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ENHANCEMENT OF DISSOLUTION RATE AND SOLUBILITY OF LOSARTAN POTASSIUM BY USING SOLID DISPERSION METHOD β-CYCLODEXTRIN AS CARRIER

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ABSTRACT

In the present study an attempt was made to increase the therapeutic effectiveness of losartan potassium,by increasing the solubility and dissolution rate via solid dispersion using β-cyclodextrin as carrier. Losartan potassium is an Antihypertensive agent but failed to show good therapeutic effect. Eight solid dispersion formulations of losartan potassium were prepared by using different drug:polymer ratios viz.1:2,1:2,1:3,1:4 by novel methods like Hot melt extrusion,Lyophilization.prepared solid dispersions were evaluated. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. All the solid dispersion formulations were compressed into orodispersible tablets with weight equivalent to losartan potassium of 25mg by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The prepared tablets were evaluated for its hardness, disintegration, weight variation, friability and invitro dissolution studies.The Infra Red spectra revealed that there is no incompatability between the drug and excipients. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 and F8 formulations showed maximum % drug release i.e.93.83%(Lyophilization), 97.10%(Hot melt extrusion method) within 45min.these are compared with pure drug which shows %drug release58.67%. The optimized formulations were subjected to different kinetic models.the formulations were found to follow zero order release. optimized formulations Were subjected to Accelerated stability study for 3 months according to ICH guidelines.The results found to satisfactory.

Considering all evaluation parameters and % drug release F8 formulation shown better % drug release compared with F4 formulation. hence F8 formulation considered as optimised formulation.

KEYWORDS: Losartan potassium, β-cyclodextrin, solid dispersion, Lyophilization, Hot melt extrusion. FTIR.

INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. This may be achieved by incorporating the drug in a hydrophilic carrier material obtaining products called solid dispersions. Depending on the properties of both, drug and carrier, and depending on their ratio, a solid solution or a solid suspension of the drug in the carrier material may be formed. The mechanisms involved in solubility and dissolution rate enhancement include transformation of unstable modifications into more stable ones or even into the amorphous state, reduction of particle size possibly to the molecular level as well as enhancement of wettability and solubility of the drug by the carrier material. However, if a solid dispersion represents a thermodynamically unstable system, it is prone to convert into a more stable state. Especially for substances according to the Biopharmaceutics Classification System, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug.

Losartan potassium is an effective Antihypertensive agent in the most of antihypertensive drugs.It is a selective, competitive angiotensin II receptor type 1 (AT_1) receptor antagonist, reducing the end organ responses to angiotensin II. Losartan potassium administration results in a decrease in total peripheral resistance (afterload) and cardiac venous return (preload) All of the physiological effects of angiotensin II, including stimulation of release of aldosterone, are antagonized in the presence of losartan potassium. There is a Reduction in blood pressure occurs.

The oral dosage forms have many advantages over other types of dosage forms like greater stability, accurate dosage, smaller bulk and easy production is possible. The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. Nearly 40% of identified

potential new drug by pharmaceutical industry are poorly water soluble. Poor water soluble compounds show decreased release rate & poor bioavailability. So Large dose is required to produce desirable effect but that may leads to toxicity of the drug. So best option for increasing release rate is improvement of the solubility through solid dispersion formulation approaches. Oral dispersible tablets of solid dispersion formulation leads to good bioavailability and dissolution rate.

MATERIALS AND METHODS

MATERIALS

Losartan and β-cyclodextrin were obtained as a gift sample from Natco labs Hyderabad. Magnesium stearate and sodium starch glycolate were obtained from SD fine chemicals, talc was obtained from merck specialities pvt ltd, microcrystalline cellulose obtained from signet Chemical Corporation.

METHODS FOR PREPARATION OF SOLID DISPERSION

Lyophilization Technique

Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

Melt extrusion method

The drug/carrier mix is typically processed with a twin screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.

PREPARATION OF ORAL DISPERSIBLE TABLETS

All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 8mm flat punch, B tooling. Each tablet contains 25 mg Losartan potassium and other pharmaceutical

ingredients. Total weight of tablet was found to be 100 mg by using direct compression method.

