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Development of fast dissolving tablets of losartan potassium using Kollidon CL-SF

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ABSTRACT

The goal of this study was to formulate and evaluate fast dissolving tablets (FDTs) of Losartan potassium so as to overcome swallowing difficulties. The key to develop successful FDT formulations by the direct compression method is to select the right superdisintegrant and compatible excipients depending on FTIR and DSC studies. The FDTs were designed using superdisintegrant such as Kollidon CL-SF in different concentrations by direct compression technique. The FDT formulations were evaluated for physicochemical characteristics including powder flowability, appearance, thickness, uniformity of weight, hardness, friability, in-vitro disintegration time, wetting time, water absorption, content uniformity and in-vitro drug release studies. All the formulations showed satisfactory physicochemical characteristics with disintegration time less than three minutes. The selected formulations were subjected to short term stability studies at 40±2°C and 75±5% RH for a period of 3 months. Thus, this work helped in understanding the effect of formulation processing variables especially different concentrations of super disintegrating agent such as Kollidon CL-SF on the disintegration time.

Keywords: Losartan potassium, Fast Dissolving Tablets, Kollidon CL-SF and Direct compression.

INTRODUCTION

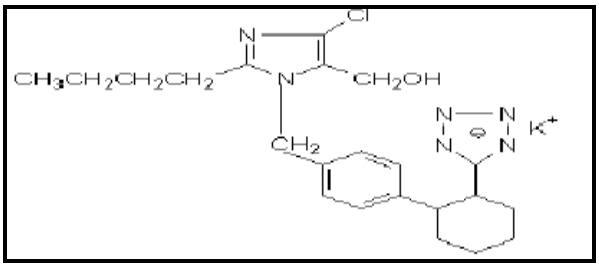
Physical problems with swallowing (Dysphagia) can occur at any age. It is particularly prevalent in the elderly and those with dementia, whereas refusal to swallow is often encountered in geriatrics, pediatrics and psychiatric patients. However, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience and patient acceptability. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy. Because of the increase in the average human life span and decline in swallowing ability with age, oral conventional tablet administration to such patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of fast dissolving or oro-dispersible dosage forms, which do not require water to aid swallowing. The dosage forms are placed in the mouth, allowed to dissolve or disperse in the saliva and then swallowed in the normal way [1]. The faster the drug into solution, quicker is the absorption and onset of clinical effect. As the tablets disintegrate inside the mouth, drug may be absorbed in the buccal, pharyngeal and gastric regions. Pre-gastric drug absorption avoids the first-pass metabolism and the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism. Thus, rapid drug therapy intervention and increased bioavailability of drug is possible [2]. The fast dissolving solid dosage form turns into a soft paste or liquid form on administration. This kind

of property in dosage form can be added by inclusion of right superdisintegrant and excipients which play a key role in formulation of fast dissolving tablets. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability. Excipients with improved functionality can be obtained by developing new chemical excipients, new grade of existing materials and new combination of existing materials. One such approach for improving the functionality of excipients is, inclusion of Kollidon CL-SF (new grade of existing materials) as a superdisintegrant [3].

Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets after putting on tongue, thereby release the drug in saliva. Thus, type, concentration and efficiency of superdisintegrants to a large extent affect the disintegrant properties [4].

Fast onset of action is a major concern in the treatment of hypertension. As the patients with sudden increased blood pressure, have markedly reduced function ability and extremely restless, in such cases rapid onset of action is of prime importance. So the patients would be benefited from acute treatment by using proposed FDT drug delivery system. FDTs can offer advantages over older formulations in terms of convenience, side effect profile, efficacy and fast onset of action [5].

Losartan potassium is an antihypertensive drug belongs to the category of Angiotensin II-receptor antagonist and is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its molecular formula is $C_{22}H_{22}ClKN_6O$ with half life of 2 hr and bioavailability of 33% due to extensive first pass hepatic metabolism.



Losartan Potassium

It blocks vasoconstriction and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the angiotensin II receptor (AT1 receptor) in vascular smooth muscle and adrenal gland [6]. Losartan potassium has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, selectivity and tolerability [7].

