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Formulation and evaluation of fast dissolving tablets of losartan potassium by using superdisintegrant crosspovidone and its kneading mixture

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Abstract
Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. Superdisintegrants are agents added to tablet formulations to promote the breakup of the tablet into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug. A disintegrant used in granulated formulation processes can be more effective if used both "intragranularly" and "extragranularly" thereby acting to break the tablet up into granules and having the granules further disintegrate to release the drug substance into solution. Losartan potassium tablet were designed with a view to enhance the patient compliance and provide a quick onset of action. Losartan potassium is used in the management of hypertension. It has low bioavailability due to its first pass metabolism. The main objective of the present work was to enhance the solubility, dissolution rate and bioavailability of Losartan potassium by preparing its kneading mixture with crosspovidone in order to develop its fast dissolving tablets. In the first step crosspovidone was examined for suitability as solubility enhancer in kneading method. The characteristics of different kneading mixture samples were compared to the respective physical mixtures and active pharmaceutical ingredient to access the effect of various processes. Further it was evaluated which technique is better. The solid state of kneading mixture was evaluated with infrared spectroscopy and was correlated with *in-vitro* dissolution behavior.

Keywords: Fast dissolving tablets, Crosspovidone, Losartan potassium, Kneading mixture

Introduction
Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oral route of drug administration have wide acceptance of up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage form are being tablets and capsules and important drawback of these dosage forms for some patients however is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablets when water is not available in the case of motion sickness and sudden episodes of coughing during the common cold, allergic conditions and bronchitis. This dosage forms dissolve or disintegrates in the patient's mouth within 15 sec to 3 min without the need of water or chewing. Despite various terminologies used, Fast dissolving tablet are here to offer unique form of drug delivery with many advantages over the conventional oral solid dosage form. The basic approach used in development of FDT is the use of super disintegrants such as Crosspovidone, crosscarmellose, sodium starch glycolate etc. that provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and due to pre-gastric absorption of saliva

Advantages of FDTs
- Administered without water, anywhere, any time
- Leave minimal or no residue in mouth after administration
- Rapid drug therapy intervention.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- Administration to the patients who cannot swallow, such as the elderly, stroke victims.
- Bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- Achieve increased bioavailability due to absorption through pregastric region of drugs from mouth, pharynx & Esophagus.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension, and life cycle management

Material and Methods

Preparation of kneading mixture

A batch of kneading mixture blend of Losartan potassium with crosspovidone (1:1.5) was prepared. The weighed quantity of Losartan potassium and Crosspovidone in selected ratios (w/w) was placed in mortar and then the mixture was kneaded with small volume of water for 45 min to produce a homogenous dispersion. Once homogeneous slurry was obtained, sample where dried in oven at 40-45 °C until dryness. The dispersions after drying were pulverized using a glass mortar and pestle. The pulverized mass then shifted through sieve no.90 to obtain a uniform particle size and stored in a desiccator at room temperature until further use. Five blends of kneading mixture of Losartan potassium (1:1.5) by kneading method were prepared by wet granulation method using formula as shown in Table-1.

Optimization of Kneading Mixture

On the basis of solubility and % drug release profile, the Losartan potassium kneading mixture ratio 1:1.5 have maximum solubility and *in-vitro* release profile. Hence formulation of kneading mixture with crosspovidone ratio 1:1.5 was selected for further study.

Preparation of fast dissolving tablets

Losartan potassium tablets were prepared by wet granulation method containing kneading mixture equivalent to 200 mg. The granules were compress into tablets of average weight 200 mg containing 50 mg of Losartan potassium on a 16 station rotary tablet machine tooling 7mm flat round punch.

Table 1: Composition for fast dissolving tablets (mg/tab)

Ingredients(mg)	A_1	A_2	A_3	A_4	A_5
Kneading mixture (1:1.5)	16.6	16.6	16.6	16.6	16.6
Microcrystalline Cellulose Phosphate	139	137	135	133	131
Dicalcium phosphate	20.8	20.8	20.8	20.8	20.8
Maize starch	13.2	13.2	13.2	13.2	13.2
Magnesium stearate	2.6	2.6	2.6	2.6	2.6
Talc	2.6	2.6	2.6	2.6	2.6
Sodium saccharine	2.6	2.6	2.6	2.6	2.6
Orange flavor	2.6	2.6	2.6	2.6	2.6
Crosspovidone	-	2	4	6	8

Results and Discussion

Determination of absorption maxima (λ max) and preparation of calibration curve of Losartan potassium in different media

UV scan of Losartan potassium was done in 0.1N HCl, distilled water and pH 7.4 phosphate buffer, λ max at 205 nm was observed.