Table No 1: Formulation table showing various compositions

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	Pure drug
Losartan potassium (mg)	25	25	25	25	25	25	25	25	25
Sodium Starch Glycollate (mg)	20	20	20	20	20	20	20	20	20
Magnesium Stearate(mg)	8	8	8	8	8	8	8	8	8
Talc(mg)	2	2	2	2	2	2	2	2	2
Microcrystalline cellulose(mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total wt(mg)	100	100	100	100	100	100	100	100	100

Evaluation of tablets

The formulated tablets were evaluated for the following parameters.

1. Thickness

The thickness of the formulated tablets was measured by using Vernier caliper.

2. Weight variation

The formulated tablets were evaluated for uniformity of weight.20 tablets were weighed together and individually. From the total weight, average weight was calculated. Each tablet weight was then compared with average weight to make certain whether it is within acceptable limits or not.

%Deviation = Average weight – Individual weight X100

Average weight

3. Hardness

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Pfizer tablet hardness tester.

4. Friability

The Roche friability tester was used to determine friability of tablets.pre weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The % friability was calculated using the formula

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

5. Drug content

Losartan potassium 20 tablets are weighed and powdered. An accurately weighed quantity of powder is then dissolved in methanol and analyzed by preparing appropriate dilutions.

6. Invitro drug release studies

The release rate of Losartan potassium oro dispersible tablets was determined using USP Dissolution type II testing apparatus (paddle type). The dissolution test was studied in 900ml of phosphate buffer 6.8pH for 45min at 37±0.50c and at 50 rpm. Aliquots of 10ml were withdrawn hourly from the dissolution media for 45min and the samples were replaced with fresh dissolution medium. After filtration and suitable dilution amount of drug release was calculated from the calibration curve.

7. Kinetic Model Data Analysis

The dissolution data of optimised formulation was fitted to kinetic models i.e., zero order release rate kinetics, first order release rate kinetics, Higuchi release kinetics, Hixson-Crowell model and korsmeyer –peppas kinetic model to find out the drug release pattern and mechanism.

8. Stability studies

The best formulation was sealed in aluminium foil and kept in humidity chamber maintained at 40 ±2°c/ 75±5% RH for a period of three months.

RESULTS

Table No.2: Organoleptic properties of Losartan potassium

S.No	Properties	Results
1	Description	Powder
2	Taste	Tasteless
3	Odour	Odourless
4	Colour	White-off white

Solubility TEST

Table No. 3: solubility of drug

Water, 0.1 HCl ,p^H 6.8 buffer	Soluble
Chloroform	Slightly soluble
Ethanol,methanol,Acetone	Slightly soluble
Dichloromethane	Soluble

Table No 4: Pre-compression parameters					
Formulations	**Bulk Density (gm/cm^2)**	**Tap Density (gm/cm^2)**	**Carr's Index (%)**	**Hausner ratio**	**Angle Of Repose(Ɵ)**
F_1	0.41±0.03	0.49±0.07	18.18±0.01	1.22±0.006	27.91±0.21
F_2	0.47±0.01	0.52±0.04	14.58±0.03	1.17±0.008	28.32±0.27
F_3	0.50±0.02	0.54±0.05	13.79±0.02	1.16±0.003	29.34±0.32
F_4	0.46±0.08	0.55±0.04	16.36±0.01	1.19±0.002	26.71±0.24
F_5	0.50±0.07	0.58±0.02	13.59±0.04	1.14±0.004	29.34±0.26
F_6	0.47±0.09	0.55±0.03	14.54±0.05	1.17±0.002	28.23±0.33
F7	0.42±0.04	0.57±0.01	16.31±0.07	1.12±0.001	26.21±0.41
F8	0.40±0.07	0.52±0.05	18.12±0.06	1.18±0.01	26.30±0.30

Mean± SD, n = 3

Table No 5: Pre-compression parameters					
Formulations	**Bulk Density (gm/cm^2)**	**Tap Density (gm/cm^2)**	**Carr's Index (%)**	**Hausner ratio**	**Angle Of Repose(Ɵ)**
F_1	0.41±0.03	0.49±0.07	18.18±0.01	1.22±0.006	27.91±0.21
F_2	0.47±0.01	0.52±0.04	14.58±0.03	1.17±0.008	28.32±0.27
F_3	0.50±0.02	0.54±0.05	13.79±0.02	1.16±0.003	29.34±0.32
F_4	0.46±0.08	0.55±0.04	16.36±0.01	1.19±0.002	26.71±0.24
F_5	0.50±0.07	0.58±0.02	13.59±0.04	1.14±0.004	29.34±0.26
F_6	0.47±0.09	0.55±0.03	14.54±0.05	1.17±0.002	28.23±0.33
F7	0.42±0.04	0.57±0.01	16.31±0.07	1.12±0.001	26.21±0.41
F8	0.40±0.07	0.52±0.05	18.12±0.06	1.18±0.01	26.30±0.30

