WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 1, 1188-1197. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF IMMEDIEATE RELEASE SUBLINGUAL TABLET OF LOSARTAN POTASSIUM USING FACTORIAL DESIGN

Bani Singh Kamal*, Gauniya Anju and Monika

Noida Institute of Engineering and Technology, Pharmacy Institute, Greater Noida.

Article Received on
10 Nov. 2018,
Revised on 30 Nov. 2018,
Accepted on 20 Dec. 2018
DOI: 10.20959/wjpr20191-13946

***Corresponding Author**
Bani Singh Kamal
Noida Institute of Engineering and Technology, Pharmacy Institute, Greater Noida.

ABSTRACT

Losartan potassium is mainly used to treat high blood pressure, it is a angiotensin II receptor antagonist. it keeps blood vessels from narrowing, which lowers blood pressure and improve blood flow. The basic objective of this study was to produce immediate release sublingual tablet of losartan potassium containing super disintegrants via direct compression, to improve disintegration, dissolution and to get faster onset of action. The drug-excipients interaction was investigated by FT-IR. Various formulation of losartan potassium tablets were prepared and evaluated with respect to the various quality parameters both in process parameters for granules (bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose and parameters for finished products (average weight, weight variation, friability, hardness, drug content, disintegration time, drug content, in vitro dissolution studies). Tablets were found to be satisfactory when evaluated for all evaluation parameters.

KEYWORDS: Formulation, evaluation, losartan potassium, dissolution studies, FT-IR, friability.

INTRODUCTION

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are most preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physicochemical stability in comparision to some other dosage forms. it provide accurate dosing. However, the process of manufacturing of tablets is complex. Hence, careful consideration has to be given to select

right process, and right excipients to ultimately give a high productivity and regulatory complaint product of good quality. It is freely soluble in water and soluble in alcohols. Losartan potassium is an angiotensin II receptor antagonist. It suppresses the effects of angitensin II at its receptors, thereby blocking the rennin angiotensin system.[1]

Losartan potassium, an orally active non-peptide molecule, is chemically described as 2 - butyl - 4 - chloro - 1 imidazole – 5 - methanol monopotassium salt. 2-4 Its empirical formula is $C_{22}H_{22}ClKN_6O$.

The molecular weight of losartan potassium is 461.01. It is freely soluble in water and soluble in alcohols. Losartan potassium is an angiotensin II receptor antagonist. It suppresses the effects of angitensin II at its receptors, thereby blocking the rennin angiotensin system. The rennin-angiotensin system plays a crucial role in the control of blood pressure, Losartan has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, selectively, and tolerability. Generally, losartan potassium is employed in the management of essential hypertension with lower incidence of side-effects like cough. It is readily absorbed. The pharmacokinetics of both losartan and its active metabolite are linear, and not affected by repetitive dosing. Although clearance is both by hepatic and renal mechanisms, only hepatic impairment appears to affect plasma half-life.

In the present study, we made an attempt to develop a stable formulation of oral immediate-release losartan potassium tablets with optimum properties. To achieve this goal, various formulation of losartan potassium tablets were prepared and evaluated with respect to the various quality parameters both in process parameters for granules (loss on drying, bulk density, tapped density, compressibility index, Hausner's ratio) and parameters for finished products (average weight, weight variation, tablet thickness, friability, hardness, disintegration time, drug content, dissolution studies).

Then, the invitro dissolution profile of optimized losartan potassium tablets evaluated.[2,3,4,5]

MATERIALS AND METHODS

Materials

Losartan potassium tablets were manufactured for nine batches F1 to F9 using different ratios of superdisintegrant (sodium starch glyconate) and dissolver (cross-povidone) mentioned in

the (Table No. 3). Losartan potassium, cross-povidone, sodium starch glycolate, magnesium stearate, purified talc, and maize starch were used. All the materials used were of the best quality available.

Experimental design (3^2)

Factorial design is an experimental design technique, from which the factor involved and its relative concentration can be assessed. In the present study a 3^2 full factorial design was employed in which 2 factors were evaluated at 3 levels. Experimental trails were performed at all possible 9 combinations. the independent variables selected for this study were concentration of crosspovidone (X1) and sodium starch glycolate (X). % drug release for 5min, 10min, 15min, 20min, 25min and drug content were as dependent variables. Tablet weight was not constant for all batches because that does not require diluents which may causes variation in drug release profile.