Drug Excipients compatibility study

Drug was subjected to the compatibility study with different excipients and polymer at 25 °C and 40 °C (physical compatibility) was observed for physical changes (color change, liquification, lump formation and odor). After two weeks there was no physical change was observed in the vials containing drug and excipients. The compatibility of polymers and excipients were selected namely crosspovidone, talc, magnesium stearate, microcrystalline cellulose phosphate, Dicalcium phosphate, starch, Sodium saccharine, Pineapple flavor.

Solution state stability study

The solution state stability of Losartan potassium was done in 0.1N HCl, Phosphate buffer pH 7.4 and distilled water. The change in initial absorbance of drug solution was measured in different media noted at different time points (0,2,4,6,24 and 48 hours) and it was observed that there was no stability problem of drug solution in different media at various time intervals.(Shown in Table-2).

Saturation solubility study of Losartan potassium

Saturation solubility study of Losartan potassium was performed in different media i.e. 0.1N HCl, Phosphate buffer 7.4 and distilled water and it shows that as increases stability of Losartan potassium as show in Table-3, as 0.1NHCl > Phosphate buffer 7.4 > distilled water

Table 2: Solution state stability over 48 hat conc. 20 µg/ml

Time (Hrs.)	Distilled water	pH 7.4 PB	0.1N HCL
0	00	00	00
2	0.945	0.750	0.720
4	0.946	0.751	0.719
6	0.945	0.752	0.721
24	0.944	0.749	0.721
48	0.947	0.753	0.722

Evaluation of Solid Dispersion

FT-IR spectroscopy analysis

Interactions between drug and carrier often lead to identifiable changes in FT-IR profile of the solid dispersion. The drug and solid dispersion were subjected to FT-IR analysis in order to evaluate possible solid –solid interaction between drug and crosspovidone. The data was compared with standard spectrum of drug and the peaks associated with specific structural characteristics of the molecule and their presence/absence in crosspovidone as well as solid dispersion was noted. The FT-IR spectra showed little shift in the characteristic peaks. This means that the drug may be present in partially amorphous form in solid dispersion and degree of chemical interaction between drug and polymer was low. This hydrogen bonding between drug and crosspovidone may prevent crystallization of the drug in solid dispersion.

The FTIR spectra of Losartan potassium and solid dispersion of Losartan potassium with crosspovidone were obtained shown in Figure-1 and 2 and interpreted in Table-4.

Table 3: Saturation solubility study of Losartan potassium

S.No.	Media	Absorbance	Conc.	Dilution	Solubility
		At 205 nm	µg/ml	Factor (DF)	(mg/ml)
1.	Water	0.38	7.5	100	0.75
2.	pH 7.4	0.215	31.5	100	3.15
3.	0.1N HCl	0.350	63.1	100	6.31

