned out to best as they showed a minimum lag time and maximum floating time with maximum release of drug percentage so it is considered as a successful.

Table 7: Dissolution Profile of Captopril Floating tablet of using synthetic polymer

Time (hr)	**F1**	**F2**	**F3**	**F4**	**F5**
1	19.21	20.45	18.35	17.96	15.35
2	25.36	22.38	24.55	20.89	19.88
3	34.25	31.85	35.36	39.25	31.58
4	49.21	45.29	47.25	40.96	42.66
5	61.45	59.03	62.38	65.34	56.69
6	72.22	76.25	78.29	81.02	76.25
8	79.65	76.25	78.65	81.02	71.04
10	83.03	80.96	84.36	88.66.	89.25

Table 8: Dissolution Profile of Captopril Floating tablet using Natural polymer

Time (hr)	F1	F2	F3	F4	F5
1	15.05	17.41	16.14	15.51	10.15
2	21.05	20.12	19.17	18.12	15.25
3	31.27	29.14	32.21	34.21	25.32
4	44.25	42.15	43.11	41.21	32.12
5	55.15	51.51	54.59	59.11	51.36
6	71.21	75.22	69.25	76.22	55.12
8	81.23	72.58	60.12	82.23	78.32
10	79.25	85.32	78.96	71.56	84.32

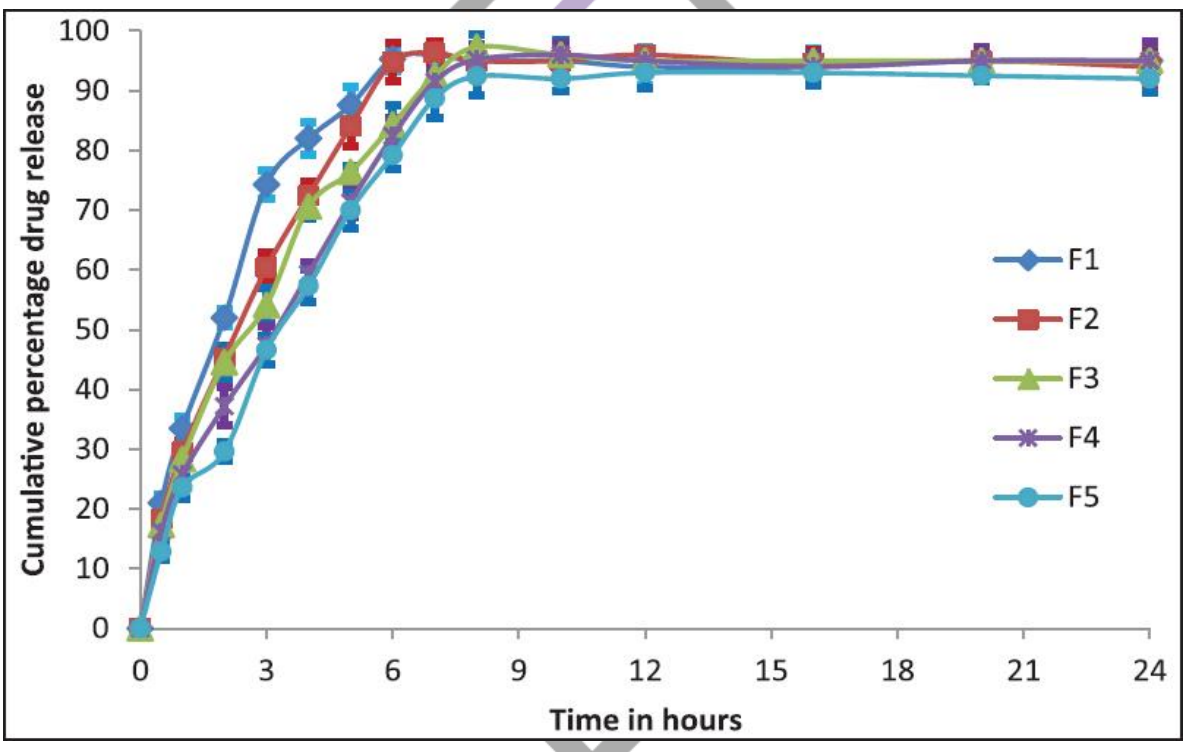

Fig 5: Dissolution curve of Captopril Floating tablet

4. Conclusion

The results of the present research work demonstrates that the formulation that prepared by using synthetic polymers turned out to be the best because they showed a minimum lag time and maximum floating time with maximum release of drug percentage. It is observed that optimum concentration was able to produce desired formulation which releases complete drug in 12 hours. So, formulation prepared by using synthetic polymers considered as a successful as compared to formulation prepared by using natural polymers.

References

[1] S. Shahi, A. Sonawane, S. Vanamore, and N. Zadbuke, "Formulation and in-vitro characterization of acyclovir floating matrix tablets: a factorial design study," Journal of Applied Pharmaceutical Science, vol. 3, no. 5, p. 65, 2013.

[2] A.Yadav and D. Jain, "Formulation development and characterization of gastroretentive floating beads," Asian Journal of Pharmacy and Medical Science, vol. 2, no. 1, pp. 1–10, 2012.

[3] Y. Kawashima, T. Niwa, H. Takeuchi, T. Hino, and Y. Itoh. "J Pharm Sci," 4; pp. 182, 1996.