Mean± SD, n = 3

Table No.6: Percentage drug release using lyophilization method

Time in minutes	**F1% drug release**	**F2 % drug release**	**F3 % drug release**	**F4% drug release**	**Pure drug**
0	0	0	0	0	0
5	27.93±0.12	33.28±0.19	31.72±0.13	42.38±0.01	9.78±0.19
10	45.48±0.15	50.37±0.18	43.26±0.11	59.31±0.24	15.20±0.15
15	57.84±0.11	63.34±0.20	58.89±0.18	70.35±0.44	26.91±0.22
20	65.35±0.10	69.83±0.26	63.72±0.25	80.13±0.32	34.18±0.42
25	70.81±0.13	73.34±0.29	69.64±0.22	85.76±0.20	39.73±0.21
30	75.85±0.19	79.15±0.33	77.89±0.17	92.46±0.55	47.16±0.10
45	83.13±0.21	85.13±0.43	86.65±0.33	93.83±0.26	58.13±0.11

MEAN ±SD N=3

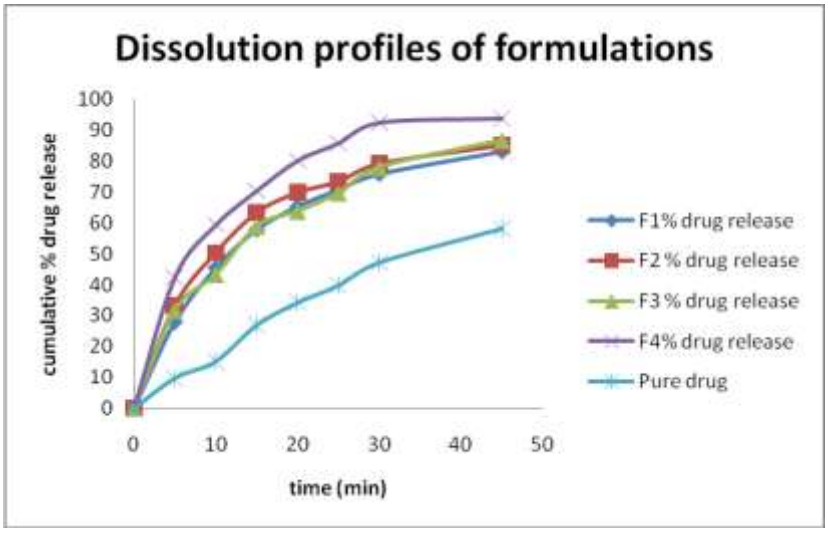


Fig No 1: Dissolution profile of formulations prepared with β-cyclodextrin as carrier byLyophilization method

Percentage Drug Release Using Hot melt extrusion process

Table No.7: Percentage drug release using Hot melt extrusion method.

Time(mins)	%drug release of F5	%drug release of F6	%drug release of F7	%drug release of F8	Pure drug
0	0	0	0	0	0
5	49.37±0.05	54.07±0.18	50.37±0.41	52.28±0.25	9.78±0.16
10	56.73±0.03	61.64±0.17	59.18±0.05	59.21±0.29	15.20±0.11
15	66.94±0.12	69.68±0.26	67.16±0.06	70.13±0.42	26.91±0.19
20	71.12±0.29	73.10±0.20	75.22±0.22	76.21±0.49	34.18±0.26
25	79.82±0.31	84.46±36	83.12±0.35	84.31±0.53	39.73±0.29
30	86.15±0.24	87.38±0.39	86.45±0.51	89.91±0.64	47.16±0.37
45	89.12±0.33	91.46±0.41	92.14±0.63	97.10±0.59	58.13±0.46