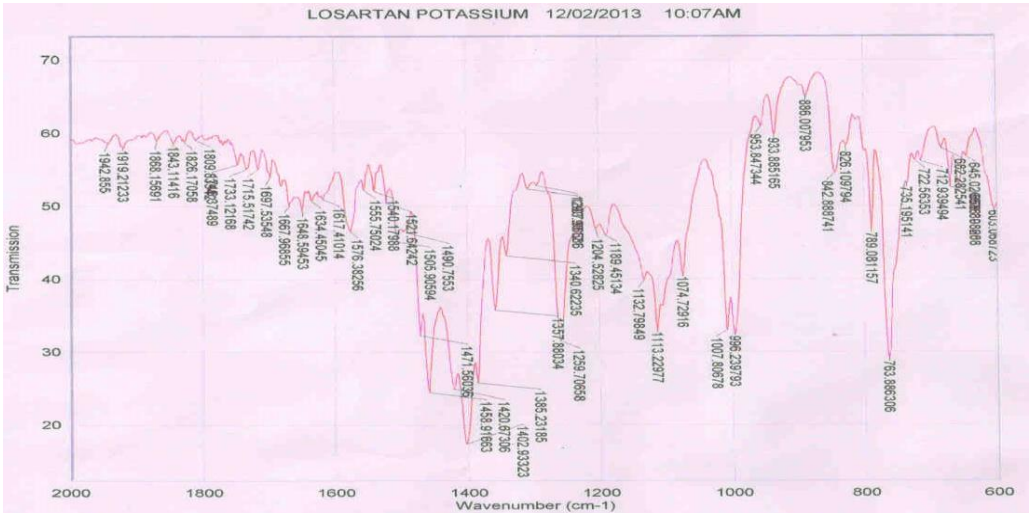

Fig 1: FT-IR spectra of Losartan potassium

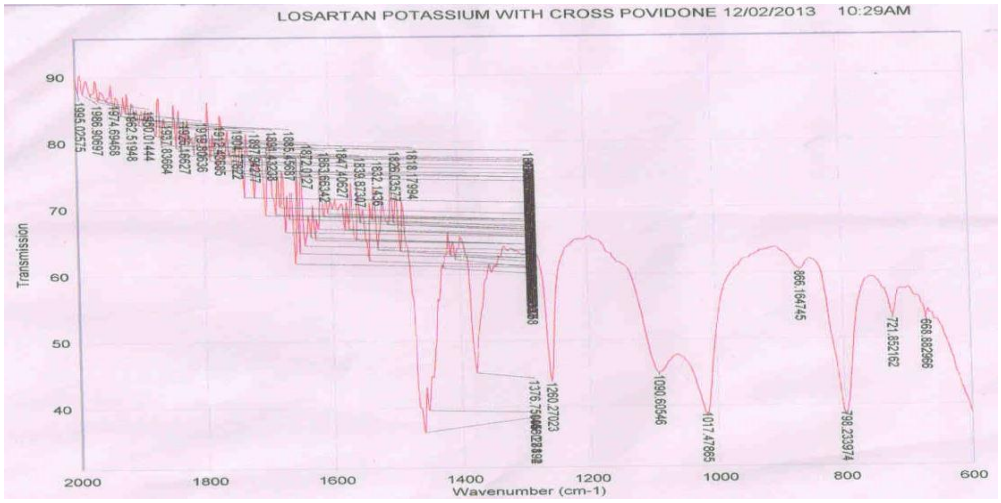

Fig 2: FT-IR spectra of kneading mixture of Losartan potassium: Crosspovidone (1:1.5)

Table 4: Interpretation of FTIR spectra of Losartan potassium

Group	IR peaks (cm^1)
-CH^2 Stretching	1458.23
- C=N Stretching	1260.52
Aromatic Ring	763.84

In-vitro dissolution studies

Table 5: Dissolution data of physical mixture (Losartan Potassium: crosspovidone)

Time (min.)	% Drug Release		
	1:05 Ratio	1:1 Ratio	1:1.5 Ratio
0	0	0	0
5	11.15±0.25	13.21±0.12	15.21±0.14
15	24. 26±0.26	27.13±0.15	30.32±0.13
25	31.32±0.98	34.24±0.17	37.25±0.26
35	40.23±1.25	43.35±0.11	53.32±0.23
45	51.30±1.25	56.33±0.14	60.14±0.21
60	57.16±1.48	63.21±0.13	69.34±0.19