[4] A. Rubinstein, D. R. Friend, "Specific delivery to the gastrointestinal tract. In Domb AJ (Ed) polymeric site-specific pharmacotherapy," wiley; Chichester; pp. 282-283, 1994.
[5] W. A. Ritschel, "Targeting in the gastrointestinal tract: new approaches, methods, Find Exp," Clin Pharmacol, vol. 13, p. 313-336, 1991.
[6] Martindale, "The Extra Pharmacopoeia," The Pharmaceutical Press, London, ed. 29th, pp. 468, 1989.
[7] K. L. Duchin, S. M. Singhavi, D. A. Willard, B. H. Migdal of and D. N. Mc kinstry, "Captopril kinetics," Clin. Pharmacol. Therr, 31, p. 452–458, 1982.
[8] K. L. Duchin, D. N. Mc Kinstry, A. I. Cohen, and B. H. Migdal of, "Pharmacokinetics of captopril in healthy subjects and in patients with cardiovascular diseases," Clinical Pharmacokinetics, vol. 14, no. (4), p. c 241–59, 1988.
[9] N.J.Brown, D.Vaughan, "Angiotensin-converting enzyme inhibitors" Circulation. 97(14), p.1411–20, 1988.
[10] C. Dollery, "Therapeutics Drugs," Churchill Livingstone, New York, p. c38–c43, 1999.
[11] B. S. Sudha, B. K. Sridhar, and A. Srinatha, "Modulation of tramadol release from a hydrophobic matrix: implications of formulations and processing variables," AAPS Pharm Sci. Tech, vol.11,no.1,pp.433–440,2010
[12] V. T. Yadav, B. D. Jayswal, K. N. Patel, B. A. Patel, and P. A. Patel, "Formulation and evaluation of floating tablet of amoxicillin trihydrate," International Journal for Pharmaceutical Research Scholars, vol.1, no.2, pp.307–309,2012.
[13] Zhao N, Augsburger LL. Functionality comparison of 3 classes of superdisintegrants in promoting aspirin tablet disintegration and dissolution. AAPS pharmscitech. 2005 Dec 1;6(4):E634-40.
[14] Pahwa R, Piplani M, Garg VK, Rao R, Lamba HS. Formulation and evaluation of orally disintegrating tablets: comparison of natural and synthetic superdisintegrants. Der Pharmacia Lettre. 2011;3(2):407-18.
[15] Hu RF, Zhu JB, Peng DY, Tang JH, Zhou A. Optimization of formulation of FufangDanshen immediate release tablet by colligation score. Zhongguo Zhongyao zazhi Zhongguo zhongyao zazhi China journal of Chinese material medica. 2006 Mar;31(5):380-2.
[16] Sekar V, Chellan VR. Immediate release tablets of telmisartan using superdisintegrant-formulation, evaluation and stability studies. Chemical and Pharmaceutical Bulletin. 2008 Apr 1;56(4):575-7.
[17] Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. New England Journal of Medicine. 1996 May 23;334(21):1349-55.
[18] Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the CarvedilolOrMetoprolol European Trial (COMET): randomised controlled trial. The Lancet. 2003 Jul 5;362(9377):7-13.
[19] J. Padmavathy, D. Saravanan, and D. Rajesh, "Formulation and evaluation of Ofloxacin floating tablets using HPMC," International Journal of Pharmacy and PharmaceuticalSciences, vol.3,no.1,pp.170–173,2011.
[20] B. Brahmaiah, G. P. Bhagath, and M. Gudipati, "Formulation and evaluation of gastroretentive floating drug delivery system of metoprolol tartarate," International Journal of Life Sciences Biotechnology and Pharma Research, vol. 2, no. 1, pp. 183–197, 2013.
[21] N.Singh, A.Bose, R.Mishra,V. Jain,S.Dhakar, and D.Bharati, "Development and evaluation of gastroretentive floating drug delivery system for tizanidine hydrochloride and its in-vivo gamma-scintigraphic studies using tc-99m tracer," Asian JournalofPharmaceuticalandClinicalResearch,vol.5,no.3,p.57, 2012.
[22] Capricorn Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. The Lancet. 2001 May 5;357(9266):1385-90.
[23] Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Bristow MR, Cohn JN, Lukas MA, Young ST, Packer M. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. New England Journal of Medicine. 2001 May 3;344(18):1358-65.
[24] Bala R, Khanna S, Pawar P. Polymers in fast disintegrating tablets–a review. Asian J Pharm Clin Res. 2012;5(2):8-14.
[25] Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L, Ross RD, Pahl E, Blume ED, Dodd DA, Rosenthal DN. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. Jama. 2007 Sep 12;298(10):1171-9.
[26] M. Varma and S. Vijaya, "Development and evaluation of gastro retentive floating drug delivery system of atenolol,"International Journal of Pharmaceutical and Chemical Sciences, vol. 1, no.2,p.869,2012.
[27] S. Chander, K. Shireesh, and B. Nagendra, "Preparation and evaluation of gastro retentive floating tablets of ketoconazole," International Journal of Pharma Research and Development,vol. 2,no.9,pp.175–176,2010.
[28] R. P. Tayade, V. M. Thakare, B. W. Tekade, and V. R. Patil, "Formulation and evaluation of captopril floating matrix tablet," International Journal of Pharmaceutical Research and Development,vol.4,no.6,p.116,2012.
[29] Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright JT, Oakes R, Lukas MA, Anderson KM. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. Jama. 2004 Nov 10;292(18):2227-36.