Thus, main objective of the present study was to formulate and evaluate fast dissolving tablets of Losartan potassium by simple and cost effective direct compression methods.

EXPERIMENTAL SECTION

MATERIALS

Losartan potassium (IP) and Kollidon CL-SF were gift samples provided by Karnataka Antibiotics and Pharmaceuticals Ltd, Bangalore. Microcrystalline cellulose (Avicel 102 PH) was procured from S.D Fine Chem. Ltd, Mumbai and Lactose, Aerosil & Magnesium stearate were procured from Loba Chemie Pvt Ltd, Mumbai. Neotame and Vanilla were gift samples obtained from Karnataka Antibiotics and Pharmaceuticals Ltd, Bangalore. All other chemicals used were of pharmaceutical grade.

METHODS

1)Preformulation Studies of Losartan potassium:

In the first stage of this study, physicochemical characteristics of Losartan potassium powder including organoleptic properties, flowability, compressibility and powder purity were investigated in the standard way [8&9].

2)Drug-excipient Compatibility:

FTIR: Pure drug and physical mixture of drug & super disintegrant (1:1) were subjected for FTIR analysis using Fourier Transformer Infra Red Spectrophotometer (8300, Shimadzu, Japan).The samples were prepared on KBr-press and scanned over wave number range of 4000 to 400 cm^{-1} and the obtained spectra were analyzed for functional groups of drug and interactions with super disintegrant.

Differential Scanning Calorimetry: This study was done to evaluate the compatibility of Losartan potassium with super disintegrant. Differential Scanning Calorimetry was used for screening. The specified samples were hermetically sealed in a flat bottomed aluminum pans and heated in the differential scanning calorimeter (Perkin-Elmer Thermal Analysis) in an atmosphere of nitrogen and the rate of flow was 25 ml/min. A temperature range of 0°C to 250°C was used and the heating rate was 10°C/min.

3)Formulation of Fast Dissolving Tablets of Losartan potassium:

Fast dissolving tablets (FDTs) of Losartan potassium were prepared by direct compression method using different concentration of super disintegrant as shown in **Table No-1**. The drug and super disintegrant selected were passed through 60-mesh sieve and mixed in a mortar with a pestle to obtain uniform mixing. The blend obtained was then lubricated by adding required quantity of magnesium stearate. The tablets were compressed using 8 mm diameter punches to an average weight of 200 mg in "Tablet punching machine (Rimek mini press-1) (10 station) Karnavati Engineering Ltd, Mehsana, Gujarat.

Table No-1: Formulation Design of Fast Dissolving Tablets of Losartan potassium

INGREDIENTS (mg)	FORMULATION CODE												
	SERIES-A								SERIES-B				
	KS1	KS2	KS3	KS4	KS5	KS6	KS7	KS8	KS9	KS10	KS11	KS12	KS13
LOSARTAN POTASSIUM	50	50	50	50	50	50	50	50	50	50	50	50	50
KOLLIDON CL-SF	6	10	20	25	37.50	50	57.50	62.50	25	37.50	50	57.50	62.50
AVICEL 102 PH	66	64	59	56.50	50.25	44	40.25	37.75	28.25	25.12	22	20.12	18.87
LACTOSE	66	64	59	56.50	50.25	44	40.25	37.75	84.75	75.36	66	60.38	56.63
MAGNESIUM STEARATE	2	2	2	2	2	2	2	2	2	2	2	2	2
AEROSIL	2	2	2	2	2	2	2	2	2	2	2	2	2
NEOTAME	6	6	6	6	6	6	6	6	6	6	6	6	6
VANILLA	2	2	2	2	2	2	2	2	2	2	2	2	2
TOTAL WEIGHT	200	200	200	200	200	200	200	200	200	200	200	200	200

4)Physicochemical Characteristics of Losartan Potassium FDT Formulations:

The physicochemical characteristics of different Losartan potassium FDT formulations including powder flowability, appearance, thickness, uniformity of weight, hardness and friability were investigated. All these physicochemical characteristics were conducted in the standard way**.** The *in-vitro* disintegration time, wetting time and water absorption ratio were investigated in the following way-

***In-vitro* disintegration time:**

Disintegration was evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract **[10].** An FDT formulation should disintegrate or dissolve in water quickly. Hence for the purpose conducting the disintegrated time test, 3 tablets from each formulation were chosen randomly and each individually dropped into a beaker containing 100 ml of pH 6.8 phosphate buffer. Then, the duration of time required for disintegration of tablets were recorded [11].