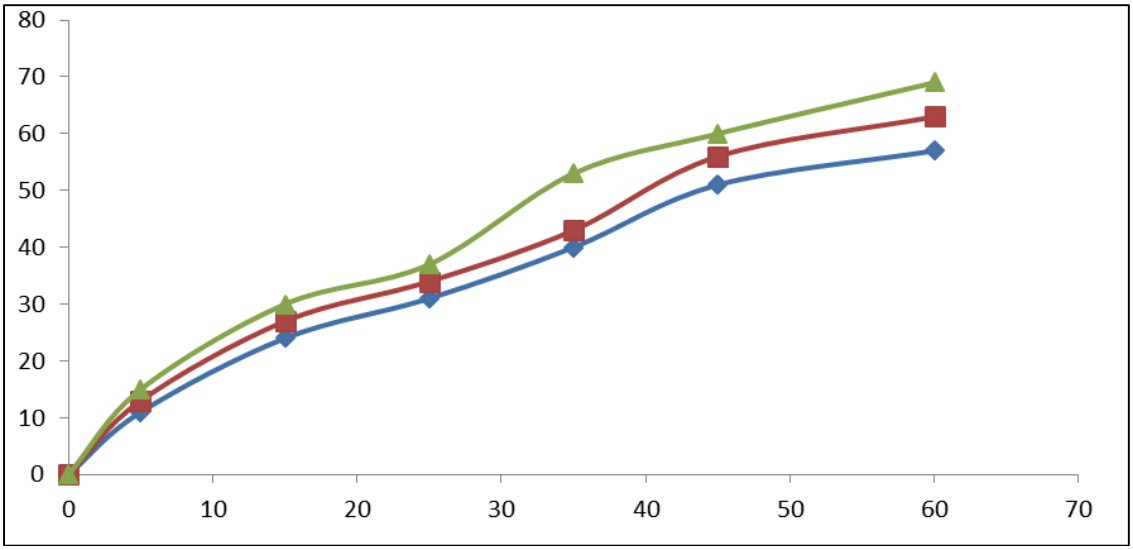

Fig 3: Dissolution profile of physical mixture (Losartan potassium: crosspovidone)

Table 6: Dissolution data of kneading mixture by kneading Method Losartan Potassium: Crosspovidone)

Time (min.)	% Drug Release		
	1:05 Ratio	1:1 Ratio	1:1.5 Ratio
0	0	0	0
5	28.51±0.25	35.14±0.17	54.12±0.14
15	39.02±0.26	44.33±0.13	72.33±0.15
25	53.33±0.98	58.46±0.18	84.54±0.19
35	62.30±0.17	79.35±0.15	94.25±0.21
45	73.35±0.25	84.34±0.14	98.12±0.28
60	83.18±0.43	93.27±0.12	99.46±0.32

Table 7: Pre-compression Parameters

Formulation Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio (Hr)	Angle of Repose (θ)
A_1	0.447	0.530	15.66	1.18	27°
A_2	0.445	0.527	15.47	1.18	27°
A_3	0.444	0.533	16.69	1.20	26°
A_4	0.497	0.592	16.04	1.19	25°
A_5	0.499	0.594	16.56	1.34	25°

