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FORMULATION AND EVALUATION OF FAST DISSOLVING FILMS OF LISINOPRIL

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Keywords:

Lisinopril, Fast dissolving film, Hydroxypropyl methylcellulose 6 cps, polyvinyl pyrrolidone and polyvinyl alcohol

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ABSTRACT

Objective of this study was to formulate Fast dissolving film of taste masked lisinopril by using water soluble polymers: Hydroxypropyl methylcellulose 6 cps, polyvinyl pyrrolidone and polyvinyl alcohol to assist patients of any age group for easy administration. Combination of HPMC 6cps with PVP and PVA provided with film having acceptable dissolving time. To optimise Experimental Design and Optimization Technique was employed. Formulation of batch C (2 cm × 2 cm film) : 6 mg HPMC 6cps, 6 mg PVA, 4.82 mg Lisinopril, 2.04mg Glycerol, 0.74 mg Sucralose, and 0.3 mg BTM agent. Study was carried out to see the effect of drug loading on the mechanical property of the film. It indicated that drastic change observed in the mechanical property of the film containing HPMC 6cps as compared to the one with PVP and PVA. Further stability study was carried out that indicated the need of moisture proof packaging for the prepared fast dissolve film.

INTRODUCTION

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, Pain avoidance and most importantly the patient compliance. The most popular solid Dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the Swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people[1,2].

Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapi-melts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics. Their growing importance was underlined recently when European pharmacopoeia adopted the term "or dispersible tablet" **as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.** According to European pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach in development of FDT is the use of super disintegrants like cross linked carboxymethyl cellulose (Crosscarmellose), sodium starch glycolate (primo gel, explotab), polyvinylpyrollidone (Polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients,

tablet compression, and disintegration addition[3]. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities.

CRITERIA FOR FAST DISSOLVING DRUG DELIVERY SYSTEM[4]:

The tablets should

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging
- Equipments at low cost.

BENEFITS OF FAST DISSOLVING FILM:

Fast dissolve film combines all the advantages of tablets (precise dosage, easy application) with those of liquid dosage forms (easy swallowing, rapid bioavailability).

- Difficulties caused from swallowing and choking of tablets are circumvented. That is especially advantageous for children and geriatric patients, or in diseases with nausea or vomiting.
- The dissolution of active ingredient is a prerequisite for absorption. Dissolution of fast dissolve film already happens in the oral cavity, which allows absorption via the oral mucosa. Therefore, target plasma levels[5] are reached quicker. Whereas, with conventional tablet quick plasma levels cannot be attained.
- The film disintegrates/dissolves immediately after application in the mouth. The resulting drug suspension/solution can easily be swallowed and the patient has no sense of a foreign body. The system ensures an excellent patient compliance even in cases of nausea.
- Children cannot spit the drug out because the film adheres to the upper gum after dissolution. Therefore, safe application is increased in the children.
- As a single dose application, the precision of the dose can be ensured, which is not the case with drops or syrups. Hence convenient dosing possible.

- No water needed while administering the dosage form.
- Taste masking and enhanced stability of drug can be achieved.
- The Film can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets.
- From a marketing perspective the fast dissolve film can be used for life cycle management especially if a substance is about to lose patent protection.
- Film can easily be carried, store and handle such is not the case with ODTs which are fragile and friable.
- Films do not require any special packing whereas ODTs require special and expensive packing system.

LIMITATIONS OF FAST DISSOLVING FILM[6]:

- It is challenging to incorporate pharmaceutical actives into Fast Dissolving Film. There is limited space available in the film. Therefore, this delivery system is not suitable for all APIs especially in case where high dose of API is to be given. To overcome this, either one can go for delivering higher loads of API by instructing the consumer to take multiple strips per day or increase film thickness. By increasing film thickness, the weight per strip will increase therefore, the load of the API will increase proportionally for the same film matrix. A negative impact of increasing the film thickness is that the dissolution rate will decrease which is not desirable. The slower dissolution rate will usually cause the filmstrip to feel gummy in the oral cavity.
- To achieve the content uniformity i.e. uniform distribution of API per film strip is a great challenge.
- Non-uniformity of a drug in film due to the agglomeration or separation of particles within the film is a problem yet to be solved.
- Taste masking of the bitter active is required and it is also challenging.

