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Design and Development of Fast Dissolving Thin Films of Losartan Potassium

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ABSTRACT

The purpose of this research work was to formulate a fast dissolving film of Losartan potassium for the treatment of hypertension. The fast dissolving films of Losartan potassium were prepared by solvent casting technique using film forming polymer HPMC 15 and 50 cps and PEG is used as plasticizer. From the preliminary physical observation of these prepared films the best were selected for incorporation of Losartan potassium. The electron microscopy showed that the films are clear, colorless with smooth surface and little pores, without any scratches on the films. All the films prepared were evaluated for Physical appearance and surface texture, weight uniformity of films, thickness of the films, folding endurance, surface pH, drug content uniformity and *in-vitro* disintegration time of films all the results were found to be satisfactory. The $t_{50\%}$ and $t_{90\%}$ values decreased with increase in the concentration of SSG, CCS and CP. The rapid increase in dissolution of Losartan potassium with the increase in CCS. Among all the film formulation FA2 and FA8 (6% CCS HPMC 15 and 50 cps) were found to be promising and showed a disintegration time of 36 and 32 sec, respectively and 50% of drug released in 9.74 and 8.19 min, and 90% of drug released in 18.00 and 17.12 min respectively. Based on the above results it can be concluded that the fast dissolving oral film of Losartan potassium may produce the rapid action thereby enhance the absorption by avoiding the first pass effect.

Keywords: Losartan potassium, HPMC, Crosscarmellose sodium, Sodium starch glycolate, Crospovidone.

INTRODUCTION

Some patients have difficulty in swallowing or chewing solid dosage forms which risk or fear of chocking and thus is a major problem in the use of solid dosage forms. [1-2] Fast dissolving film (FDF) is a new drug delivery system for oral drug delivery. FDF is used in acute conditions such as pain, emesis, migraine, hypertension, congestive heart failure, asthma etc. FDF has gained popularity due to its availability in various sizes and shapes. These are intended to disintegrate or dissolve within seconds. They offer advantages such as administration without water, ease of swallowing, rapid onset of action and convenience of dosing. For fast dissolving active pharmaceutical ingredients,

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absorption is possible through the oral mucosa and may improve bioavailability. [3-12]

The concept of oral dissolving film: [13-14]

- This delivery system consists of a thin film.
- After placing it on the top of the tongue, the film dissolves within seconds, promoting first pass metabolism as compared to tablet and other immediate release oral solid dosage forms, and may increase the bioavailability of drug.
- This dissolves in the mouth like a cotton candy.

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due [15-16] to their unique properties and advantages. They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastro-intestinal tract. [17-18] Rapidly dissolving tablets are available in the market for a variety of drugs. Rapidly dissolving films (RDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips.

However these dosage forms are introduced in the United States and European pharmaceutical markets for [19-21] therapeutic benefits. The first of this kind of oral strips were developed by the major pharmaceutical company Pfizer who named it as Listerine® pocket packs™ and were used for mouth freshening. Chloraseptic® relief strips were the first therapeutic oral thin films which contained [21] benzocaine and were used for the treatment of sore throat. The RDF are essentially prepared using water soluble and fast disintegrating polymers which also possess good film forming properties like hydroxy propyl methylcellulose (HPMC), polyethylene oxide (PEO), polyvinyl pyrrolidone (PVP) and hydroxy propyl cellulose (HPC). [19, 22]

Losartan potassium is a potent, highly specific angiotensin II type 1 receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 hours. Administration of Losartan Potassium in a sustained release dosage form with dual release characteristics i.e., burst release followed by an extended release over 8 hours, would be more desirable as these characteristics would allow a rapid onset followed by protracted anti-hypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration. [23] In present research work an attempt has been made to prepare mouth dissolving films of Losartan potassium by solvent casting technique using film forming polymer HPMC. PEG is used as plasticizer.

MATERIALS AND METHODS

Losartan potassium was obtained as a gift sample from Unimark Remedies Ltd, Mumbai. HPMC, PEG-400, Tween 80, Crosscarmellose Sodium were obtained from SD Fine chem. Mumbai. All the chemicals were of analytical grade.

