

DEVELOPMENT AND EVALUATION OF FAST DISSOLVING FILM OF LOSARTAN POTASSIUM

Dr. N. G. Raghavendra Rao and K. Divya

¹Dept of Pharmacy, GRD [PG] Institute of Management and Technology, Rajpur, Dehradun - 248009, Uttarakhand, India.

²Dept of Pharmaceutics, Jyothishmathi Institute of Pharmaceutical Science, Thimmapoor, Karimnagar - 505481, Telangana, India.

Article Received on
15 June 2018,

Revised on 05 July 2018,
Accepted on 25 July 2018

DOI: 10.20959/wjpr201815-13054

***Corresponding Author**
Dr. N. G. Raghavendra
Rao*, Director

Department of Pharmacy,
GRD [PG] Institute of
Management and
Technology, 214, Rajpur,
Dehradun - 248009,
Uttarakhand, India.

ABSTRACT

In present research work an attempt has been made to prepare mouth dissolving films of Losartan potassium which is a Angiotension II Type1 receptor Blocker used for the treatment of anti hypertensine. Losartan potassium is widely used as an antihypertensive drug, which is a potent drug candidate for developing in to Fast Dissolving Films. The fast dissolving films of Losartan potassium were prepared by solvent casting technique using film forming polymer HPMC, PVA. PEG is used as plasticizer. The compatibility of the drug in the formulation was confirmed by FTIR studies. FTIR studies reveal that there is no interaction between Losartan potassium and the excipients. 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, in-vitro disintegration time of films, in-vitro dissolution Study and all the results were found to be satisfactory. The disintegration time decreased with increased in concentration of CCS, CP and SSG up to 6% w/w. Based on the *in-vitro* disintegration time, formulation FB2 were found to be promising and showed a disintegration time of 28 sec and showed drug release of 99.00% within 18 mins. The rapid increase in dissolution of Losartan potassium with the increase in CCS may be due to rapid swelling and disintegrating films rapidly. CCS was found to be the best among the three superdisintegrants. 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, PVA, PEG, Crosscarmellose sodium, Sodium starch glycolate, Crospovidone, Disintegration time Fast dissolving films.

INTRODUCTION

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance. Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance.^[1] Many pharmaceutical companies have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity.^[2, 3] Oral Thin Films are typically the size of a postage stamp and disintegrate on a patient's tongue matter of seconds for the rapid release of one or more APIs.

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due^[4,5] 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 gastrointestinal tract.^[6,7] 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.

Some patients have difficulty in swallowing or chewing solid dosage forms which risk or fear of choking and thus is a major problem in the use of solid dosage forms.^[8-9] 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, absorption is possible through the oral mucosa and may improve bioavailability.^[10-19]

However these dosage forms are introduced in the United States and European pharmaceutical markets for^[5,20-22] therapeutic benefits. A film or strip comprises of water soluble and/or water swellable film forming polymer due to which the film or strip dissolves instantaneously when placed on the tongue in the oral cavity. 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^[22] 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).^[20,23]

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 hrs. 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 hrs, would be more desirable as these characteristics would allow a rapid onset followed by protracted antihypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration.^[24] Losartan potassium is widely used as an antihypertensive drug, which is a potent drug candidate for developing in to Fast Dissolving Films. Hence the main objective of the study was to formulate fast dissolving films of Losartan potassium to achieve a better dissolution rate and further improving the bioavailability of the drug. In present research work an attempt has been made to prepare mouth dissolving films of Losartan potassium. The fast dissolving films of Losartan potassium were prepared by solvent casting technique using film forming polymer HPMC, PVA. 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, HPMC 50 cps and PVA used as a film forming agent. A total of twelve blank films were prepared using film forming polymers like HPMC 50cps and PVA in various concentrations (Table 1). Based on film forming capacity, appearance HPMC 50 cps 750 mg and PVA 1.5 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.

Table 1: Formulations of Blank Films.