MANUFACTURING PROCESS:

One or a combination of the following processes can be used to manufacture the Fast Dissolve Film: Hot-Melt Extrusion, Solid Dispersion Extrusion, Rolling, Semi-Solid Casting, and Solvent Casting.

The current preferred manufacturing process for making fast dissolve film is solvent casting. Water-soluble hydrocolloids are completely dissolved in water in a mixing tank to form a

homogenous viscous solution. Other ingredients, including active agents, are dissolved in a small portion of aqueous solvent using a high-shear processor. The active mixture is then added to the viscous hydrocolloid solution to form a homogenous viscous solution. This viscous solution is degassed under vacuum. The resulting bubble-free solution is coated on a non-treated casting film. The coated film is subsequently sent into an aeration-drying oven. The dry film is then cut into the desired shape and size for the intended application. Hot-Melt Extrusion is one of the methods that can be used to minimize and eliminate the disadvantages of conventional solvent cast method. Much work has been done for the development of Hot-Melt Extrusion technique for film preparation.

EVALUATION OF THE FAST DISSOLVING FILM [7,8,9]:

Normally, Fast-Dissolve Film should be stiff, flat, and should not curl on the edges. The fast dissolve film strip must be robust enough to be removed from the unit-dose packaging without breaking. The strip must also dissolve readily in order to deliver the API rapidly when placed on the tongue. Mechanical property of fast dissolve film is as important as its solubility rate. So the prepared fast dissolving films were subjected to testing of following evaluation parameters:

Measurement of dissolving time:

Dissolving time was measured (n=3) for film of each batch in 10 ml of simulated saliva (12 mM KH_2PO_4, 40 mM NaCl, 1.5 mM $CaCl_2$ and NaOH to pH 6.8). Film sample (2 cm x 2 cm) was placed in 10 ml of simulated saliva. The medium was kept mildly agitated using a magnetic stirrer. The time for complete dissolution of the film was recorded as dissolving time. The average of three measurements was taken into consideration.

Measurement of Mechanical Properties:

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters - tensile strength, elastic modulus, % strain, and load at yield.

Mechanical properties of film were evaluated using universal testing machine (Software Nexygen 4.5, Hardware LS Plus, Ametek Lloyd Instrumentation, UK) with 1 N preload force. Film strip with dimension 40 mm x 25 mm was held between two clamps positioned at a distance of 40 mm. During measurement, the strip was pulled at a speed of 60 mm/min. The values of mechanical properties were recorded when the film broke. Measurements were run in triplicate for each film. Four mechanical properties namely tensile strength, elastic modulus, % strain, and load at yield of films were evaluated.

In Vitro Dissolution Studies:

The dissolution study was carried out using USP XXIII paddle apparatus (Model TDT-00T, Electrolab, Mumbai, India), at 37˚C ± 0.5˚C using 300 ml of distilled water or 300 ml of simulated saliva (12 mM KH_2PO_4, 40 mM NaCl, 1.5 mM $CaCl_2$ and NaOH to pH 6.8) as a dissolution medium. The agitation rate of paddle was 50 rpm. The drug loaded film (2cm x 2cm) was hanged in the dissolution media after fixing one side of the film on 5 g weight using two sided adhesive tape. Five ml samples were withdrawn at 10, 20, 30, 40 and 50 sec time interval and were filtered through 0.45µ and analyzed spectrophotometrically at 276nm (Model UV-1700, Pharmaspec, UV – Visible Spectrophotometer, Shimadzu, Japan). An equal volume of the fresh dissolution media, maintained at the same temperature, was added after withdrawing the sample.

Thickness of film:

The thickness of each film was measured (n=3) using calibrated ocular stage micrometer slide and microscope. Three film samples (2 cm x 2 cm) were cut from three different locations of 68 cm^2 film. The film was placed in vertical position supported by two clamps below the lens.

Measurement of folding endurance:

A film strip of 2 cm x 2 cm was repeatedly folded and unfolded at the same place till it broke (n=3). The number of times, the film could be folded at the same place, without breaking was recorded as the value of folding endurance.

Drug content uniformity:

Five film units (2 cm x 2 cm) were cut from the four corners and the central part of the film (n=3). Each film unit was placed in 100 ml of distilled water. The solutions were filtered and analyzed at 276 nm in a UV-Visible Spectrophotometer (Model UV-1700, Pharmaspec, UV-Visible Spectrophotometer, Shimadzu, Japan). The average of five films was taken as the content of drug in one film unit.