Wetting time:

A piece of tissue paper folded double was placed in a petri plate (internal diameter is 6.5 cm) containing 6 ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds [12].

Water absorption ratio:

A piece of tissue paper folded twice was kept in a petri dish (internal diameter is 6.5 cm) containing 6 ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighed. Water absorption ratio, R was determined according to the following equation [7].

$R= 100 (W_a - W_b)/ W_b$

Where $\mathbf{W_a}$ and $\mathbf{W_b}$ are the weight after and before water absorption, respectively.

Content uniformity:
At random 20 tablets were weighed and powdered. The powder equivalent to 50 mg was weighed accurately and dissolved in 100 ml of phosphate buffer of pH 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No.1 filter paper. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 206.5 nm. The concentration of the drug was computed from the standard curve of the Losartan potassium in phosphate buffer of pH 6.8.

***In-vitro* dissolution testing:**
In-vitro dissolution study of Losartan potassium was carried using Electrolab TDL-08L dissolution test apparatus (Mumbai). The dissolution test was performed using 900 ml of phosphate buffer (pH 6.8) as the dissolution media at 50 rpm and 37°C ±5°C. 5 ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were determined spectrophotometrically at 206.5 nm for drug dissolved at that time.

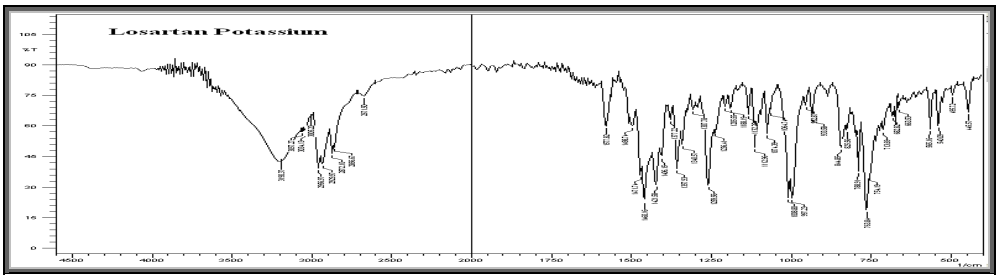
5)Stability studies:
The optimized formulations were tested for Hardness, Disintegration time and Content uniformity at temperature of 40±2°C and 75 ±5% RH for a period of 3 months by storing the samples in a stability chamber (Lab care). **(Table No-4)** [13 & 14].

RESULTS AND DISCUSSION

The present study was undertaken with an aim to formulate and evaluate Fast Dissolving Tablets of Losartan Potassium using direct compression method with the addition of super disintegrant such as Kollidon CL-SF in different concentrations and physicochemical parameters such as *in-vitro* disintegration time, wetting time, water absorption and *in-vitro* drug release were determined. This formulation strategy could be cost-beneficial and can be easily adopted by the pharmaceutical companies.

Preformulation studies:
Drug was characterized for flow properties, bulk density, tapped density, angle of repose, % compressibility and Hausner's ratio. Results obtained from the standardization of the drug were found within the specification as per official standards [9]. The result of powder purity was 102.0%, showing compliance with the acceptable range of NLT 98.0% & NMT 102.0% mentioned in the literature [9].

Drug-excipient Compatibility:
The FTIR spectra of drug alone and physical mixture of drug and superdisintegrant were recorded over the wave number range of 400 to 4000 cm^{-1}. The characteristic peaks were observed with Losartan Potassium & physical mixture of drug with Kollidon CL-SF in the following wave number region. C-O-H (Bending)-1421.58 & 1423.51 cm^{-1}, C-Cl (Stretching)-713.69 & 669.32 cm^{-1}, C=C (Stretching)-1498.74 & 1494.88 cm^{-1}, N-H (Stretching)-3190.37 & 3441.12 cm^{-1}, N=N (Stretching)-1577.82 & 1579.75 cm^{-1}, C-H (Stretching) -3034.13 & 2996.97 cm^{-1} and C-N (Stretching) 1340.57 & 1357.93 cm^{-1} respectively.