Preparation of blank films

HPMC is known for its good film forming properties and has excellent acceptability hence, various grades of HPMC namely HPMC (15 and 50 cps). A total of fourteen blank films were prepared using film forming polymers like HPMC (15cps) and HPMC (50 cps) in various concentrations (Table 1). Based on film forming capacity, appearance HPMC 15 cps 1000 mg and HPMC 50 cps 750 mg were selected as film forming agents. From the preliminary physical observation of these prepared films the best were selected for incorporation of Losartan potassium.

Calculation of dose [24]

The dose of Losartan potassium is 25 mg. Therefore the amount of Losartan potassium in a film of diameter 1.5 cm is 25 mg.

- Area of the petridish of 9 cm diameter is 63.64 cm^2
- Area of the film of 1.5 cm diameter is 1.77 cm^2
- Amount of drug to be present in 1.77 cm^2 of film is 25 mg
- Amount of drug present to be added to the 63.64 cm^2 area of petridish is 900 mg

The amount of Losartan potassium required for petridish of area 63.64 cm^2 is 900 mg so that each film of 1.5 cm diameter contains 25 mg of Losartan potassium.

Formulation of Fast Dissolving Films of Losartan potassium [24]

The fast dissolving films of Losartan potassium were prepared by solvent casting technique using film forming polymer HPMC 50 cps and HPMC 15 cps. PEG is used as plasticizer. The required amount of polymer was dispersed in water with continuous stirring using magnetic stirrer. The calculated amount of Losartan potassium was dissolved in distilled water and added to polymer solution along with the other excipients and stirred to form homogenous solution. The solution was casted on to Petri dish (area of 66.31 cm^2) then kept in hot air oven at 40°C for 24 hours. The films were punched in to size of 1.5 cm diameter (an area of 1.77 cm^2) containing 25 mg of Losartan potassium. The detail compositions of the films are given in Table 2.

EVALUATION OF FAST DISSOLVING FILMS [24-25]

All the films prepared were evaluated for Physical appearance and surface texture and other following parameters were studied.

Weight variation: For weight variation three films of every formulation were taken weighed individually on digital balance then average weight was calculated.

Film thickness: The thickness of each film was measured using micrometer screw gauge at different positions of the film and the average was calculated.

Surface pH: Film is slightly wet with the help of water. The pH is measured by bringing the electrode in

contact with the surface of the oral film. This study is performed on three films of each formulation and mean ± S.D calculated.

Folding endurance: The folding endurance was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Drug content: A circular film of 1.5 cm diameter was cut and dissolved in 100 ml of 0.1N HCl and filtered. The contents were transferred to a volumetric flask (100 ml). The drug is determined spectroscopically after appropriate dilution.

Table 1: Formulation of Blank Films

FC	HPMC (15CPS) (mg)	HPMC (50CPS) (mg)	PEG 400 (mg)	Tween 80 (ml)	Water (ml)	Remarks
F1	100	-	300	0.2	10	+
F2	200	-	300	0.2	10	+
F3	300	-	300	0.2	10	+
F4	400	-	300	0.2	10	++
F5	500	-	300	0.2	10	++
F6	750	-	300	0.2	10	++
F7	1000	-	300	0.2	10	+++
F8	-	100	300	0.2	10	+
F9	-	200	300	0.2	10	++
F10	-	300	300	0.2	10	++
F11	-	400	300	0.2	10	++
F12	-	500	300	0.2	10	++
F13	-	750	300	0.2	10	+++
F14	-	1000	300	0.2	10	++

*Formulation Code

Disintegration time: Disintegration test was performed in the USP disintegration time testing apparatus. One film from formulation was introduced into the each tube of disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in 0.1 N HCl and operated until the film disintegrated.

***In-vitro* dissolution studies:** *In-vitro* dissolution of fast dissolving film was studied in USP paddle dissolution test apparatus using 0.1N HCl as the dissolution medium. The temperature was maintained at 37± 0.5°C throughout the experiment. 5 ml Sample was withdrawn at 2 min intervals and the same quantity was replaced with 0.1 N HCl. The cumulative percentage of drug released was determined using UV visible spectrophotometer at 205.