MEAN±SD N=3

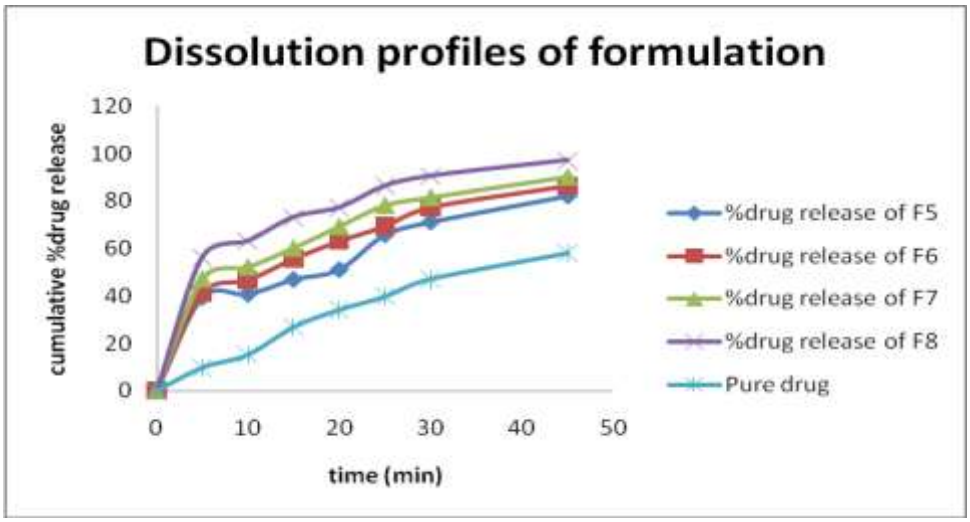


FIGURE No. 2: Dissolution profiles of formulations F5,F6,F7,F8 and pure drug

Table No.8: Stability studies of Formulation F4(Mean±SD,n= 3)

S.No	Evaluation parameters	Initial amount	After 3 months
1.	Weight variation(mg)	101±1.20	102±0.21
2.	Friability(%)	0.47±0.01	0.49±0.2
3.	Thickness(mm)	1.58±0.06	1.58±0.3
4.	Hardness(kg/cm^2)	2.6±0.3	2.9±0.2
5.	Drug content(%)	99.34±0.3	98.32±0.6

STABILITY STUDIES

Table No.9: Stability studies of Formulation F8 (Mean±SD, n=3)

S.No	Evaluation parameters	Initial amount	After 3 months
1.	Weight variation(mg)	104±3.1	105± 2.8
2.	Friability(%)	0.34±0.01	0.36±0.2
3.	Thickness(mm)	1.56±0.07	1.56±0.06
4.	Hardness(kg/cm$^{2)}$	2.6±0.9	2.8±0.8
5.	Drug content(%)	99.44±0.6	99.42±0.9