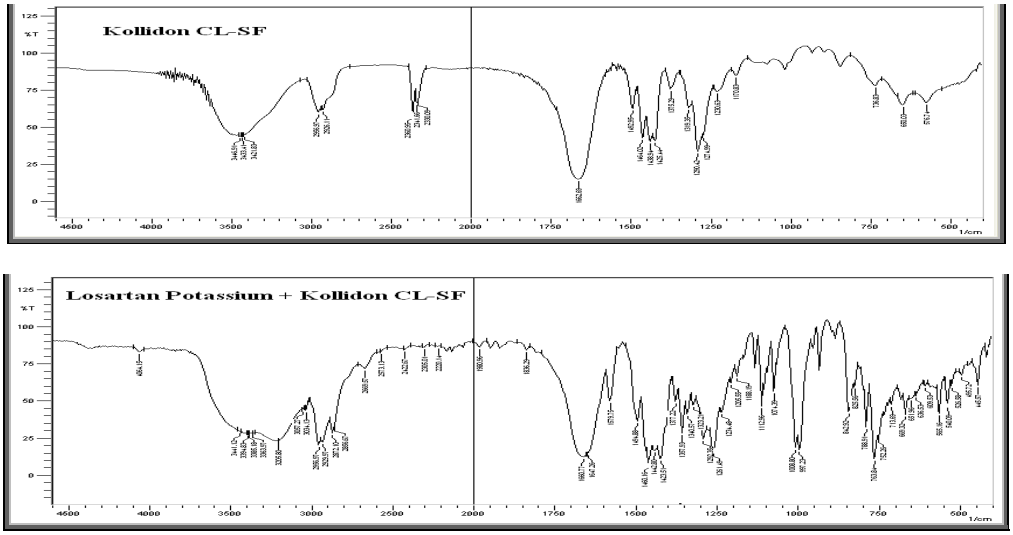
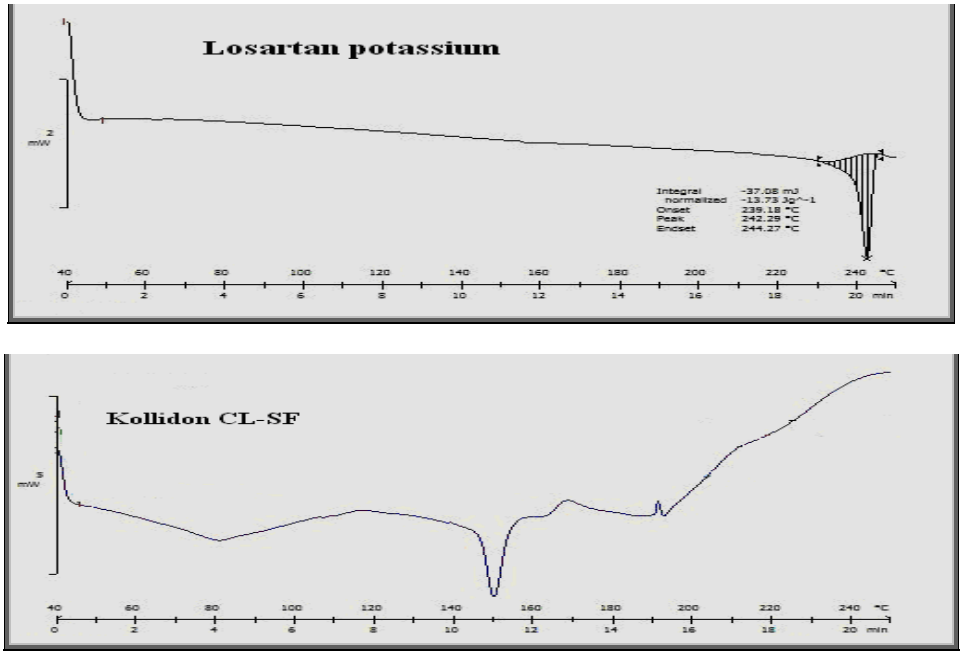