FC	HPMC (50CPS) (mg)	PVA (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	-	0.5	300	0.2	10	+
F9	-	1.00	300	0.2	10	++
F10	-	1.50	300	0.2	10	+++
F11	750	1.00	300	0.2	10	++
F12	750	1.50	300	0.2	10	++++

FC= Formulation Codes

Calculation of dose^[25]

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

- Area of the Petri dish of 9cm diameter is 63.64cm².
- Area of the film of 1.5cm diameter is 1.77cm².
- Amount of drug to be present in 1.77cm² of film is 25mg.
- Amount of drug present to be added to the 63.64cm² area of Petri dish is 900mg.

The amount of Losartan potassium required for Petri dish of area 63.64cm² is 900mg so that each film of 1.5cm diameter contains 25mg of Losartan potassium.

Formulation of Fast Dissolving Films of Losartan potassium^[25]: The fast dissolving films of Losartan potassium were prepared by solvent casting technique using film forming polymer HPMC, PVA. 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 66.31cm²) then kept in hot air oven at 40⁰C for 24 hrs. The films were punched in to size of 1.5cm diameter (an area of 1.77cm²) containing 25 mg of Losartan potassium. The detail compositions of the films are given in Table 2.

Table 2: Formulation of Fast Dissolving Films of Losartan potassium.

FC	Losartan potassium (mg)	HPMC (50CPS) (mg)	PVA (mg)	CCS (%w/w)	CP (%w/w)	SSG (%w/w)	PEG 400 (mg)	Tween 80 (ml)	Aspartame (%w/w)	Water (ml)
FB1	900	750	1.5	3	-	-	300	0.2	4	10
FB2	900	750	1.5	6	-	-	300	0.2	4	10
FB3	900	750	1.5	-	3	-	300	0.2	4	10
FB4	900	750	1.5	-	6	-	300	0.2	4	10
FB5	900	750	1.5	-	-	3	300	0.2	4	10
FB6	900	750	1.5	-	-	6	300	0.2	4	10

FC= Formulation Codes

EVALUATION OF FAST DISSOLVING FILMS^[25-27]

Drug-Excipients 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.

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, in-vitro disintegration time of films, in-vitro Dissolution Study.

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

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 $37 \pm 0.5^\circ\text{C}$ throughout the experiment. 5ml Sample was withdrawn at 2min 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 Testing: The optimized film formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at $40^\circ\text{C} / 75\%$ RH for 3months and evaluated for their physical appearance, drug content and in-vitro dispersion time at specified intervals of time.

RESULTS AND DISCUSSIONS

In present research work an attempt has been made to prepare mouth dissolving films of Losartan potassium by solvent casting method.

The possible interaction between drug and excipients used in the formulation development of Losartan potassium was studied by FTIR spectroscopy. The FT-IR spectra of pure drug and FB1 and FB2 formulations are shown in Fig 1.

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 containing FB1 and FB2 formulations exhibited 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.