Stability studies: The purpose of the stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage condition, re-test periods and shelf life. Stability studies were carried out as per ICH International Conference of harmonization guidelines at 40°C / 75% RH for 3 months. The optimized film formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40°C / 75% RH for 3 months and evaluated for their physical appearance, drug content and *in-vitro* dispersion time at specified intervals of time.

Table 2: Formulation of Fast Dissolving Films of Losartan potassium

FC	Losartan potassium (mg)	HPMC (15CPS)(mg)	HPMC (50CPS)(mg)	CCS (% w/w)	CP (% w/w)	SSG (% w/w)	PEG 400 (mg)	Tween 80 (ml)	Aspartame (% w/w)	Water (ml)
FA1	900	1000	-	3	-	-	300	0.2	4	10
FA2	900	1000	-	6	-	-	300	0.2	4	10
FA3	900	1000	-	-	3	-	300	0.2	4	10
FA4	900	1000		-	6	-	300	0.2	4	10
FA5	900	1000		-	-	3	300	0.2	4	10
FA6	900	1000		-	-	6	300	0.2	4	10
FA7	900	-	750	3	-	-	300	0.2	4	10
FA8	900	-	750	6	-	-	300	0.2	4	10
FA9	900	-	750	-	3	-	300	0.2	4	10
FA10	900	-	750	-	6	-	300	0.2	4	10
FA11	900	-	750	-	-	3	300	0.2	4	10
FA12	180	-	750	-	-	6	300	0.2	4	10

*Formulation Code

Table 3: Evaluation of Fast Dissolving Films of Losartan potassium

FC	Weight (gm) ± SD	Thickness (mm) ± SD	Surface pH ± SD	Folding endurance ±SD	Disintegration time (sec) ±SD	Drug content (%) ±SD
FA1	1.10 ± 0.178	0.112 ± 0.013	4.65 ± 0.125	254 ± 6.08	49.67 ± 1.15	96.77 ± 1.745
FA2	1.30 ± 0.289	0.196 ± 0.007	4.50 ± 0.323	260 ± 5.13	36.33 ± 2.08	97.12 ± 0.460
FA3	1.15 ± 0.065	0.118 ± 0.004	4.45 ± 0.065	263 ± 1.15	68.00 ± 2.00	97.82 ± 0.204
FA4	1.00 ± 0.121	0.137 ± 0.012	4.40 ± 0.272	278 ± 4.04	57.33 ± 3.57	98.07 ± 0.825
FA5	0.96 ± 0.061	0.177 ± 0.005	4.37 ± 0.207	263 ± 2.65	91.33 ± 0.58	96.20 ± 0.276
FA6	1.44 ± 0.552	0.179 ± 0.019	4.46 ± 0.133	247 ± 2.65	72.00 ± 2.00	97.33 ± 0.270
FA7	1.26 ± 0.351	0.123 ± 0.005	4.46 ± 0.250	265 ± 3.06	51.67 ± 1.15	96.53 ± 0.948
FA8	1.54 ± 0.564	0.140 ± 0.026	4.49 ± 0.325	248 ± 2.08	32.33 ± 1.53	97.51 ± 1.529
FA9	1.00 ± 0.100	0.156 ± 0.005	4.31 ± 0.258	262 ± 4.58	69.33 ± 1.53	98.68 ± 0.771
FA10	1.61 ± 0.190	0.102 ± 0.005	4.37 ± 0.291	232 ± 4.73	53.67 ± 1.15	95.54 ± 0.550
FA11	1.07 ± 0.306	0.133 ± 0.033	4.35 ± 0.167	255 ± 7.51	89.33 ± 1.15	98.18 ± 0.524
FA12	1.51 ± 0.069	0.191 ±0.018	4.75 ± 0.135	254 ± 2.65	69.67 ± 5.51	97.57 ± 0.536