Fig-1: Compatibility of Losartan Potassium with Kollidon CL-SF by FTIR

In the present study, it was observed that, there was no appearance of new peaks and no disappearance or no major shifts in characteristics peaks in the mixture shows that there was no interaction between drug and superdisintegrant **(Fig-1).**

The DSC thermogram of Losartan Potassium showed a sharp endothermic peak at 242.29°C due to the melting of the solid drug. The elicited value of the peak is very close to the reported value of Losartan Potassium melting point, which is 240-245°C. This peak was reserved in the thermogram of 1:1 physical mixture of the drug with Kollidon CL-SF (242.38°C), which confirms the compatibility of drug with Kollidon CL-SF **(Fig-2).**



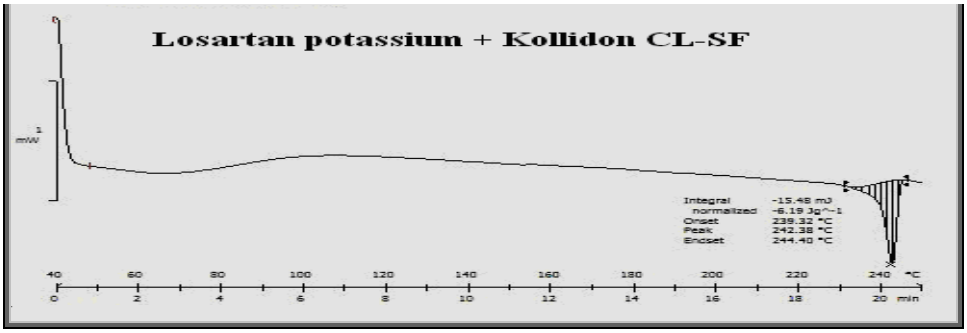


Fig-2: Compatibility of Losartan Potassium with Kollidon CL-SF by DSC studies

Table No-2: The results of physicochemical tests conducted on series A and B Losartan Potassium FDT formulations
(results are presented as mean ± standard deviation)

Formulation code		Flowability (n=3)	Appearance (n=10)	Thickness (mm) (n=10)	Uniformity of weight (mg) (n=20)	Hardness (Kg/cm^2) (n=3)	Friability (%) (n=20)	Disintegration time (sec) (n=3)
SERIES (A)	KS1	Between good to excellent	Desirable	4.2±0.21	200.2±0.83	3.1±0.01	0.21	300.0±2.01
	KS2	Between good to excellent	Desirable	4.1±0.82	200.3±0.57	3.0±0.13	0.23	270.0±1.55
	KS3	Between good to excellent	Desirable	4.2±0.01	200.2±0.43	3.0±0.10	0.30	190.1±2.05
	KS4	Between good to excellent	Desirable	4.1±0.01	200.2±0.62	3.0±0.11	0.21	92.33±2.51
	KS5	Between good to excellent	Desirable	4.0±0.96	200.1±0.67	3.0±0.11	0.26	77.67±2.51
	KS6	Between good to excellent	Desirable	4.3±0.02	200.1±0.72	3.0±0.07	0.25	47.00±2.00
	KS7	Between good to excellent	Desirable	4.0±0.01	200.1±0.64	3.1±0.10	0.22	60.66±2.08
	KS8	Between good to excellent	Desirable	4.1±0.01	200.0±0.72	3.1±0.11	0.29	86.33±3.51
SERIES (B)	KS9	Between good to excellent	Desirable	4.0±0.09	200.0±0.55	3.0±0.09	0.37	120.5±2.40
	KS10	Between good to excellent	Desirable	4.3±0.01	200.1±0.77	3.0±0.04	0.33	95.65±1.18
	KS11	Between good to excellent	Desirable	4.1±0.81	200.3±0.37	3.0±0.08	0.28	89.32±2.08
	KS12	Between good to excellent	Desirable	4.2±0.07	200.1±0.52	3.0±0.13	0.39	98.33±1.99
	KS13	Between good to excellent	Desirable	4.0±0.09	200.0±0.84	3.1±0.10	0.41	110.2±3.0