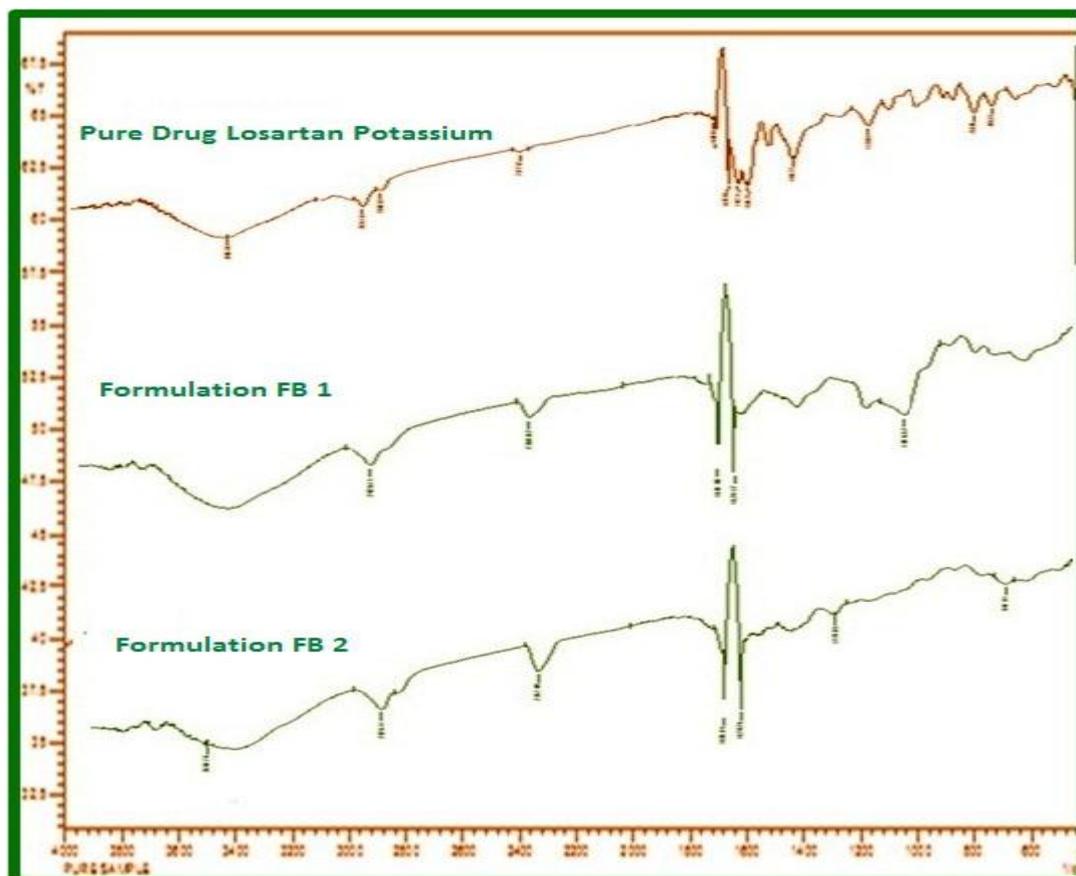


Fig 1: FTIR spectrum of pure drug and formulations of FB1 and FB2.

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 Figs 2 to 3.

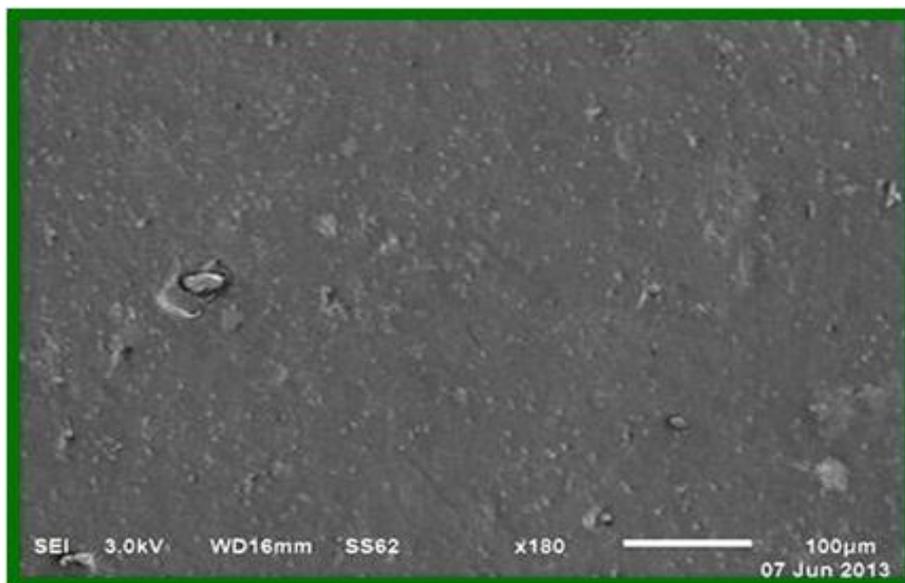


Fig 2: SEM of formulation FB1.