Table 1: 3^2 full factorial design and level of independent variables.

Trail No.	Coded value (X1)	Coded value (X2)
F1	-1	-1
F2	0	-1
F3	+1	-1
F4	-1	0
F5	0	0
F6	+1	0
F7	-1	+1
F8	0	+1
F9	+1	+1

Table 2: Independent variables.

Coded value	X1	X2
-1	70	35
0	100	50
+1	130	65

X1 is amount of crosspovidone in mg, X2 is amount of sodium starch glycolate in mg.

Preparation of Losartan Potassium tablets

Various formulation of losartan potassium tablets were prepared by direct compression method.

All the ingredients were dispensed as per the batch size. Losartan potassium, maize starch (dried), cross-povidone, purified talc, sodium starch glycolate were shifted through mesh size

(#) 60 separately. These above ingredients were mixed geometrically ratio and blended for 15 minutes in a cone blender. Then magnesium Stearate were shifted through # 60 and mix with the above blend for further 3 minutes. After that, these above blends were compressed using the tear drop shaped punches.

Table 3: Composition of losartan potassium tablets in mg.

Name of ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan potasium	100	100	100	100	100	100	100	100	100
Maize starch	10	10	10	10	10	10	10	10	10
Cross-povidone	70	100	130	70	100	130	70	100	130
Sodium starch glyconate	35	35	35	50	50	50	65	65	65
Mag. Stearate	3	3	3	3	3	3	3	3	3
talc	2	2	2	2	2	2	2	2	2

Drug–excipient interaction study

The drug and excipients must be compatible with one another to produce a product i.e. stable, efficacious, attractive, easy to administer and safe. The compatibility studies provide the frame work for the drugs combination with the excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically API will not undergone any changes, after it has been subjected to processing steps during formulation of tablets.[6,7]