Physicochemical parameters:
Various formulations were prepared using Avicel PH 102 and lactose as diluents in different proportions in two series i.e. 1:1 in series A (KS1 to KS8 with 3 to 31.25% of Kollidon CL-SF) and 1:3 in series B (KS9 to KS13 with 12.5 to 31.25% of Kollidon CL-SF). The physicochemical properties of each series including flowability, appearance, thickness, uniformity of weight, hardness, friability and *in-vitro* disintegration time were investigated. The results have been shown in **Table No-2.**

The **flowability** of all the formulations was between good to excellent. **Appearance** for all formulations was desirable i.e., tablets were found to be circular with no cracks and white in colour. **Thickness** for all the formulations was between the ranges of 4.0±0.01 to 4.3±0.02. **Hardness** of all the formulations was approximately 3 kg/cm^2. However, FDT formulations should have a lower hardness in order to be disintegrated quickly within the buccal cavity. **Friability** of all the formulations was less than 1% ensuring the sufficient mechanical integrity and strength of prepared tablets. **Weight variation** was observed within the limit of ±7.5 %, which is well accepted for uncoated tablets as per IP [9].

All formulations, except formulations KS1 to KS3 were disintegrated within 3 minute, fulfilling the official requirement of USP. The delay in **disintegration time** of first three formulations was due to less concentration of super disintegrant i.e., 3%, 5%, 10% respectively. Disintegration mechanism of formulation KS6 is shown in **Fig-3.**

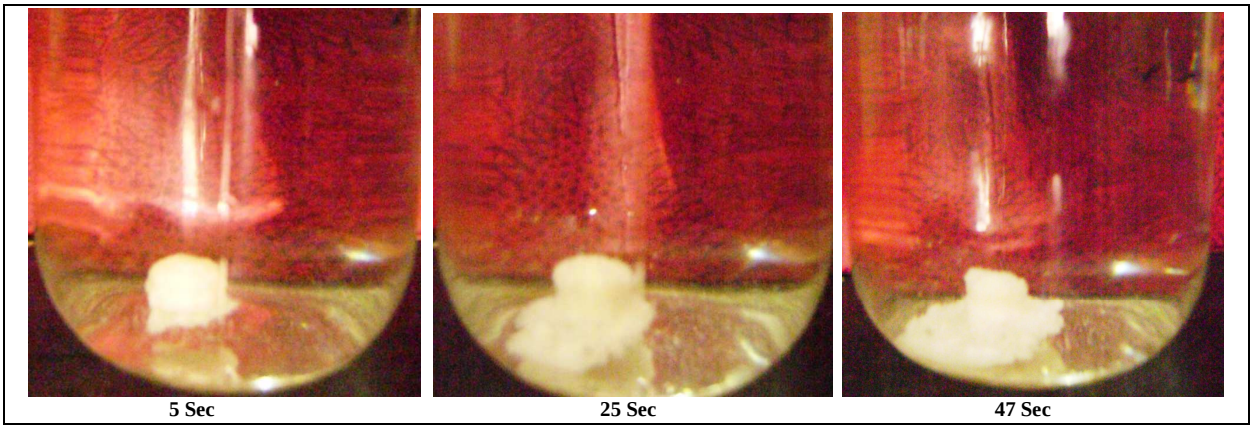


Fig-3: Disintegration of Formulation KS6

It was observed that formulations (KS7, KS8, KS12 & KS13) containing more than 25% of Kollidon CL-SF shown increase in disintegration time with further increase in concentration of super disintegrant. This delay in disintegration time might have occurred due to probable blockade of capillary pores in tablet mass as a result of formation of viscous plug by Kollidon CL-SF, which subsequently, prevents free access of fluid into tablets [7].

Series-B formulations (KS9 to KS13) exhibited decrease in disintegration time with increase in concentration of super disintegrant but comparatively disintegration time was more than series-A formulations (KS4 to KS8). This could be due to more proportion of lactose and its higher water activity coefficient which hinders swelling mechanism of super disintegrant [15].