*Average of three determinations, FC=Formulation codes

Table 4: Release profile of the Losartan potassium fast dissolving films

Formulations Code	$t_{50\%}$ (min)	$t_{90\%}$ (min)
FA1	10.20 ± 0.12	19.70 ± 0.29
FA2	9.74 ± 0.26	18.00 ± 0.26
FA3	10.20 ± 0.21	19.46 ± 0.32
FA4	9.15 ± 0.51	19.94 ± 0.18
FA5	12.20 ± 0.54	21.63 ± 0.27
FA6	10.45 ± 0.45	21.05 ± 0.34
FA7	9.15 ± 0.43	19.95 ± 0.54
FA8	8.19 ± 0.29	17.12 ± 1.25
FA9	10.44 ± 0.43	21.09 ± 0.59
FA10	10.97 ± 0.43	20.24 ± 0.54
FA11	10.21 ± 0.29	19.71 ± 1.25
FA12	10.69 ± 0.43	21.09 ± 0.59

*Average of three determinations

Table 5: Stability study data at 40°C/75% RH

FC	Month	Disintegration time (sec)	Surface pH	Drug content (%)
FA2	1st	36.33	4.50	97.12
	2nd	36.00	4.53	97.28
	3rd	35.84	4.51	97.36
FA8	1st	32.33	4.31	97.51
	2nd	32.00	4.26	97.58
	3rd	32.00	4.32	97.64

*Average of three determinations, FC=Formulation codes

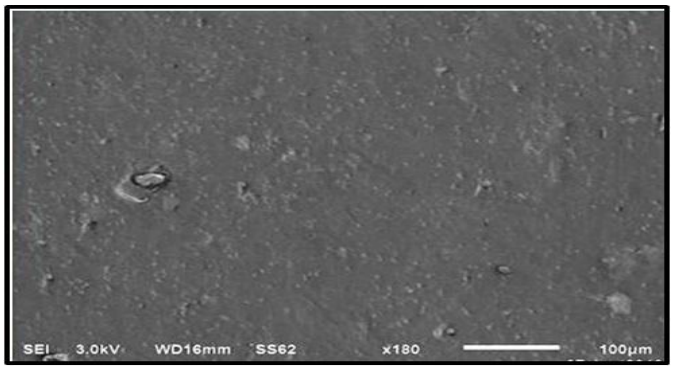

Fig. 1: SEM of formulation FA2

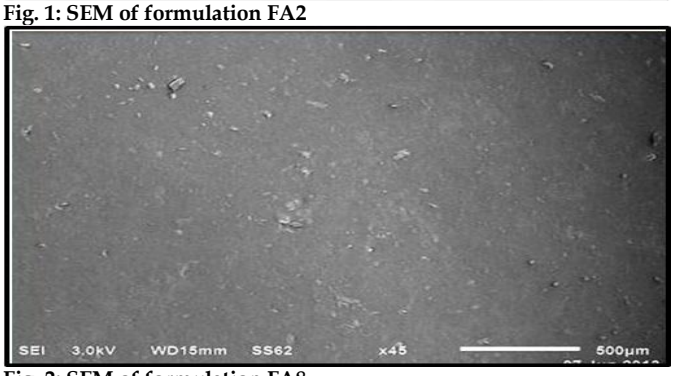

Fig. 2: SEM of formulation FA8

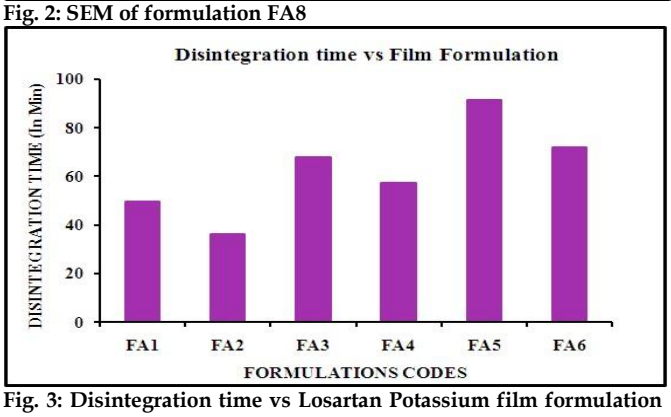

Fig. 3: Disintegration time vs Losartan Potassium film formulation (F1-F6)