Morphology study:

Morphology of the optimized film was observed using light microscope (Labomed) to which color CCD Camera (AVC 550P/NL, DC 12 V 150 mA) was attached.

MATERIALS AND METHODS

Lisinopril IP was procured by Lincoln Pharmaceuticals, Ahmedabad, Hydroxypropyl methylcellulose USP 2910 by Signet, Mumbai, Polyvinyl Pyrrolidone (PVP) (K – 30) IP, Polyvinyl Alcohol (PVA) USP by Laser Laboratories, Ahmedabad.

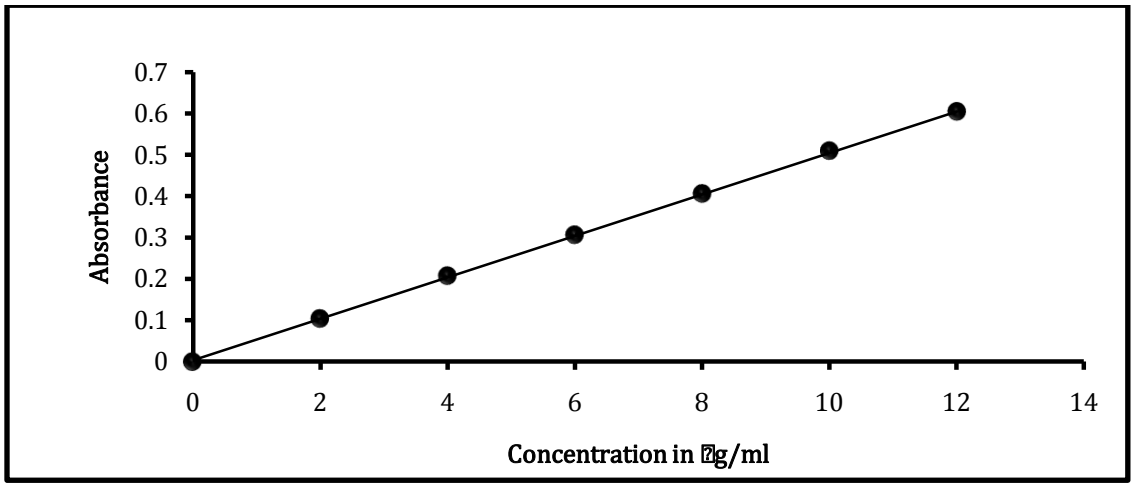
Spectroscopic Analysis of Lisinopril:

In the present work, lisinopril was estimated by UV-Visible Spectrophotometric method using dissolution media Simulated Saliva.The results are shown in Table 1.

Table 1 : Results of spectrophotometric analysis of Lisinopril in simulated saliva

Sl No.	Concentration (µg/ml)	Absorbance at 206 nm
1	2	0.104
2	4	0.207
3	6	0.305
4	8	0.404
5	10	0.507
6	12	0.602

Figure 1: Standard curve of lisinopril



Results of Weighted Linear Regression:

Y = 0.049x + 0.005, R2 = 0.999

PREPARATION OF THE FILM

Films of single polymer and their combinations were prepared by **solvent-casting** method. The polymer, optimized amount of plasticizer, optimized amount of sweetner, flavor and the required amount of drug were dissolved in 20 ml distilled water. The aqueous solution was stirred for 5 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a plastic petridish having 68 cm^2 surface areas and was dried at controlled room temperature (25° - 30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the petridish and was cut into size required for testing. The films were stored in airtight plastic bags till further use.