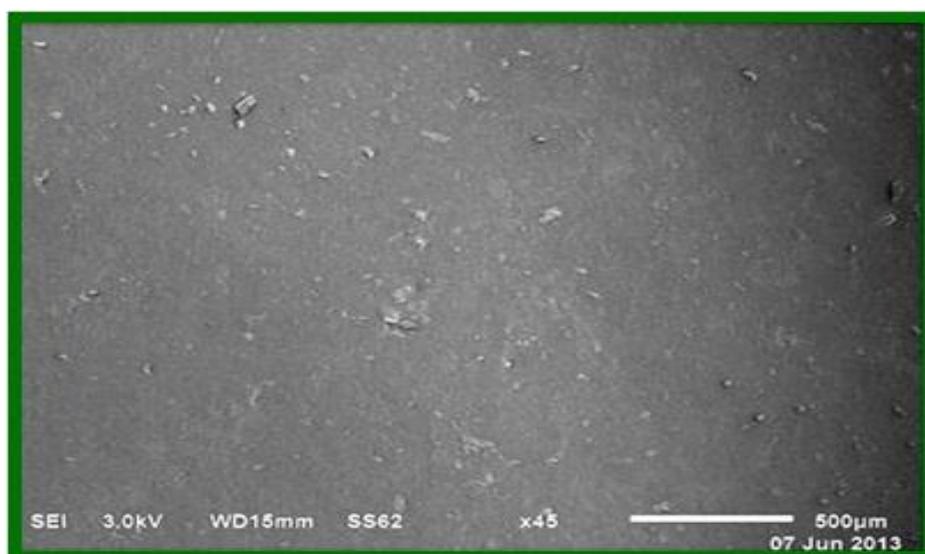


Fig 3: SEM of formulation FB2.

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 all the results were found to be satisfactory [results were shown in Table 3]. The In-vitro disintegration time of films prepared with HPMC and PVA was in the range of 28.00 to 87.00 sec. As the concentration of superdisintegrants increases the in-vitro disintegration time of the films decreases. Based on the *in-vitro* disintegration time, formulation FB1 and FB2 were found to be promising and showed a disintegration time of 38.67 and 22.00 sec respectively. The results are given in Table 3 and Fig 4.

The In-vitro disintegration time of films prepared with HPMC and PVA was in the range of 22.00 to 97.00 sec. As the concentration of superdisintegrants increases the in-vitro disintegration time of the films decreases. Based on the *in-vitro* disintegration time, formulation FB1 and FB2 were found to be promising and showed a disintegration time of 22.00 and 38.67 sec respectively. CCS containing films rapidly exhibit high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrate the film rapidly. The results are given in Table 3.

Table 3: Evaluation of Fast Dissolving Films of Losartan potassium

FC	Weight (mg) \pm SD	Thickness (mm) \pm SD	Surface pH \pm SD	Folding endurance \pm SD	Disintegration time (sec) \pm SD	Drug content (%) \pm SD
FB1	1.06 \pm 0.092	0.128 \pm 0.0081	6.55 \pm 0.227	267 \pm 1.53	38.67 \pm 1.53	97.43 \pm 0.761
FB2	1.06 \pm 0.061	0.208 \pm 0.0047	6.20 \pm 0.062	253 \pm 4.04	22.00 \pm 1.73	98.53 \pm 0.761
FB3	1.00 \pm 0.171	0.208 \pm 0.0053	6.38 \pm 0.187	264 \pm 9.61	65.00 \pm 1.73	98.95 \pm 1.100
FB4	1.01 \pm 0.045	0.206 \pm 0.0072	6.57 \pm 0.222	256 \pm 4.04	49.33 \pm 0.58	98.42 \pm 0.772
FB5	1.88 \pm 0.880	0.186 \pm 0.0060	6.59 \pm 0.355	256 \pm 7.37	97.00 \pm 1.00	98.69 \pm 1.213
FB6	1.48 \pm 0.061	0.199 \pm 0.0048	6.37 \pm 0.344	242 \pm 2.08	78.67 \pm 1.15	98.14 \pm 0.339

