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Formulation and Evaluation of Fast Dissolving Oral Film of Losartan Potassium

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Abstract: ***Losartan potassium is an angiotensin-receptor blocker (ARB) used in the management of hypertension. The purpose of this research work was to formulate a fast dissolving film of Losartan potassium for the treatment of hypertension, by using polymers such as Hydroxy Propyl Methyl Cellulose E15 (HPMC) and Hydroxy Propyl Methyl Cellulose E5 (HPMCE5) in different concentrations. Films of Losartan potassium were prepared by solvent casting method using polymers such as HPMC E15 and HPMC E5 in different ratios. Propylene glycol and Glycerine was used as a plasticizer. The prepared films were subjected to different evaluation parameters like morphological properties, film thickness, folding Endurance, Surface pH, content uniformity, in vitro disintegration time and in vitro dissolution studies. The optimized formulation was subjected to stability studies, revealed that no significant changes occurs after 1 month of test period. Results of FTIR data of optimized formulation (X5) revealed that there was no incompatibility observed between the drug and excipients used in the formulation. These findings suggest that the fast dissolving oral film containing Losartan potassium is considered to be potentially useful for the treatment of Hypertension where quick onset of action is desirable.***

Keywords: Fast dissolving Film, HPMC E15, HPMC E5, Solvent - casting method

1. Introduction

The oral route is most popular route for the administration of therapeutic agents because of the low cost of therapy and ease of administration lead to high levels of patient compliance. The most popular oral solid dosage forms are tablets and capsules. Many patients find it difficult geriatric patients and do not lake their medicines as prescribed. Difficulty in swallowing or dysphagia is seen to afflict nearly 35% of the general population. [1] The fast dissolving drug delivery system a repreferred dosage form due to ease of transportation, specially designed for the drugs which have extensive manufacturing and more patient compliance. First pass metabolism and have low dose, for the generally geriatric, pediatric and bedridden patient enhancement of bioavailability experience difficulties in swallowing the conventional oral dosage form. To overcome this problem a novel formulation was developed i.e. Oral fast dissolving films. Fast-dissolving oral delivery systems are solid dosage forms. [2] Which disintegrate or dissolve within 1 min when placed in the mouth without drinking or chewing. Fast mouth dissolving films have become popular as a new delivery system because they are easy to administer and sudden-onset of drug action is possible as the films are taken through the sublingual route. [3] Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements to be made because of their some drawbacks rebated to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms.[4,5]

Advantages of orally fast dissolving film

1) No risk of chocking.
2) Convenient dosing or accurate dosing.
3) No need of water to swallow or chew.
4) Small size for unproved patient compliance.
5) Rapid onset of action.
6) Ease of handling and transportation.
7) Improve bioavailability for certain therapeutic ingredient.
8) Enhanced stability.
9) Ease of administration to pediatric, geriatric, bedridden patients and psychiatric patients who refuse to swallow tablets.
10) No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling.
11) Rapid dissolution and absorption of drug, which may produce rapid onset of action.
12) Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.[5]

Disadvantages of fast dissolving film

1) It is hygroscopic in nature so it must be kept in dry places.
2) It also shows the fragile, granule property.
3) They require special packaging for the products stability and safety.
4) High dose cannot be incorporated into the oral film.
5) Drugs which are unstable at buccal ph cannot be administered.
6) Drugs which irritate the mucosa cannot be administered by this route.
7) Drug with small dose requirement can only be

administered.

8) Taste masking- most drugs have bitter taste, and need taste masking.[5]

Components of fast dissolving film

Mouth dissolving film is a thin film with an area of 5-20 cm2 containing an active ingredient. The immediate dissolution, in water or saliva respectively, is reached through a special matrix from water-soluble polymers. Formulation considerations (plasticizers etc.) Have been reported as important factors affecting mechanical properties of the films, such as shifting the glass transition temperature to lower temperature.

A typical composition contains the following:

- Drug 1-25%
- Water soluble polymer 40-50%
- Plasticizers 0-20%
- Fillers, colors, flavors etc. 0-40%.[6]

2. Materials and Methods

Losartan Potassium were received as gift sample from **Mylan Pharma, Aurangabad,** India. HPMC E15 and HPMC E5 (Zim lab. Nagpur, India), Glycerine (S.D fine chemicals, Mumbai, India) All other chemicals were commercially available and used as received.