Table 2: Preparation of polyvinyl pyrrolidone (PVP) films (Optimisation of plasticizer)

Ingredients	Batch P_1	Batch P_2	Batch P_3	Batch P_4
Lisinopril (mg)	25	25	25	25
Polyvinyl pyrrolidone K-30 (mg)	200	200	200	200
Glycerol (% of Polymer)	5	10	15	20
Distilled Water (ml)	20	20	20	20
Separability	-	-	-	-
Physical Characteristics	Sticky	Very sticky	Very sticky	Very sticky

Table 3: Preparation of polyvinyl pyrrolidone films (Optimisation of polymer concentration)

Ingredients	Batch P_5	Batch P_6	Batch P_7	Batch P_8
Lisinopril (mg)	25	25	25	25
Polyvinyl pyrrolidone K-30 (mg)	200	300	400	500
Glycerol (% of Polymer)	5	5	5	5
Distilled Water (ml)	20	20	20	20
Separability	-	-	+	+
Physical Characteristics	Sticky	Sticky	Poor handibility	Poor handibility

Table 4: Preparation of polyvinyl alcohol (PVA) films (Optimisation of plasticizer)

Ingredients	Batch V_1	Batch V_2	Batch V_3	Batch V_4
Lisinopril (mg)	25	25	25	25
Polyvinyl alcohol (mg)	200	200	200	200
Glycerol (% of Polymer)	5	10	15	20
Distilled Water (ml)	20	20	20	20
Separability	-	-	-	-
Physical Characteristics	Very sticky	Very sticky	Very sticky	Very sticky

Table 5: Preparation of polyvinyl alcohol films (Optimisation of polymer concentration)

Ingredients	Batch V_5	Batch V_6	Batch V_7	Batch V_8
Lisinopril (mg)	25	25	25	25
Polyvinyl alcohol (mg)	200	300	400	500
Glycerol (% of Polymer)	5	5	5	5
Distilled Water (ml)	20	20	20	20
Separability	-	+	+	+
Physical Characteristics	Very Sticky	Sticky & Poor handibility	Poor handibility	Poor handibility

<u>Hydroxypropyl Methylcellulose Films</u> :(Optimisation of plasticizer and Selection of HPMC grade)

Table 6 : Preparation of hydroxypropyl methycellulose (HPMC) 6cps films

Ingredients	Batch A_1	Batch A_2	Batch A_3	Batch A_4
Lisinopril (mg)	25	25	25	25
Hydroxypropylmethycellulose **6 cps** (mg)	200	200	200	200
Glycerol (% of Polymer)	5	10	15	20

Distilled Water (ml)	20	20	20	20
Separability	+	+	+ +	+ +
Physical Characteristics	No stickiness	No stickiness	No stickiness	Slightly sticky
Dissolving Time (sec)	79	72	73	85

Table 7: Preparation of hydroxypropyl methycellulose (HPMC) 15cps films

Ingredients	Batch B_1	Batch B_2	Batch B_3	Batch B_4
Lisinopril (mg)	25	25	25	25
Hydroxypropylmethycellulose **15 cps** (mg)	200	200	200	200
Glycerol (% of Polymer)	5	10	15	20
Distilled Water (ml)	20	20	20	20
Separability	+	+	+ +	+ +
Physical Characteristics	No stickiness	No stickiness	No stickiness	Slightly sticky
Dissolving Time (min)	1.3	1.45	1.25	1

Table 8: Preparation of hydroxypropyl methycellulose (HPMC) 50cps films

Ingredients	Batch C_1	Batch C_2	Batch C_3	Batch C_4
Lisinopril (mg)	25	25	25	25
Hydroxypropylmethycellulose **50 cps** (mg)	200	200	200	200
Glycerol (% of Polymer)	5	10	15	20
Distilled Water (ml)	20	20	20	20
Separability	+	+	+	+ +
Physical Characteristics	No stickiness	No stickiness	No stickiness	No stickiness
Dissolving Time (min)	1.75	1.85	1.73	2.1

Table 9: Formulation of taste masked film using sweetner (sucralose) and flavor (BTM Agent)

Ingredients	Batch A_{31}	Batch A_{32}	Batch A_{33}	Batch A_{34}
Lisinopril (mg)	25	25	25	25
Hydroxypropylmethycellulose 6 cps (mg)	200	200	200	200
Glycerol (% of Polymer)	15	15	15	15
Sucralose (% of drug)	**5**	**10**	**15**	**20**
BTM Agent (0.5% dispersion) (ml)	**1**	**1**	**1**	**1**
Distilled Water (ml)	20	20	20	20
Bitter Index Level	**2.5**	**1**	**0**	**0**