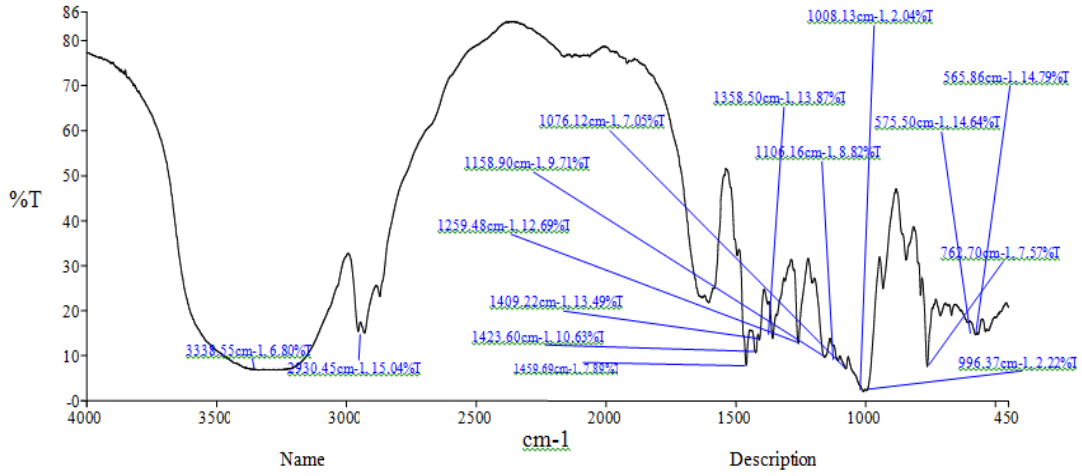

Fig 1: Losartan potassium with sodium starch glycolate

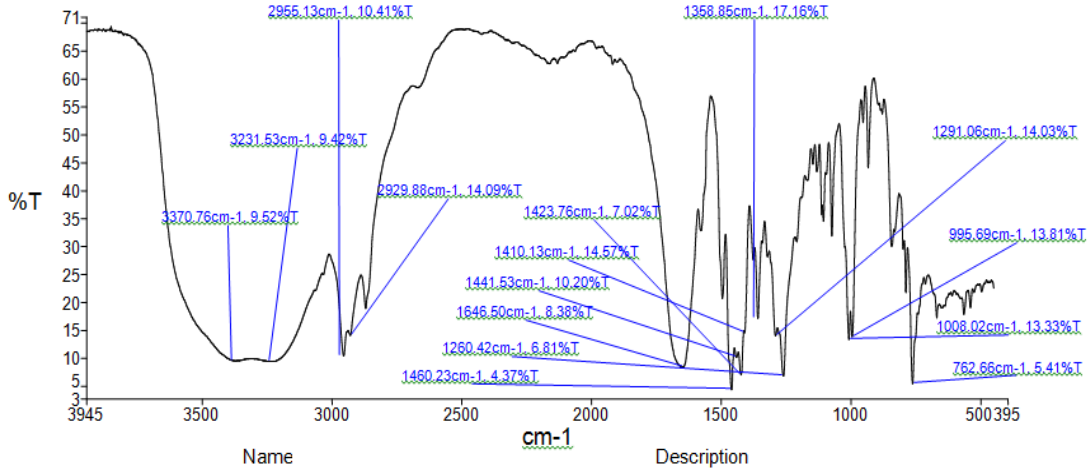

Fig 2: Losartan potassium with cross-povidone

Pre Compression Studies[8,9,10]

Bulk density (dB)

Density is determined by dividing weight of powder by volume of powder in g/cm^3. Bulk denity is determined by weight of dry powder and the bulk volume in a graduated cylinder.

Tapped density (dT)

Tapped volume is measured by tapping of cylinder filled with bulk powder from a constant hight on flat horizontal surface for 100 times. This tapped volume gives tapped density by dividing weight of dry powder by tapped volume.

Hausner ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by the formula HR= dT/dB. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Carr index

It is also known as compressibility index. Carr index gives the important properties of powder or granules and is calculated by following equation,

CI = dT- dB x100 dT

Angle of repose (Ɵ)

It is calculated by fixed funnel method. The values obtained for angle of repose of all formulations were tabulated in table no.4. The values were found to be in the range from

48˚.58′ to 58˚.01′ this indicate poor flow properties of powder. The angle of repose is determined by using following equation,

Θ =tan¯1 2H/d

Table 4: Pre-Formulation Studies Results.

PARA- METERS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density (gm/ml)	0.29	0.27	0.28	0.26	0.29	0.28	0.25	0.28	0.28
Tapped density (gm/ml)	0.44	0.41	0.40	0.36	0.40	0.39	0.34	0.40	0.36
Compressibility Index (%)	14.1	15.0	17.5	18.5	11.8	19.7	16.5	12.0	12.8
Hausner's Ratio	1.13	1.12	1.14	1.10	1.15	1.16	1.19	1.20	1.14
Angle of repose	25	25.5	27	24	28	25	26.2	26	28

Quality control study of the prepared tablets

The prepared tablets from each formulation were subjected to the tablets quality control tests as drug content, weight uniformity, disintegration time, hardness and friability.

Weight variation test of tablet

20 tablets for weight variation as per USP weight variation test. Calculate the average weight and comparing the individual tablet weights to average weight. Standard deviation from mean weight was also calculated.

Friability testing

Friability was determined by weighing 10 tablets and placing them in a Roche type friabilator and rotating it at 25rpm for 4min. After that, tablets were weighed for their final weight and % friability was calculated.

% Friability was calculated by:

% Friability = [(Weight initial- Weight final)/ Weight initial] × 100

Hardness testing

Monsanto hardness tester used to measure the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. 3 tablets were used and force was measured in kg/cm^2.[11,12]

Drug content

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 100mg of losartan potassium was transferred to 100ml of methanol. then take 1ml of this

solution and transfer it in 100ml of methanol. Take 1ml of above solution and dilute it to 10ml with methanol. Take absorbance of sample in uv spectrophotometer at 234nm.

In vitro disintegration time

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration. The results are shown in table 5. This was determined as per I.P for all the formulations. All the formulations show disintegration time less than 2 minutes. Crospovidone has high water uptake and swelling pressure which leads to faster disintegration. Sodium starch glycolate shows disintegration time.

Table 5: Weight Variation, Hardness, friability, and Disintegration time of finished Losartan Potassium tablets.