*Average of three determinations

FC= Formulation Codes

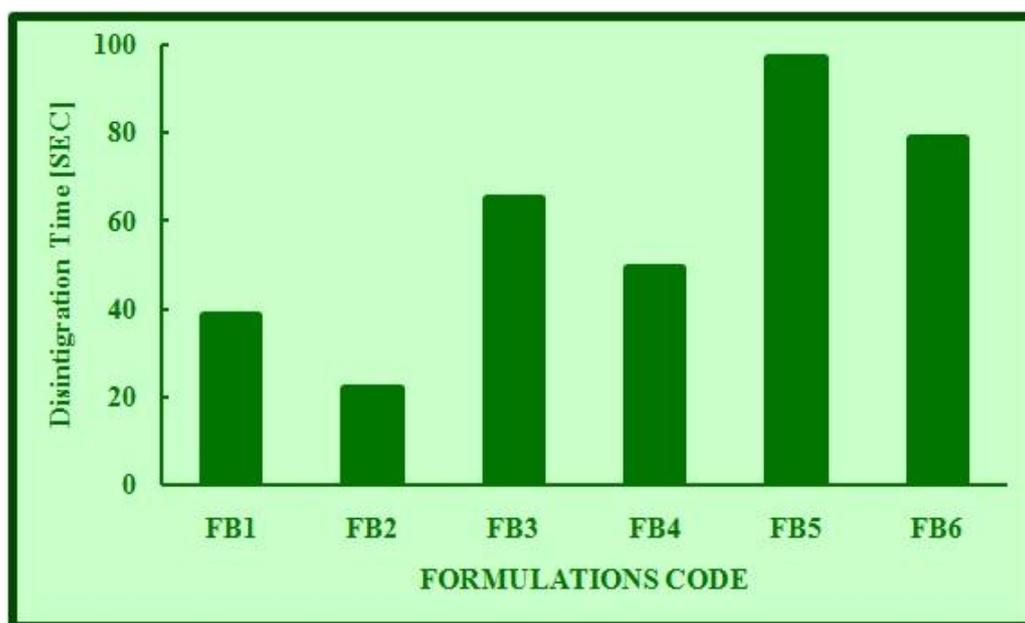


Fig 4: Disintegration time vs Losartan Potassium film formulation (FB1-FB6).

In-vitro Dissolution Study: In-vitro dissolution studies of the prepared films were performed in 0.1N HCl using USP type II (paddle) dissolution apparatus for 30 min. The dissolution studies were conducted in triplicate in using 0.1N HCl solution as dissolution medium for a period of 30 min.

The plot of % Cumulative drug release verses time (min.) were plotted and shown in Fig 5. The dissolution rate was found varied with increasing concentration of superdisintegrant. The drug release for the formulations (FB1 – FB2) which contains 750 mg HPMC15cps, 1.5 mg of PVA and increasing concentration of CCS (3 and 6%) was about 99.35% and 99.19% within 20 and 18 min respectively. The formulations (FB3 – FB4) contains 750 mg HPMC15cps, 1.5 mg of PVA and increasing concentration of CP (3 and 6%) drug release around 85.01% and 98.97% in 24 and 22 min respectively. Finally the formulations (FB5 – FB6) contains 750 mg HPMC15cps, 1.5 mg of PVA and increasing concentration of SSG (3 and 6%) drug release will be around 97.04% and 99.11% in within 26 and 24 min respectively. The rapid increase in dissolution of Losartan potassium with the increase in CCS may be due to rapid swelling and disintegrating films rapidly. CCS was found to be the best among the three superdisintegrants. Based on the *in-vitro* dissolution studies the formulation FB2 was found to be promising and showed drug release of 99.19%, in 18 mins. The fast dissolving films of Losartan potassium can be prepared by solvent casting method with film forming polymers HPMC, PVA and the superdisintegrants. CCS was found to be the best among the three superdisintegrants.