Table 10: Preparation of film using blend of polymers

Ingredients	F1	F2	F3	F4
Lisinopril (mg)	25	25	25	25
Hydroxypropylmethycellulose 6 cps (mg)	100	**100**	--	100
Polyvinyl pyrrolidone K-30 (mg)	100	--	100	50
Polyvinyl alcohol (mg)	--	**100**	100	50
Glycerol (% of Polymer)	15	**15**	15	15
Sucralose (% of drug)	3.75	3.75	3.75	3.75
BTM Agent (0.5% dispersion) (ml)	1	**1**	1	1
Distilled Water (ml)	20	**20**	20	20

Figure 2 – Morphology of optimized batch F2

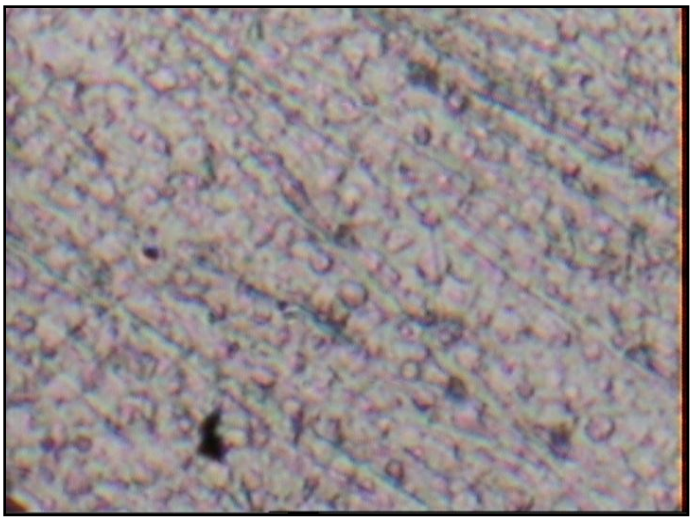
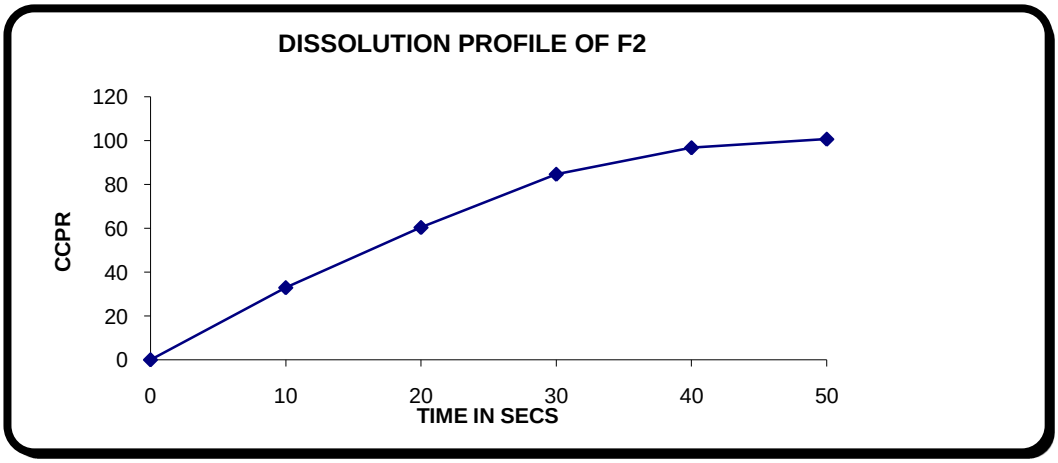


Table 11 – Evaluation parameters of Lisinopril fast dissolving films

Formulation code	F1	F2	F3	F4
Thickness (mg)	0.34 ± 0.02	0.44 ± 0.02	0.24 ± 0.02	0.54 ± 0.02
Folding endurance	>300	>300	>300	>300
Disintegration (secs)	27.6 ± 1.07	26.8 ± 2.03	27.9 ± 2.03	27.02 ± 1.02
Tensile strength (kg/cm^2)	1.143 ± 0.030	1.326 ± 0.020	1.476 ± 0.025	1.496 ± 0.035
Separability	++	++	-	+ +
Physical Characteristics	No stickiness and good handibility	**No stickiness and good handibility**	Very sticky and poor handibility	No stickiness and good handibility