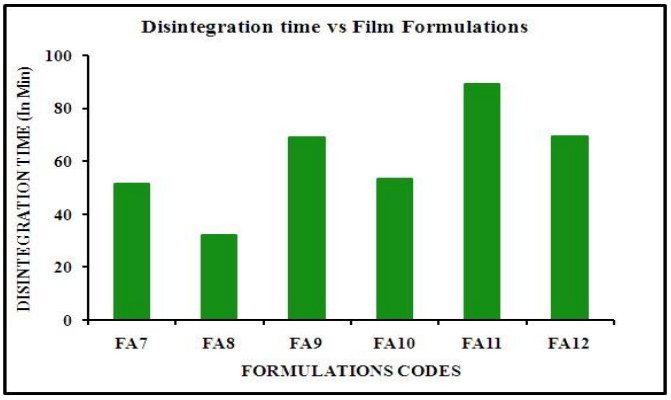

Fig. 4: Disintegration time vs Losartan Potassium film formulation (F7-F12)

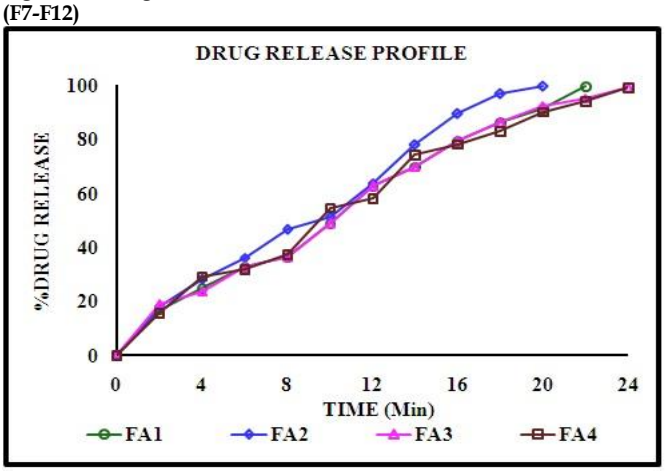

Fig. 5: *In-vitro* Drug Release profile of formulations FA1- FA4

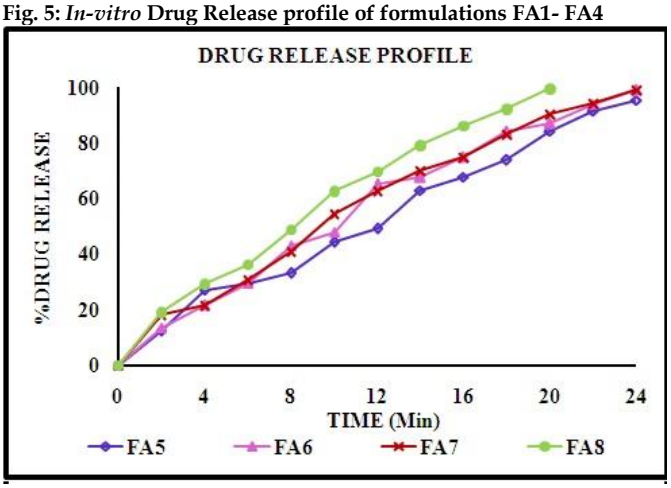

Fig. 6: *In-vitro* Drug Release profile of formulations FA5- FA8.