Post Compression Parameters

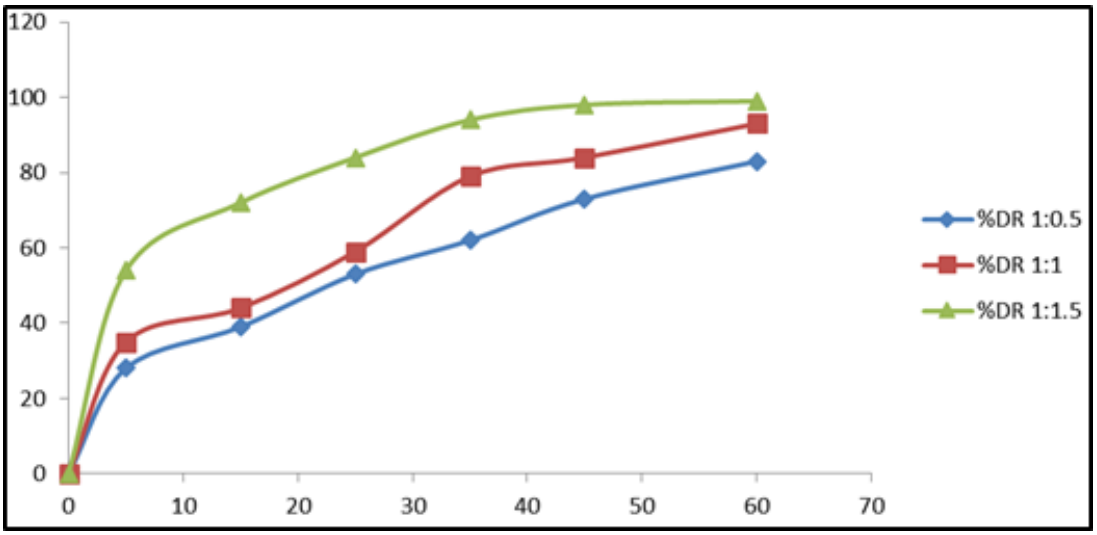

Fig 4: Dissolution profile of kneading mixture

Table 8: Post Compression Parameters

Formulation Code	Weight Variation	Drug content (%) (in 5 minutes)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec.)
A_1	Pass	85.13±0.29	3.2±0.05	0.35±0.36	9±0.28
A_2	Pass	89.22±0.18	3.2±0.09	0.44±0.24	8±0.29
A_3	Pass	92.14±0.23	3.1±0.06	0.38±0.36	8±0.29
A_4	Pass	94.17±0.19	3.1±0.36	0.43±0.23	7±0.29
A_5	Pass	98.16±0.29	3.0±0.08	0.36±0.17	6±0.35

Table 9: Drug release from different formulations

Time (minutes)	% Drug released from A_1	% Drug released from A_2	% Drug released from A_3	% Drug released from A_4	% Drug released from A_5
0	0	0	0	0	0
3	61.12±0.87	65.18±0.53	69.22±0.87	74.21±0.87	78.21±0.87
5	85.13±0.79	89.22±0.78	92.14±0.79	94.11±0.79	98.13±0.79
7	91.32±0.26	95.23±0.26	97.34±0.26	98.31±0.26	99.13±0.88
9	98.29±0.58	99.19±0.58	99.22±0.58	99.29±0.58	99.18±1.64
11	99.38±1.42	99.18±0.37	99.28±1.42	99.38±1.42	99.29±0.38
13	99.19±0.45	99.24±0.39	99.19±0.45	99.19±0.45	99.39±0.39

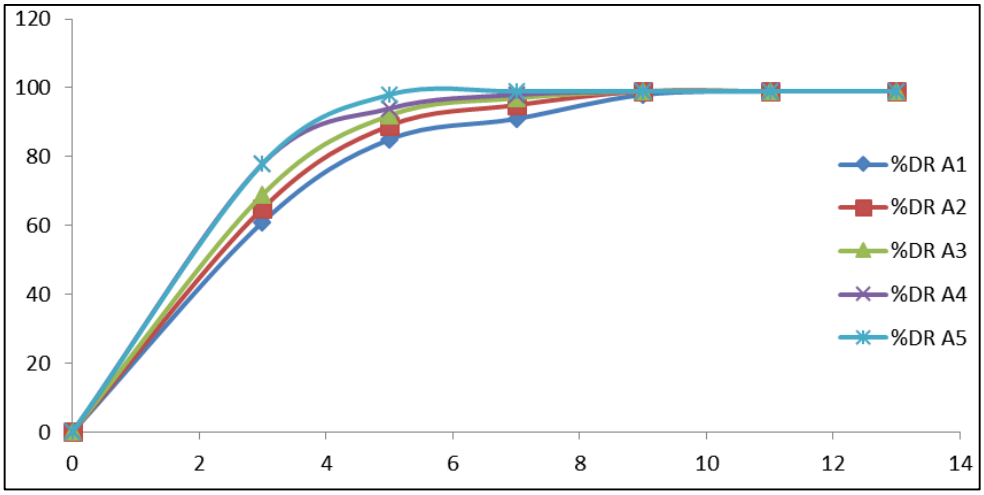

Fig 5: Dissolution profiles of compressed tablets

Comparison between prepared FDTs and Commercial tablets of Losartan Potassium.