Formulation code	Weight variation(mg)	Hardness(N)	Friability(%)	Dis-integration time	Drug content
F1	221.2 ±0.2	3.0	0.99	1.58	97.10
F2	251.1 ±0.3	3.1	0.64	1.56	96.20
F3	280.6 ± 0.2	3.0	0.78	1.48	96.01
F4	235.1 ± 0.3	3.2	0.93	1.50	93.34
F5	265.5 ± 0.4	3.2	1.35	1.52	94.50
F6	295.1 ± 0.4	3.0	1.01	1.55	91.02
F7	240.4 ± 0.3	3.6	1.32	1.40	92.10
F8	280.4 ± 0.1	3.5	0.92	1.30	95.78
F9	310 .6 ± 0.4	3.2	0.58	1.42	93.06

In vitro dissolution study

Drug release was assessed using a USP type II dissolution apparatus at 50rpm in 900mL 6.8 PH buffer maintained at 37ºC ± 0.5ºC Sample of 5ml was withdrawn at regular intervals and replaced with the same volume of prewarmed (37ºC ± 0.5ºC) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper and drug content in each sample was analyzed after suitable dilution, the amount of losaratan potassium dissolved was determined spectro photometrically at 234nm.[13]

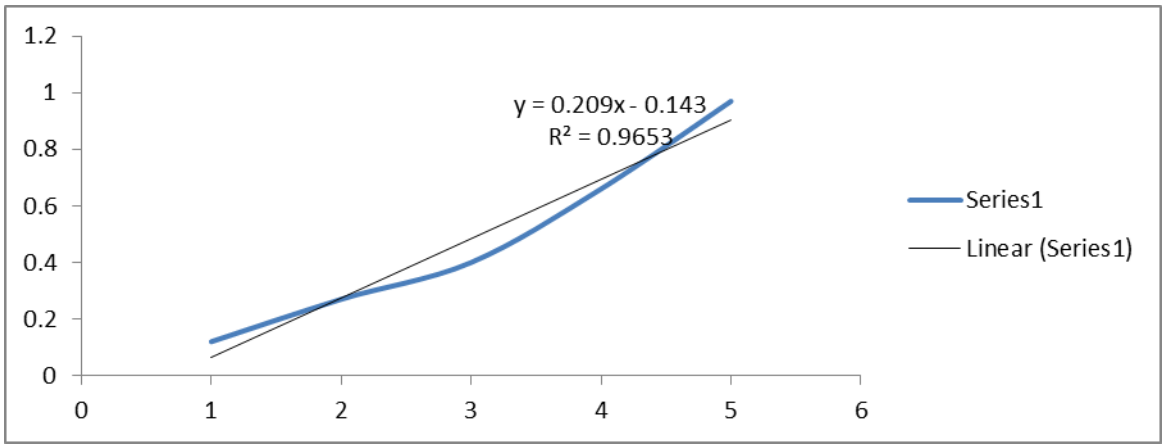

Fig. 3: Calibration curve of losartan potassium drug.

Table 6: Result of In-vitro dissolution study of sublingual tablets of Losartan Potassium.

Formulation code	After 5min % release	After 10min %release	After 15min %release	After 20min %release	After 25min %release
F1	13.05	29.02	48.19	72.84	98.71
F2	13.45	28.84	47.69	70.14	94.30
F3	10.8	23.2	38.43	57.64	78.11
F4	12.87	26.68	44.00	61.41	83.59
F5	12.42	27.45	43.56	60.34	81.89
F6	11.7	26.14	42.7	64.48	87.97
F7	11.24	24.83	41.43	59.79	81.79
F8	10.8	24.21	40.63	60.07	82.70
F9	12.10	28.43	46.79	68.57	92.28