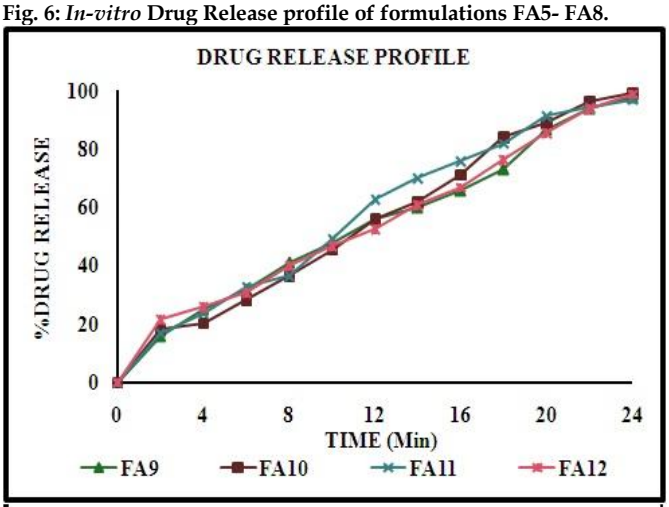

Fig. 7: *In-vitro* Drug Release profile of formulations FA9- FA12

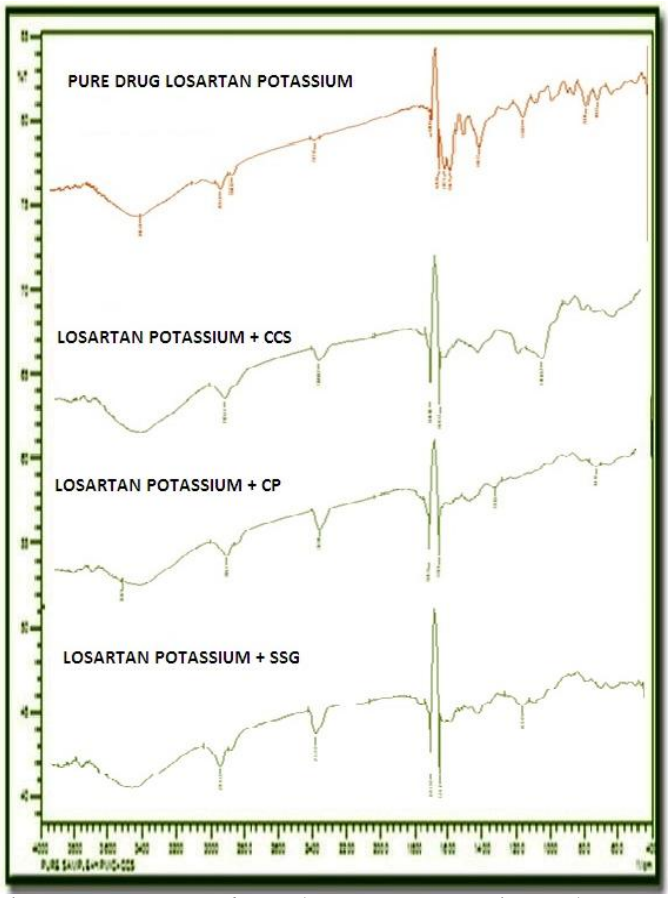

Fig. 8: FTIR spectrum of pure drug Losartan potassium and Drug + CCS, Drug + CP and Drug + SSG formulations.

Drug-Excipient Compatibility Study by FTIR: The compatibility of drug in the formulations was confirmed by IR spectra of pure drug and formulations were determined using Shimadzu FTIR-8400S Spectrophotometer by KBr Disc method.

RESULTS AND DISCUSSIONS

In present research work an attempt has been made to prepare mouth dissolving films of Losartan potassium by solvent casting method. HPMC is known for its good film forming properties and has excellent acceptability. A total of fourteen blank films were prepared using film forming polymers like HPMC (15 cps) and HPMC (50 cps). Based on film forming capacity, appearance HPMC 15 cps 1000 mg and HPMC 50 cps 750 mg were selected as film forming agents. From the preliminary physical observation of these prepared films the best were selected for incorporation of Losartan potassium.

The electron microscopy showed that the films are clear, colorless with smooth surface and little pores, without any scratches on the films. SEM was shown in Figures 1 to 2.

Physical appearance and surface texture of films were found to have smooth surface and they are elegant enough to see. The weight of the prepared films was determined by using digital balance. All the films were tested for uniformity of weight and the results are given in Table 3. The films showed weight variation ranging from 0.9606 ±0.061gm to1.61 ± 0.190 gm. In all the cases the standard deviation values are very low which suggest the prepared films were uniform in weight. All the films have uniform thickness throughout. The thickness of all the formulations ranged between 0.112 ± 0.013 to 0.196 ± 0.007. In all the cases the standard deviation values are very low which suggest the prepared films were uniform in thickness. The folding endurance was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance. The folding endurance of all the formulations was in the range of 232 to 278. The surface pH was found to be in the range of 4.31 ± 0.258 to 4.75 ± 0.135. Which is close to salivary pH, which indicates that films may have less potential to irritate the oral mucosa, thereby they are comfortable. The drug content of all the films was in the range of 95.54 ± 0.550 to 98.68 ± 0.771 suggesting that drug was uniformly dispersed throughout all films.