Thus, only series-A formulations (KS4 to KS8) were selected for further post-compression studies based on their faster disintegration time (Fig-4). The probable reason for fast disintegration of Kollidon CL-SF is due to its rapid swelling without gelling [12 & 4]. These particles are found to be granular and highly porous which facilitates wicking of liquid into the tablet particles to generate rapid disintegration.

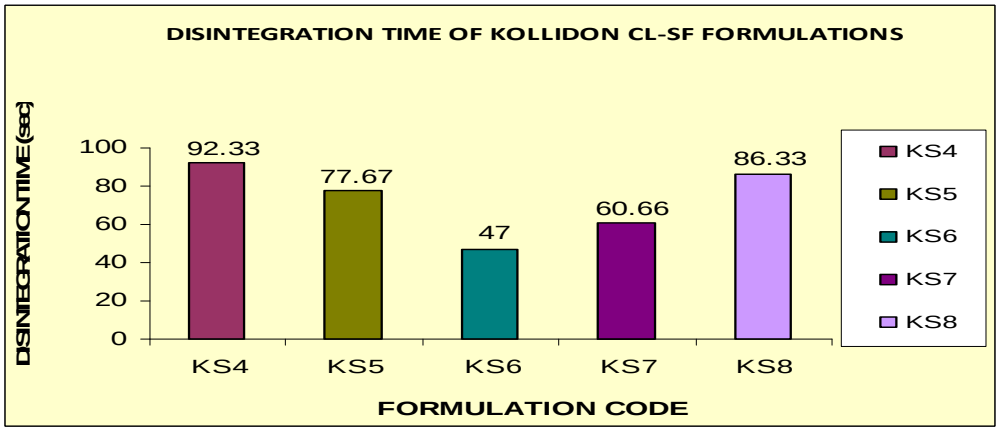


Fig-4: Disintegration time of selected formulations of series–A

Wetting time was used as a parameter to correlate with disintegration time in oral cavity. Wetting is related to the inner structure of the tablets and hydrophilicity of the components. It was observed that concentration of the disintegrant affected the wetting time; a lower wetting time implies a quicker disintegration of the tablet. This

method will duplicate the *in vivo* disintegration, as the tablet is motionless on the tounge [16]. The formulation KS6 containing 25% of Kollidon CL-SF have the shortest wetting time of 18.66±1.52 seconds, (**Table No-3)** which may due to strong wicking action of super disintegrant.

Table No-3: Post-compression parameters of selected formulations of series–A

Formulation Code	Wetting Time (sec)* (n=3)	Water Absorption Ratio* (n=3)	Content Uniformity (%)* (n=10)
KS4	38.00±2.00	48.00±2.51	95.36±0.95
KS5	26.00±2.00	52.66±2.51	93.37±0.62
KS6	18.66±1.52	58.33±1.52	97.53±0.85
KS7	32.66±2.51	62.00±3.00	96.58±0.59
KS8	48.33±3.51	70.66±3.05	97.36±0.50

(- results are presented as mean ± standard deviation)*

Water absorption ratio

Water absorption ratio, which is important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water, was calculated (17). Water absorption ratio, 'R' increased with an increase in super disintegrant concentrations from 12.5 to 25%**.** The increase in 'R' was most likely due to increased water uptake capacity of the super disintegrant at higher concentrations. The percentage of **drug content** for the formulations (KS4 to KS8) complied with official specifications, indicating uniformity of the drug content in the prepared tablets **(Table No-3).**

The ***in-vitro*** **dissolution** process of a tablet depends on the wetting followed by disintegration of the tablet. The influence of concentration of super disintegrant on the dissolution of Losartan Potassium from the FDTs is shown in **Fig-5.**The figure depicts that, there is an increase in cumulative % drug release with optimum concentration of superdisintegrant.