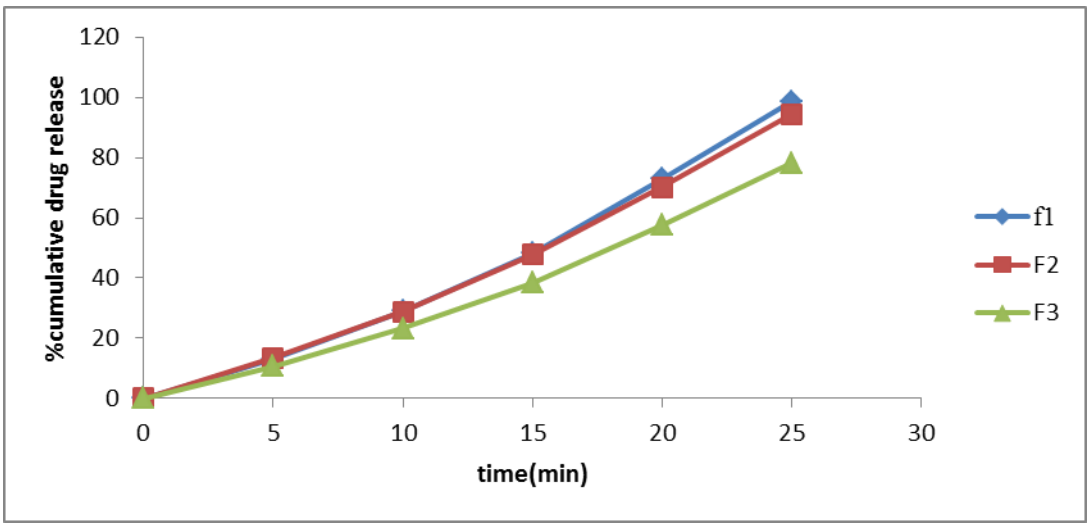

Fig. 4: In-vitro release of losartan potassium (F1-F3).

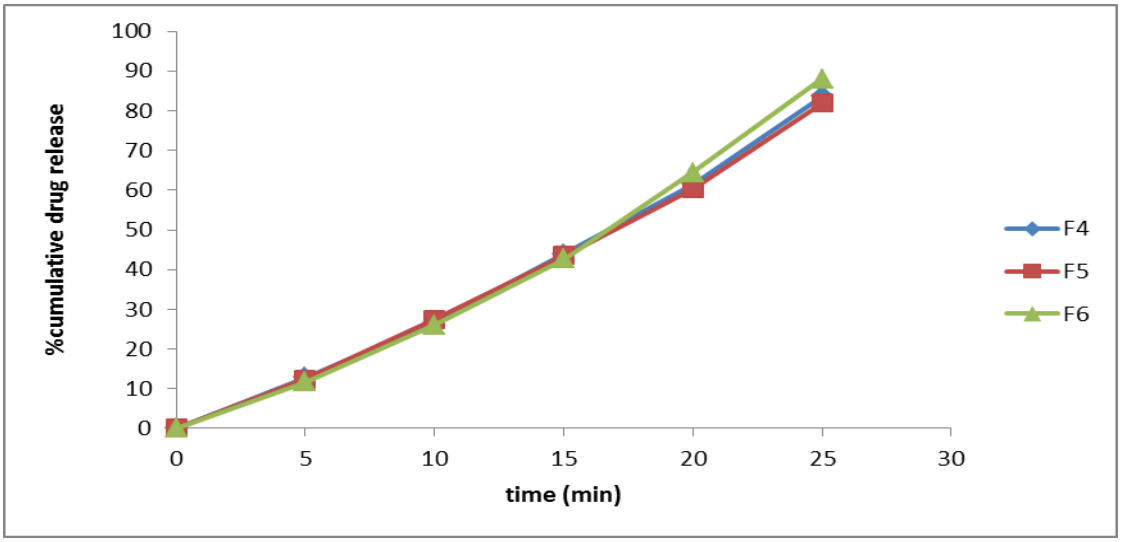

Fig. 5: In-vitro release of Losartan potassium (F4-F6).