The *In-vitro* disintegration time of films prepared with HPMC 15 CPS was in the range of 36.33 ± 2.08 to 91.33 ± 0.58 sec with SSG, CP and CCS in various concentrations. In case films were prepared with HPMC 50 CPS disintegration time in the ranges of 32.33 ± 1.53 to 89.33 ± 1.15. As the concentration of superdisintegrant increases the *in-vitro* disintegration time of the films decreases. The *in-vitro* disintegration of film formulations data is tabulated in the Table 3 and Figures 3-4.

In-vitro dissolution studies of the prepared films were performed in 0.1N HCL using USP type II (paddle) dissolution apparatus for 25 min. The dissolution studies were conducted in triplicate in using 0.1 N HCL solution ass dissolution medium for a period of 25 min. The plot of % cumulative drug release verses time (min) were plotted and shown in Figures 5-7. The dissolution rate was found varied with increasing concentration of superdisintegrant. As the concentration is increases the release is also increases. In all the formulations around 90 % of drug released within 24 min. The release study results $t_{50\%}$ and $t_{90\%}$ are shown in Table 4. The $t_{50\%}$ and $t_{90\%}$ values decreased with increase in the concentration of SSG, CCS and CP. The rapid increase in dissolution of Losartan potassium with the increase in CCS may be due to rapid swelling and disintegrating films rapidly. [26] Among all the film formulation FA2 and FA8 (6 % CCS HPMC 15 and 50 cps) were found to be promising and showed a disintegration time of 36 and 32 sec, respectively and 50% of drug released in 9.74 and 8.19 min, and 90% of drug released in 18.00 and 17.12 min respectively. Based on the in-vitro disintegration time and *in-vitro* dissolution studies the formulation FA2 and FA8 was found to be promising and showed a disintegration time of 36 and 32 sec and showed drug release of 99%, within 20 mins**.**

The promising formulation was subjected to short term stability studies. Based on the *in-vitro* disintegration time and *in-vitro* dissolution studies the formulation FA2 and FA8 was found to be promising and showed a disintegration time of 36 and 32 sec and showed drug release of 99%, within 20 mins**.** The formulations FA2 and FA8 were stored at 40°C/75% RH and tested for three month. The films were again analyzed for the Surface pH, drug content uniformity and disintegration time. The increase in the disintegration time was observed. The drug content of the formulations was found to be within the permissible limits and the results were shown in the Table 5.

Drug-Excipient Compatibility Study by FTIR: The possible interaction between drug and Excipient used in the formulation development of Losartan potassium was studied by FTIR spectroscopy. The FT-IR spectra of pure drug Losartan potassium and drug + CCS, Drug + CP and Drug + SSG and excipients are shown in Fig 8. The FTIR spectrum of Losartan potassium pure drug exhibited characteristic broad absorption band at 3406 cm^{-1} representing the presence of OH group (OH stretching). The aromatic C-H stretching and aliphatic C-H stretching bands were appeared at 2924 cm^{-1} and 2860 cm^{-1} respectively. Whereas a characteristic absorption band at 1680 cm^{-1} is due to the presence of C=O of COONa (C=O stretching). Similarly the IR spectrum of Losartan potassium and other polymers showed characteristic absorption bands for the functional groups OH, Aromatic CH=CH, aliphatic CH=CH and C=O at or near that of Losartan potassium absorption bands values indicating that there was no chemical and physical change in the functional groups present in Losartan potassium. FTIR studies reveal that there is no interaction between Losartan potassium and the excipients.

In present research work, an attempt has been made to prepare mouth dissolving films of Losartan potassium by solvent casting method using film forming polymer HPMC 15 cps and 50 cps. Based on the *in-vitro* disintegration time and *in-vitro* dissolution studies the formulation FA2 and FA8 was found to be promising and showed a disintegration time of 36 and 32 sec and showed drug release of 99%, within 20 mins**.** Hence it can be inferred that the fast dissolving oral film of Losartan potassium may produce the rapid action thereby enhance the absorption by avoiding the first pass effect.

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