COMPARATIVE DISSOLUTION STUDY OF FORMULATION F4 AND F8

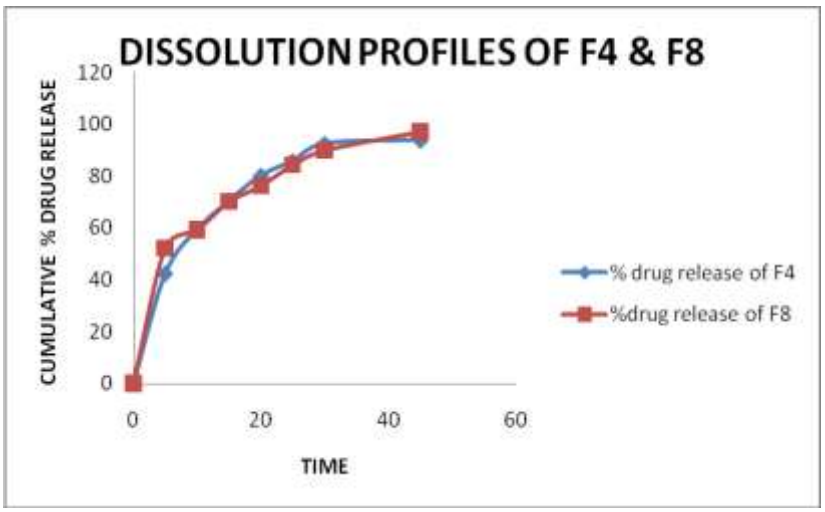
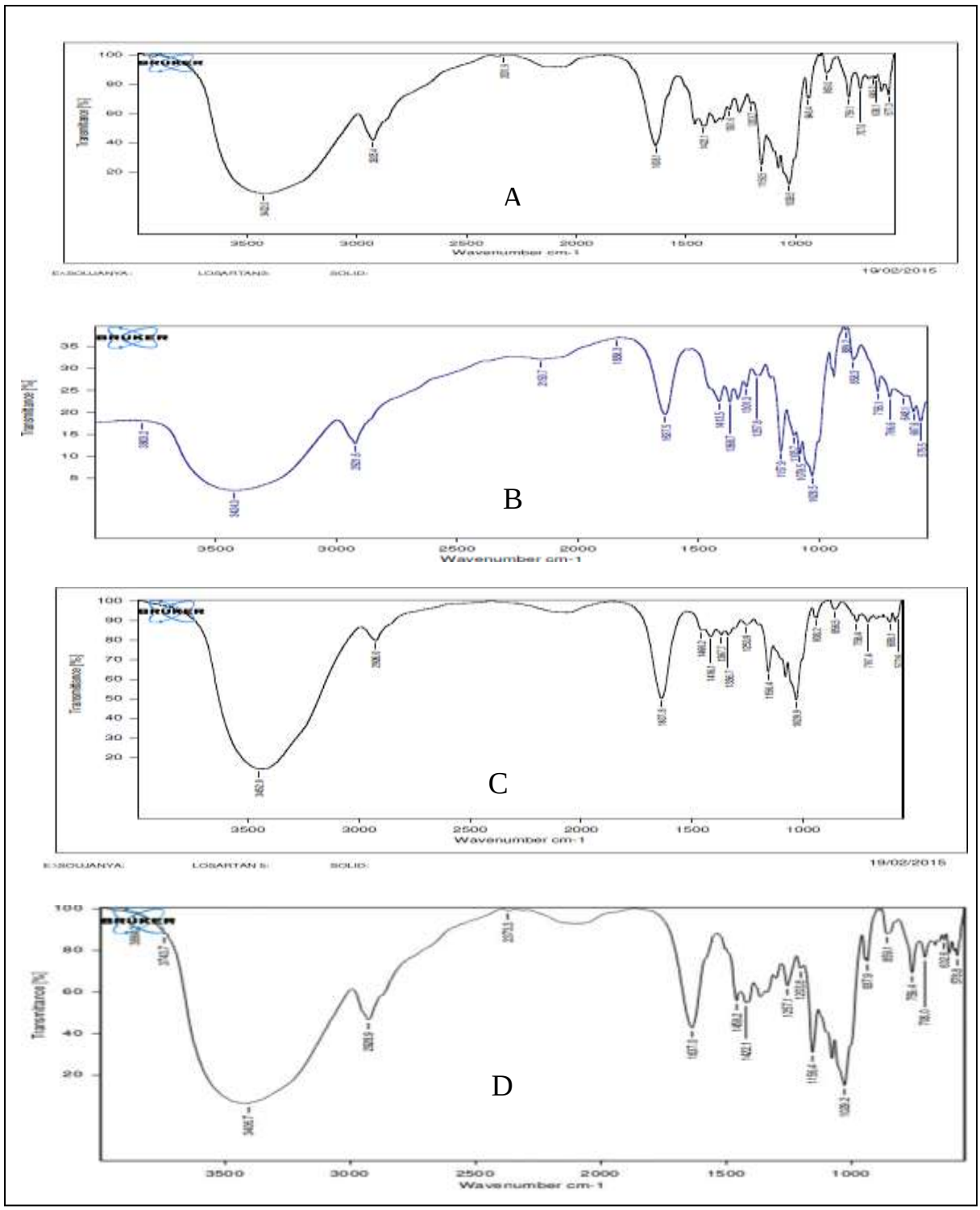


FIGURE No. 3: Comparative Dissolution profiles of formulations F4 and F8

Table No 10: Comparative dissolution studies formulation F4 and F8.

Time	%drug release of F4	% drug release of F8
0	0	0
5	42.38	52.28
10	59.31	59.21
15	70.35	70.13
20	80.13	76.21
25	85.76	84.31
30	92.46	89.91
45	93.83	97.1

Drug excipient compatability studies of Losartan potassium Orodispersible tablets.



A=FTIR spectra of Losartan potassium, B= β-cyclodextrin, C= Losartan+β-cyclodextrin, D=Optimized formulation

CONCLUSION

Losartan potassium is belongs to class II drugs, that is, characterized by low solubility and low permeability therefore, the enhancement of its solubility and dissolution profile is

expected to significantly improve its bioavailability and reduce its side effects. The precompression blends of Losartan were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** The precompression blend of all the batches indicates well to fair flowability and compressibility. Among all the formulations F8 formulation, showed good result that is 97.10 % in 45 minutes. As the concentration of polymer increases the drug release was decreased.

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