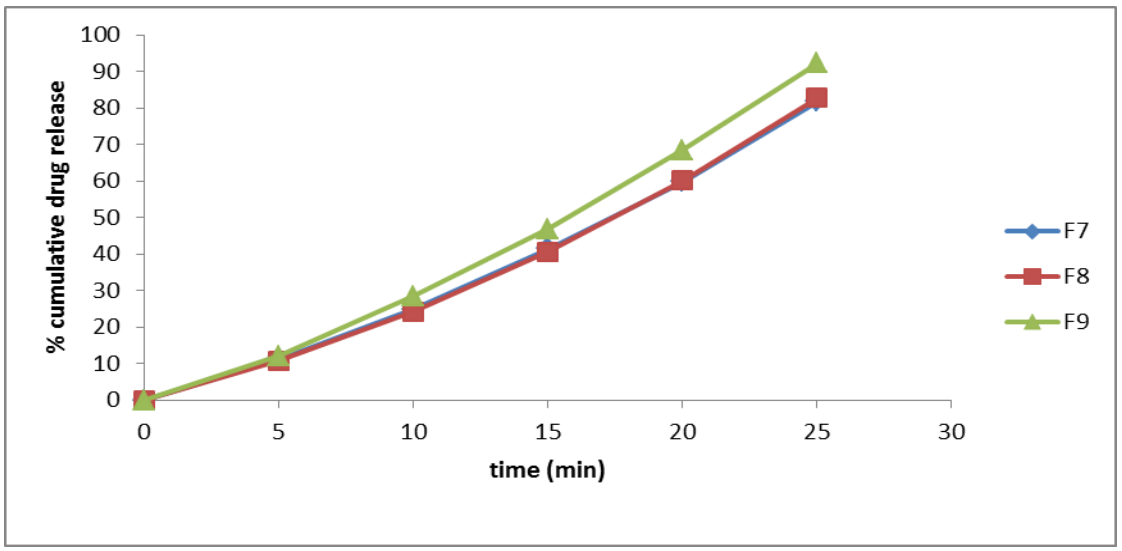

Fig. 6: In-vitro release of Losartan Potassium (F7-F9).

CONCLUSION

Sublingual formulation improves bioavailability, redused drug waste and dosing frequency. To formulate tablets of losartan potassium 3^2 full factorial design was imployed in which 2 factors were evaluated at 3 levels. The preformulation studies of Losartan potassium were performed; FT-IR analysis revealed that the super disintegrant sodium starch glycolate and excipients used were compatible with losartan potassium. Immediate release sublingual tablet of losartan potassium were successfully prepared by direct compression method. In conclusion, it could be determined that formulation f1 was the optimized products which possessed satisfactory quality parameters both in process parameters for granules and

parameters for finished products. A part from all the formulations, F1 formulation showed maximum drug release (98.71%).

REFERENCES

1. Behera A.K, Nayak A.K, Mohanty R, Barik B, Development and optimization of losartan potassium tablets.
2. Gokel Y, Satar S, Paydas S. A comparison of the effectiveness Of sublingual losartan, captopril and sublingual nifedipine in Hypertensive urgency. Tr J Med Sci., 1999; 29: 655-660.
3. Dos Paasos Maio VM, Dias CL, Bergold AM. Validation of an Isocratic HPLC assay of losartan potassium in pharmaceutical Formulations and stress test for stability evaluation of drug Substance. Acta Farm Bonaerense, 2005; 24(2): 250-255.
4. Mcintyre M, Caffe SE, Michalak RA, Reid JL. Losartan, an orally Active angiotensin (AT1) receptor antagonist: a review of its Efficacy and safety in essential hypertension. Pharmacol Ther., 1997; 74(2): 181-1948.
5. Goa KL, Wagstaff AJ. Losartan potassium: a review of its Pharmacology, clinical efficacy and tolerability in the Management of hypertension. Drugs, 1996; 51(5): 820-845.
6. M. S. Gambhire1, K. N. Gujar1, A. A. Vaidhya2. Formulation, Optimization and Evaluation of Immediate Release Tablet of Apixaban.
7. Brahmaiah B., Sasikanth K., Nama S., Suresh P., Patan A., "Formulation and dissolution study of valsartan immediate release tablets" Int. J. Inno. Drug Disc., 2013; 3(1): 33-38.
8. SL Rough, DI Wilson, DW York. Effect of solids formulation on the manufacture of high shear mixer agglomerates. Adv Powder Technol., 2005; 16: 145-169.
9. B Prakash Rao, Neelima Ashok Kottan, Snehith VS, Ramesh C. Development of Gastro retentive drug delivery system of cephalexin by using factorial design. ARS Pharmaceutics, 2009; 50: 8-24.
10. RA Garcia, RA Flores, CE Mazenko. Factors contributing to the poor bulk behavior of meat and bone meal and methods for improving these behaviors. Bioresource, 2007.
11. Rudnic, E.M., Schwartz, J.B. Remington: the science and practice of pharmacy. 21th ed. Lipponcott Williams and Wilkins, 2007.
12. Lachman, L., Liberman, H.A., Kaing, J.L. Theory and practice of industrial pharmacy. 4th ed. CBS Publishers and distributors, 2009.
13. Indian Pharmacopoeia. The Indian Pharmacopoeia Commission, Ghaziabad. Vol II, 2007.