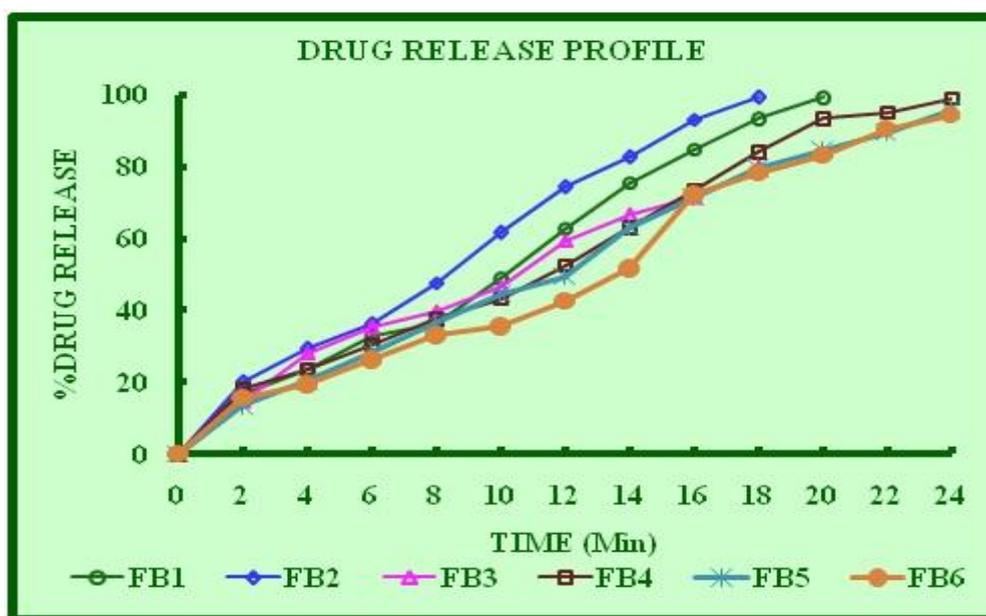


Fig 5: In-vitro Drug Release profile of formulations FB1- FB6.

CONCLUSION

The fast dissolving films of Losartan potassium can be prepared by solvent casting method with film forming polymers HPMC, PVA and different superdisintegrants exhibit quick disintegration and improved drug dissolution. Based on the *in-vitro* disintegration time, formulation FB2 were found to be promising and showed a disintegration time of 22.00sec. Based on the *in-vitro* dissolution studies the formulation FB2 was found to be promising and showed drug release of 99.19%, within 18 mins. CCS was found to be the best among the three superdisintegrants. However this FDF is useful for the improving of the bioavailability of the Losartan potassium.

ACKNOWLEDGEMENTS

The authors are thankful to **Sri. Sardar Raja Singh Sir**, Chairman and **Mrs. Latha Gupta Madam**, Director Admin, GRD (PG) Institute of Management and Technology, Dehradun, providing the facilities to carry out this research and to publish the research work.

REFERENCES

1. Galey WR, H K. Lonsdale and S. Nacht. Clinical The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water. J. Investigative Dermatol, 1976; 67(6): 713-717.
2. Crama A, Breitzkreutz J, Desset-Brèthes S, Nunnd T and Tuleuf C. Challenges of developing palatable oral pediatric formulations, Int J Pharm, 2009; 365: 1-3.
3. Florence AT, Neglected diseases, neglected technologies, neglected patients? Int J Pharm. 2008; 350: 1-2.
4. Liang AC, Chen LH. Fast Dissolving Intraoral Drug Delivery Systems. Exp. Opin. Ther. Patents, 2001; 11(6): 981-6.
5. Borsadia S, O'Halloran D, Osborne JL. Quick Dissolving Films-A Novel Approach to Drug Delivery. Drug Delivery Technology, 2003; 3(3): 63-66.
6. Klancke J. Dissolution Testing of Orally Disintegrating Tablets. Dissolution Technologies, 2003; 10(2): 6-8.
7. Parakh SR, Gothoskar AV. Review of Mouth Dissolving Tablet Technologies. Pharma Tech, 2003; 27(11): 92-100.
8. Jaysukh J Hirani, Dhaval A Rathod, Kantilal R Vadalia. Orally Disintegrating Tablets: A Review. Trop J Pharm Res, April 2009; 8(2): 161-172.