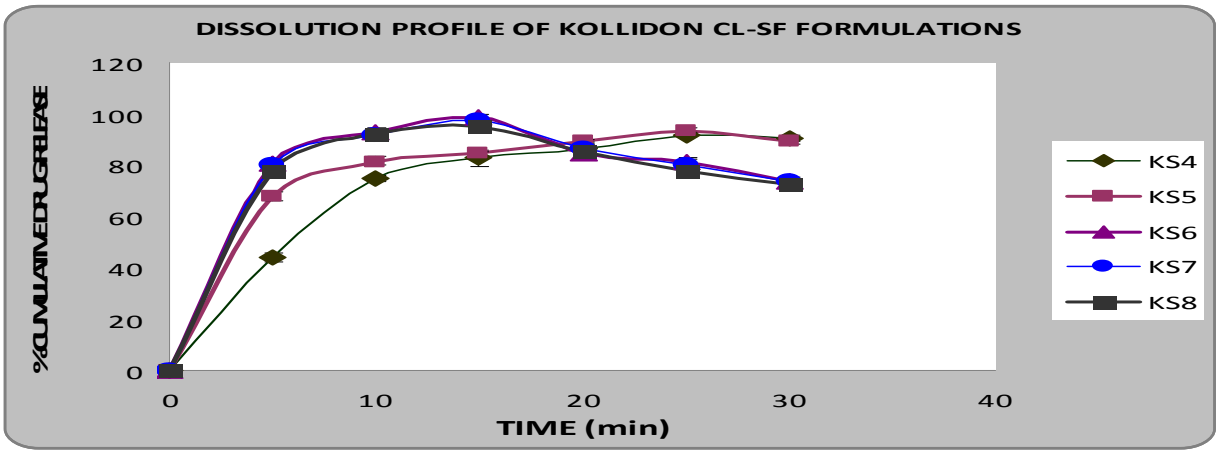


Fig-5: *In-vitro* dissolution profile of selected formulations of series–A

The dissolution of the drug from the tablets of KS6 formulation had been quicker than the other formulations and showed the better drug release of 99.49% at the end of 15th minute ensure fast dissolution of the drug from this formulation. The rapid drug dissolution might be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium because of its granular and highly porous nature which is responsible for faster water uptake; hence it facilitates wicking action of Kollidon CL-SF in bringing about faster disintegration of tablets into relatively large fragments of loosely associated particles and promote drug dissolution by providing larger surface area for drug dissolution to take place. Furthermore it can form hydrogen bonds with compounds with complementary structures for improved dissolution [18]. However formulations KS7 and KS8 containing increased concentration of Kollidon CL-SF did not improve the dissolution rate but in fact retarded it. This was probably due to formation of viscous plugs by particles.

The results obtained from the physicochemical tests (Disintegration time - 47 seconds, Drug release of 99.49% within 15 minutes) conducted on formulation KS6 were desirable and acceptable in terms of all the tests conducted and as a result this formulation was chosen as the optimized formulation.

The accelerated stability studies (40±2° C and 75±5% RH) performed for a period of three months indicated that there was no significant change in physical and chemical parameters (hardness, disintegration time and drug content) of the tablets, hence the formulation was found to be stable. Results have been shown in **Table No-4.**

Table No-4: Stability Studies

Time in months	Hardness (Kg/cm^2) (n=3)	Disintegration time (sec) (n=3)	Content uniformity (%) (n=3)
KS6 FORMULA			
Before	3.00 ± 0.07	47.00 ± 2.00	97.53 ± 0.85
After 1 month	3.05 ±0.02	46.55 ± 1.08	96.75 ± 0.46
After 2 month	3.03 ±0.04	46.16 ± 1.52	96.34 ± 0.76
After 3 month	3.00 ±0.05	45.98 ± 1.68	96.12 ± 0.68

(- results are presented as mean ± standard deviation)*

CONCLUSION

The present study reveals that the prepared Losartan Potassium Fast Dissolving Tablets containing Kollidon CL-SF as a superdisintegrant disintegrate within few seconds without need of water so as to overcome swallowing difficulties. Therefore, in the years to come, their modification aimed at the development of better material for drug delivery systems.

Acknowledgments
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[18] A BASF: The Chemical Company: BASF SE - Pharma Ingredients & Services Products.