Film Manufacturing methods [7,8]

Fast dissolving films are manufacture with the help of different methods. One or combination of the following process can be used to manufacture the mouth dissolving films-

1) Solvent casting
2) Semisolid casting
3) Hot melt extrusion
4) Solid dispersion extrusion
5) Rolling

Solvent casting method

In solvent casting method water soluble polymers are dissolved in water and the drug. Along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the petri plate and dried.

Semisolid casting

In semisolid casting method firstly a solution of water soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. Cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion.

- Fewer Operation Units
- Better Content Uniformity
- An Anhydrous Process.

Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means Of dies.

Rolling method

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutter into desired shapes and sizes. Other ingredients including active agents dissolved in small portion of aqueous solvent using high shear processor water soluble hydrocolloids dissolved in water to form homogenous viscous solution.

Preformulation Studies

FTIR spectroscopy studies:

The FTIR spectroscopy was employed to further characterize the possible interaction between drug and excipients in the solid state on an Infrared spectrophotometer (Shimadzu Affinity-1) by conventional KBr plate method. 5mg of drug sample was mixed with 500 mg of powdered potassium bromide. The mixture was passed with 25,000 psi pressure in a press to formed a small pellet. IR spectrum of drug was recorded
in the frequency range 400-4000 cm^{-1}.

The Drug-Excipients Interaction studies:

DSC thermograms of pure drug Losartan Potassium and its physical mixture with polymer were carried out to investigate any possible interaction between the drug and polymer. The drug-excipients interaction study was carried out by using FTIR spectrophotometer and Differential scanning calorimetry.

Standard calibration curve of Losartan Potassium in Phosphate buffer 6.8:

100 mg of Losartan Potassium was accurately weighed, it was transferred in to 100 ml volumetric flask and and dissolved in small quantity (15- 20 ml) of Phosphate buffer 6.8. The volume was made up to the mark with Phosphate buffer 6.8 to get the concentration of l00µg/ml. This was treated as working standard. From solution having concentration 100 µg/ml aliquots of 0.5, 1 , 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5 ml were pipette out into 10ml volumetric flasks. The volume was made up to the mark with Phosphate buffer 6.8 to get the final concentration of 5, 10, 15, 20, 25, 30, 35 and 40, 45 and 50 µg/ml respectively. The absorbance of each concentration was measured at 230 nm.

Preparation of Fast Dissolving Film by solvent casting method:

Fast Dissolving Film of Losartan Potassium were prepared using hpmc E15 as polymer by solvent casting method. The hpmc E15 were dissolved in 8 ml water by using magnetic stirrer, similarly aspartame were dissolved in remaining 2 ml of hot water and to this mixed sucralose. Drug was dissolved in polymer solution. Plasticizer and citric acid were added to

polymer solution. Sweetener solution also added to polymer solution. The solution was allowed to stand for 30 min to allow deaeration to take place. The solution was casted on a petridish and dried at room temperature for 24 hr. The film was removed and cut into the required size of 3 x 2 cm^2.

Table 1: Formulation Batches of Fast Dissolving Film Of Losartan Potassium.

Formulation Batches	*Drug (mg)*	*HPMC (mg)*	*PEG 400 (mg)*	*Aspartame (mg)*	*Sucralose (mg)*	*Citric Acid (mg)*	*Water (ml)*
X1	15	400	100	40	20	20	10
X2	15	400	120	40	20	20	10
X3	15	400	140	40	20	20	10
X4	15	500	125	50	25	25	10
X5	15	500	150	50	25	25	10
X6	15	500	175	50	25	25	10
X7	15	600	150	60	30	30	10
X8	15	600	180	60	30	30	10

3. Evaluation of Fast Dissloving Films.[9]

a) Physical appearance
This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch.

b) Weight uniformity of films
Three films of the size 3×2 cm^2 were weighed individually using digital balance and the average weights were calculated.

c) Thickness of films
Thickness of the films was measured using screw gauge with a least count of 0.01mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken.

d) Folding endurance of films
The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (approximately 3x2 cm) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

e) In vitro disintegration time of films
In vitro disintegration time is determined visually in a Petri dish of 10 ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

f) Mechanical Properties
The Film were evaluated for the measurement of mechanical properties using tensile strength apparatus. Film of dimension 3 x 0.5 Cm^2 were held between two clamps at a distance of 2.5 cm. The Film were pulled by the clamp as weight is applied through one end. The mechanical properties like tensile strength and % elongation were calculated for the Film as described below.

Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture as a mean of three measurements and the cross-sectional area of the fractured film as described in the equation-

$$\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of die film (mm}^2\text{)}}$$

Percentage elongation was calculated by the following equation-

$$\text{Percentage elongation} = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

g) Surface pH of films
Surface pH was determined to reduce the irritation of oral mucosa due to alkaline or acidic pH. It was kept in the range of salivary pH. Surface pH was determined by the films were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode near the surface of films and allowing equilibrate for 1 min. Reading was recorded in pH meter.

h) Drug content uniformity study of films
The films were tested for drug content uniformity by UV-Spectrophotometric method. Films of 1×1 cm^2 were cut from three different places from the casted films. Each film was placed in 10 ml volumetric flask and diluted with Phosphate buffer 6.8 up to 10 ml. The absorbance of the solution was measured at 256 nm using UV/visible spectrophotometer (Shimadzu UV-1800). The percentage drug content was determined.

i) Taste evaluation
Taste acceptability was measured by a taste panel consisting of human volunteers (n=5) with 25 mg drug and subsequently film sample containing 15 mg drug held in mouth until disintegration, then spat out and the bitterness level was recorded. The volunteers were asked to gargle with distilled water between the drug and sample administration. Following scale was used for the indicating taste masking values.

j) In vitro Dissolution Study
In vitro dissolution of Losartan potassium oral dissolving films was studied in USP XXIV dissolution test apparatus 900ml Phosphate buffer 6.8 solution was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution medium was maintained at 37±0.5°C throughout the experiment One film was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe. Solution was filtered with whatman filter paper. Sample were withdraw after 2, 5, 10,

15, 20, 25, 30 minute intervals of time and analyzed for drug release by measuring the absorbance at 256 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium Cumulative percent Losartan potassium released was calculated and plotted against time.

k) Stability Studies:[10,11]

The purpose of 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, light and enables recommended storage conditions, re-test periods and shelf lives to be established. International Conference on Harmonization specifies the length of study and storage conditions:

Long term testing: 25°C ± 2°C *1*60 % RH ± 5 % for 12 months.

Accelerated testing: 45°C ±2°C *1*75 % RH ± 5 % for 6 months.

In the present study, stability studies were carried out at Room Temperature and 45°C ±2°C *1*75 % RH ± 5 % for a specific time period up to 28 days for the optimized formulation. The optimized formulation was analyzed for the Physical appearance, Drug content, Disintegration Time.

4. Result and Discussion

Drug-Excipient Interaction studies by FTIR: The spectrum of Losartan Potassium showed sharp peaks obtained in FTIR of pure drug for groups are found respective, C-H :- 3000-3100 cm"[1], CH :- 2800-3000 cm"[1], -C=O :- 1625-1750 cm"[1], C=C 1600-1675 cm"[1], Al-CH 1440-1500 cm"[1], Ar-CH 1091-1100 cm"[1], Ar-CH :- 913,655 cm"[1].