9. Bhyan Bhupinder, Jangra Sarita, Formulation and Evaluation of Fast Dissolving Sublingual Films of Rizatriptan Benzoate. *Int. J. Drug Dev. & Res*, 2012; 4(1): 133-143.
10. Supriya S, Sheetal PM, Vilas Rao K. Fast Disintegrating Palatable Theophylline Tablets for Pediatrics. *The International Journal of Pediatrics and Neonatology*, 2007; 9(1).
11. Swapnil L. Patil, Paresh R. Mahaparale, Madhavi A. Shivnikar, Shradha S. Tiwari, Ketan V. Pawar, Prashant N. Sane. Fast Dissolving Oral Films: An Innovative Drug Delivery System. *IJRRPAS*, 2012; 2(3): 482-496.
12. Bala R, Pawar P, Khanna S, Arora S. Orally Dissolving Strips: A New Approach to Oral Drug Delivery System. *Int J Pharma Investig*, 2013; 3: 67-76.
13. Arun Arya, Amrish Chandra, Vijay Sharma and Kamla Pathak. Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form. *Int. J. Chem Tech Res*. 2010; 2(1): 576- 583.
14. Manjunath B. Mendon and Roopa Karki. Design of Novel Oral Films as Drug Delivery System. *Int. J. of Pharm. & Life Sci*, 2013; 4(3): 2425-2431.
15. Honey Goel, Parshuram Rai, Vikas Rana and Ashok K. Tiwary. Orally Disintegrating Systems: Innovations in Formulation and Technology. *Recent Patents on Drug Delivery & Formulation*, 2008; 2: 258-274.
16. Farhana Sultana, Mohammad Arafat, Saiful I. Pathan. Preparation and Evaluation of Fast Dissolving Oral Thin Film of Caffeine. *IJPBS*, 2013; 3(1): 153- 161.
17. Debjit Bhowmik, Chiranjib.B, Krishnakanth, Pankaj, R.Margret Chandira. Fast Dissolving Tablet: An Overview. *Journal of Chemical and Pharmaceutical Research*, 2009; 1(1): 163-177.
18. Naziya Khatoon, Raghavendra Rao NG, Mahipal Reddy B. Overview on Fast Dissolving Oral Films. *Int. J. Chem. Pharm. Sci*, 2013; 1(1): 63-75.
19. K. Patel Nibha and SS. Pancholi. An Overview on: Sublingual Route for Systemic Drug Delivery. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2012; 3(2): 913-923.
20. Vondrak B, Barnhart S. Dissolvable films for flexible product format in drug delivery *Pharm Tech*, 2008; Suppl: S20-28.
21. Arnum PV. Outsourcing Solid Dosage Manufacturing. *Pharma Tech*, 2006; 30(6): 44–52.
22. Ghosh T, Pfister W. *Drug Delivery to the Oral Cavity: Molecules to Market*. Florida: CRC Press, Taylor & Francis, 2005.
23. Corniello CM. Quick-Dissolving Strips: From Concept to Commercialization. *Drug Delivery Technology*, 2006; 6(2): 68-71.

24. Richard Prasanna Raj K, Raghavendra Rao NG, Kistayya C, Sanjeev Nayak B. Effect of Natural Gums on Formulation of Oral Sustained Release Matrix Tablets of Losartan Potassium. International Journal of Pharmaceutical and Phytopharmacological Research. (eIJPPR). Int. J. Pharm. Phytopharmacol. Res, 2014; 3(6): 436-443.
25. Naziya Khatoon, Raghavendra Rao NG, Mahipal Reddy B. Formulation and Evaluation of Oral Fast Dissolving Films of Montelukast Sodium. International Journal of Pharmaceutical Sciences and Research. IJPSR, 2014; 5(5): 1780-87.