In-vitro drug release of A_5 formulation was compared with drug release of commercial tablets which is shown in Table-10

Table 10: Percent drug release from prepared fast dissolving tablets and Commercial Tablets of Losartan potassium**.**

Time (min)	Cumulative % drug release from prepared FDTs	Cumulative % drug release from commercial tablets
0	0	0
3	78.21±0.87	16.17±0.65
5	98.13±0.79	32.31±0.35
7	99.13±0.88	58..35±0.24
9	99.18±0.64	67.26±0.69
11	99.29±0.38	82.18±0.72
13	99.39±0.39	87.19±0.75

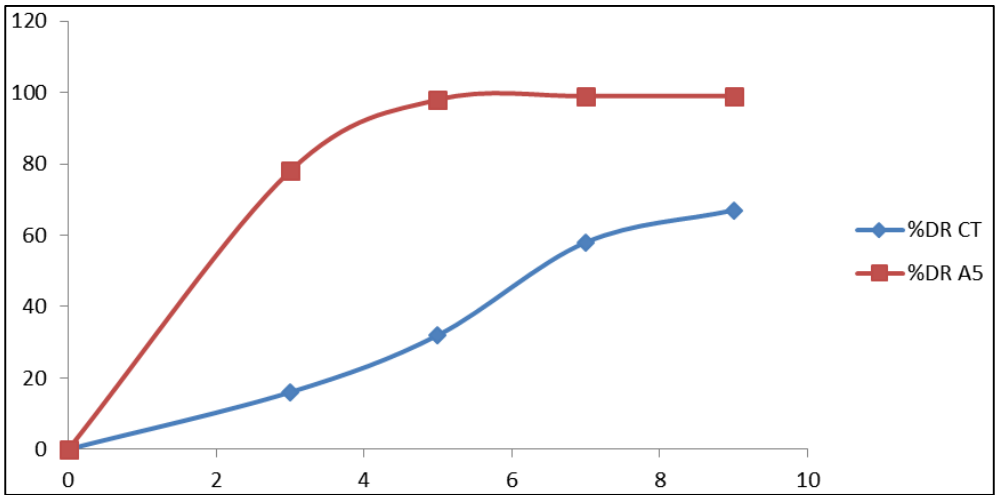

Fig 6: Dissolution Profile of fast dissolving tablets and commercial tablets of Losartan potassium

Conclusion

The blend of optimized kneading mixture i.e. with Crosspovidone in ratio of 1:15 by kneading method was formulated using wet granulation method. The prepared granules were evaluated for parameters like Bulk density, Tapped density, Compressibility index, Angle of repose and Hausner's ratio. On the basis of above parameters the granules found to be having good flow properties. The compressed tablets were evaluated for parameters like Weight variation, Drug content, Hardness, Friability, and Disintegration time and Dissolution profile. The dissolution profile of both Five formulation was done which shows that A_5 formulation possess better dissolution of 99.13±0.88 in 7 minutes because of crosspovidone.

The dissolution studies of prepared FDTs and commercial tablets were done. The Fast dissolving tablets prepared by above methods possessed ideal characteristics of disintegration time of 6 second and 99.13±0.88% drug release in 7 minutes as compared to commercial tablets which shows only 87.19±0.75 drug release in 13 minutes. This means that the prepared FDTs have fast dissolution and onset action as compared to the commercial tablets available in the market.

The objective of this project work was to formulate and characterize kneading mixture for the enhancement of dissolution and solubility of a drug. Formulated tablet dosage form proved its significance for enhancing the dissolution and solubility of drug (Losartan potassium)

References

1. Abogner RH, Wilkosz MF. Fast dissolving tablet- new dosage convenience for patients US pharm 2002; 27:34-43.
2. Ahad HA, Anuradha CM. Novel approach in formulation and evaluation of mouth dissolving tablets of ondansetron hydrochloride. International Journal of Applied Biology and pharmaceutical technology. 2010; 1(2):582-88.
3. Bhandari S, Mittapalli RK, Gannu R, Rao YM. Orodispersible tablets: an overview, Asian J Pharm. 2008; 1:1-11.
4. Bhowmik D, Chiranjib B, Krishnakanth, Pankaj, Chandira MR. Fast Dissolving Tablet: An Overview, Journal of Chemical and Pharmaceutical Research. 2009; 1(1):163-177.
5. Divate S, Kavitha K, Sockan GN. Fast Disintegrating Tablets an emerging trend, International Journal of Pharmaceutical Sciences Review and Research. 2011; 6(2):115-116.
6. Indurwade NH, Rajyaguru TH, Nakhat PD. Novel approach- fast dissolving tablets Indian Drugs 2002; 39(8):405-9.