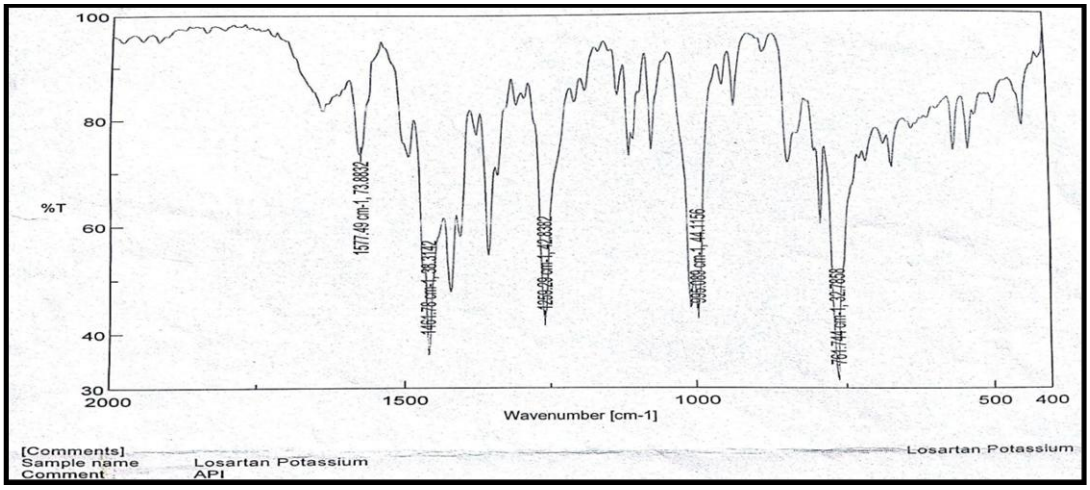

Figure 1: FTIR spectrum of Losartan potassium

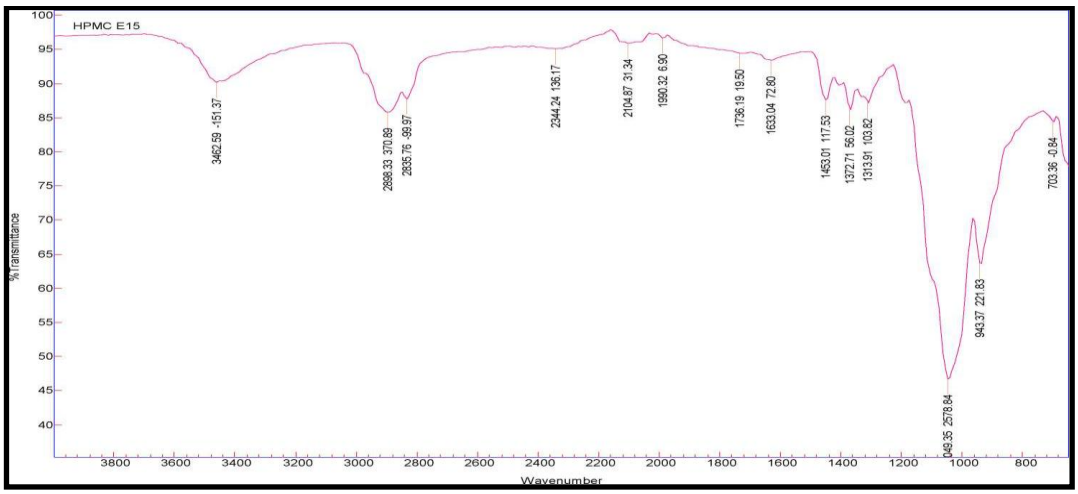

Figure 2: FTIR spectrum of Hpmc E15

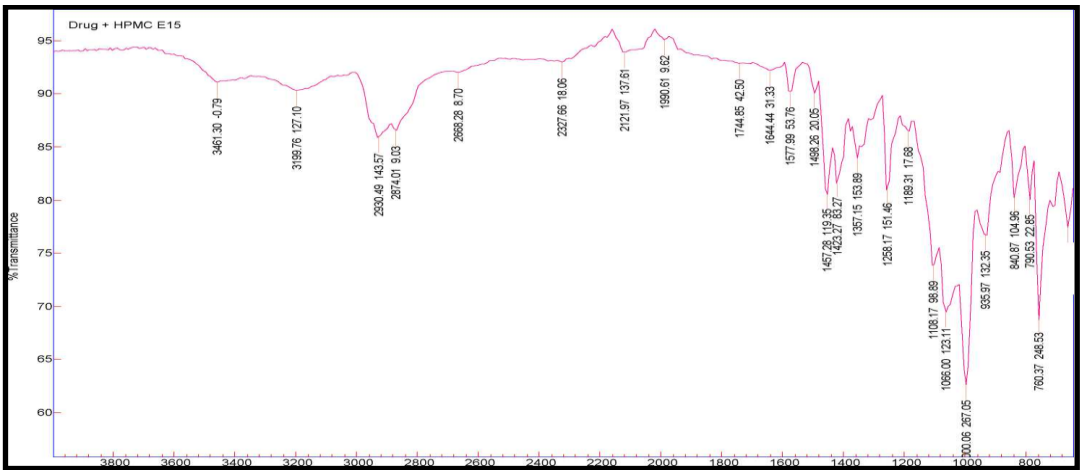

Figure 3: FTIR spectrum of Losartan Potassium and Hpmc E15

Calibration Curve of Losartan Potassium in Phosphate buffer pH 6.8:

After scanning 10 µg/ml solutions, only one peak at 230 nm was observed and considered as λ max. From the standard curve, it was observed that the drug obeys Beer's law in concentration range of 5-50 pg/ml in Phosphate buffer pH 6.8. Drug showed good linearity with regression of coefficient (r^2 = 0.996) and equation for this line obtained was found to be (y = 0.112x + 0.103) which is used for the calculation of amount of drug and dissolution study.

Table 2: Standard calibration curve of Losartan Potassium at 230 nm in Phosphate buffer 6.8:

Sr. No.	*Concentration (µg/ml)*	*Absorbance*
1	5	0.340
2	10	0.616
3	15	0.884
4	20	1.149
5	25	1.378
6	30	1.602
7	35	1.837
8	40	2.051
9	45	2.279
10	50	2.453

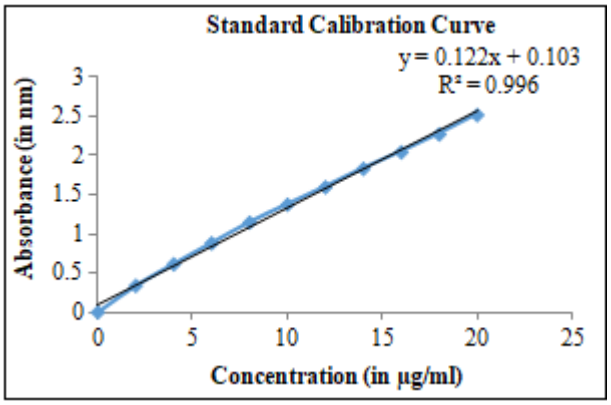

Figure 4: Calibration Curve of Losartan Potassium in Phosphate buffer pH 6.8:

Table 3: Evaluation of Fast Dissolving Film Formulation Batches X1 to X8 (Final Formulation)

Batch no.	*Appearance*	*Folding endurance*	*DT (Sec)*	*Thickness (MM)*	*Tensile strength (gm/mm^2)*	*% Elongation*
X1	Transparent	82±0.57	09	0.063±0.0018	5.09	13.33
X2	Transparent	136±1.52	10	0.066±0.008	4.80	16.66
X3	Transparent	125±1.02	11	0.068±0.0008	4.49	20.00
X4	Transparent	185±1.15	11	0.077±0.0008	5.65	20.00
X5	Transparent	257±2.51	04	0.079±0.001	5.32	26.66
X6	Transparent	201±1.59	13	0.082±0.001	4.89	30.00
X7	Transparent	166±1.20	15	0.086±0.0013	6.98	26.33
X8	Transparent	223±1.61	16	0.089±0.002	6.29	30.00

5. Evaluation Parameter

a) Physical appearance: This parameter was cheeked simply with visual inspection of films and evaluation of texture by feel, or touch, The observation suggests that the films were having smooth surface and Transparent.

b) Weight uniformity of films: Three films of the size 3x2 cm^2 were weighed individually using digital balance and the average weights were calculated. Weight of Films in formulation X1 to X8 were about 51.4 ±042, 51.9 ± 0.15,52.5 ±0.22, 53.9 ± 0.10, 54.3 ±0.24, 54.8 ± 0.18, 55.6 ±0.15, 60 ± 0.10 mg respectively. Film were found to be uniform in weight with same concentration of polymer.

c) Thickness of films: The thickness of the films was measured using micro meter screw gauge and the average thickness of all films was given in Table 27. The average thickness of X1 to X3 were found to be 0.063±0.0018, 0.066±0.008, 0.068±0.0008 respectively. The average thickness of X4 to X6 were found to be 0.077±0.0008, 0.079±0.001, 0.082±0.001 respectively. Where as the average thickness of X7 to X8 were found to be 0.086±0.0013,0.089±0.002 respectively. From the above observation it was observe that increased in polymer concentration increases thickness of the film. Similarly increased in plasticizer concentration slightly increases film thickness.

d) Folding endurance of films: The folding endurance of the films was determined by repeatedly folding a small strip of the films at the same place till it broke and the average folding endurance of all films. The folding endurance of prepared films were about 82±0.57, 136±1.52, 125±1.02 for X1 to X3 batches respectively. For X4 to X6 batches it were 185±1.15, 257±2.51, 201±1.59 respectively and for X7 to X8 batches it were about 166±l.20, 223±1.61 respectively. From all batches X5 batch shows higher folding indurance.

e) In vitro disintegration time of films: The average disintegration time of different formulation was shown in Table 28. The in vitro disintegration time of the films prepared with final formulation shows disintegration time 09,10,11,11,12,13,15,16 second for X1 to X8 batches From the observation it was observe that as the concentration of polymer increase disintegration time increased.

f) Mechanical Properties: Mechanical properties such as Tensile strength and % Elongation of different formulation was shown in Table 27. The Tensile strength of all formulation Xl to X8 were found to be 5.09, 4.80, 4.49, 5.65, 5.52, 4.89, 6.98, 6.29 respectively. Similarly % Elongation was in the range of 13.33 to 30.00 % respectively for all batches. From above observation it was concluded that Tensile strength decreased with increase in plasticizer concentration and % Elongation increased with increase in plasticizer concentration.

g) Surface pH of films:
Surface pH was measured to determined formulation having range of salivary pH. Acidic or alkaline pH may produced irritation to oral mucosa.Surface pH for all formulation XI to X8 were found in the range of 6.5 to 6.6. The surface pH of all the films was within the range of salivary pH . No significant difference was found in surface pH of different films.

h) Drug content uniformity study of films: Drug content uniformity for all formulation were shown in Table 28. Drug content for all formulation was found to be in the range of 96 % to 99% which shows uniformity of drug content in all formulation.

Dissolution study

The in vitro drug released study of fast dissolving film from each batch X1 to X8 was carried out in phosphate buffer 6.8 solution for 30 min. The plot of % cumulative drug release V/s time (min) were plotted % cumulative drug release from batch X1 to X3 were about 96.89, 97.26, 96.86 % respectively. % cumulative drug release from batch X4 to X6 were about 96.02, 94.89, 93.56 % respectively. % cumulative drug release from batch X7 to X8 were about 91.92, 89.56 % respectively. From the above observation it was observe that as the concentration of polymer increased drug released from film decreases. About 90 to 98 % drug release within a 30 min and in all formulation 60 to70 % drug release with in 5 min.

Table 4: Cumulative% Drug Release of oral fast dissolving film of Losartan Potassium

Sr No.	Time (min)	Cum. Drug Released (mg)	% Cum. Drug Released	% CD Remaining	Log % CD Remaining
1	0	0	0	100	2
2	2	6.702	26.81	73.19	1.8644
3	5	16.702	66.81	33.19	1.5210
4	10	19.52	78.11	21.89	1.3402
5	15	21.895	87.58	12.42	1.0941
6	20	22.922	91.69	8.31	0.9196
7	25	23.482	93.93	6.07	0.7831
8	30	23.722	94.89	5.11	0.7084

6. Conclusion

The present study has been a satisfactory attempt to formulate fast dissolving film of Losartan potassium with a view of improving its oral disintegration and giving a rapid release of the drug. From the experimental results it can be concluded that. The various polymers were used for screening amongst them the films prepared by Hpmc E15 shows good disintegration time.

X5 formulation showed best possible result and was selected as optimized batch. Formulated film gives satisfactorily result for various evaluation of films like physical appearance, and surface texture, weight uniformity, thickness uniformity, Folding endurance , Surface pH, Drug content uniformity, In vitro Disintegration time, In vitro drug release. Formulation showed fairly acceptable values for all the evaluation test. From evaluation it was concluded that disintegration time of the film increased with increased in polymer concentration. Hence, finally it was concluded that the prepared film of Losartan potassium may prove to be potential candidate for safe and effective fast dissolving drug delivery.

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