Figure 3 - The dissolution profile of formulation the optimized formulation F2



DISCUSSIONS

The films were prepared by using polyvinyl pyrrolidone as shown in Table 2 . The casted solution dried by application of microwaves gave film of unacceptable characteristics. Film obtained by drying the casted solution at controlled room temperature showed poor separability and also has unaccepatable physical characteristics. So further the films with varied concentration of polyvinyl pyrrolidone were prepared as shown in Table 3 (dried at controlled room temperature) which also showed very poor mechanical properties. This may be because the molecular compactness required for better mechanical properties cannot be obtained with polyvinylpyrrolidone. So further studies was carried with polyvinyl alcohol as in Table 4 which gave films of unacceptable characteristics. Film obtained by drying the casted solution at controlled room temperature showed poor separability and also has unaccepatable physical characteristics. So further the films with varied concentration of polyvinyl alcohol were prepared in Table 5 which had no required mechanical properties since it may be lacking in molecular compactness.

The casted solution subjected to microwaves was unacceptable since HPMC is known to get gelled even at 50˚C. So it was not possible to follow drying by microwave oven. From the results film formed (dried at controlled room temperature) with acceptable physical characteristics (No stickiness and good handibility) in all the batches. With respect to dissolving time, film of batch A is more acceptable then batch B and C, because it showed lowest dissolving time (in terms of seconds) which is preferred. Film of batch A_1 and A_2 showed moderate separability, it may be due to the inadequate amount of plasticizer. While film of batch A_4 showed slight stickiness which may be due to the slight increased amount of plasticizer. Film of Batch A_3 shows good separability, no stickiness and low dissolving time and hence acceptable. So further studies were carried out using HPMC 6 cps as polymer system (Table 6, 7, 8). Drying at controlled room temperature was followed. Moreover plasticizer concentration was kept 15% of polymer (since with batch A_3 good separability obtained) in further studies.

Further approaches was tried to mask the bitter taste of the formulation was addition of sweetner and flavour as shown in Table 9. To batch A_3, sucralose was added in concentration: 5, 10, 15 and 20 % of the polymer. To the same 1ml of 0.5 % dispersion of BTM agent was added. Out of the four concentrations the bitterness of the drug was masked by addition of about 12.3 mg (i.e 15 % of drug) of sucralose and 5 mg of BTM agent. That is batch A_3 gives taste masked film.

Later film was prepared using combination of polymers. HPMC 6 cps polymer system gives good quality film with acceptable physical characteristics as well as satisfying dissolving criteria. But still there is a need for reducing the dissolving time since film that remains about 80 sec to 1 min in oral cavity will make patient uncomfortable and will have gummy feeling. So attempt was made to have film with less dissolving time by preparing it using combination of polymers i.e. combination of HPMC 6 cps, polyvinyl pyrrolidone and polyvinyl alcohol. From Table 10, it could be said that all batches give acceptable film except F3. As discussed earlier due to lack of molecular compactness with PVP and PVA, film of F3 did not give good quality film. Films of batch F_1, F_2, and F_4 are upto the required criteria, especially low dissolving time; this may be due to the incorporation of PVP and PVA. PVP and PVA are known to have hydrogen bond potential and hence faster dissolution thus the optimized batch is F2.

All the four films F1, F2, F3 and F4 prepared with different polymer concentrations were found to be flexible, smooth, transparent, nonsticky and homogeneous, indicating that the polymers used in the study had good film-forming properties. The four films F1, F2, F3 and F4 prepared were evaluated for various parameters as shown in Table 11. Morphology of the optimized film (F2) was observed as shown in figure 2 using light microscope (Labomed) to which color CCD Camera was attached. The film of lisinopril was translucent. Morphology study of the film with light microscope showed some little pores. Drug crystals were not observed. Striations were observed which may be due to the rough surface of the plastic petridish. The thickness of 4 films of each formulation was determined using a micrometer screw gauge, and the average thickness was determined. The values were found to be in the range of 100–200 μm, which is said to be acceptable for fast-dissolving films. The films with increased polymer content showed a moderate increase in thickness. All the formulations showed a good folding endurance value of greater than 300.The in-vitro disintegration time was found to be in the range of 26.8 –27.9 seconds. The tensile strength gives an indication of the strength and the elasticity of the film reflected by the parameters tensile strength and elongation at break (E/B). The percentage drug content of all formulations was found to be in the range of 95–97%. In-vitro dissolution testing of the optimised formulation F2 was carried out in phosphate buffer pH 6.8 and was found to release 100% in just 50 seconds as shown in figure 3.

CONCLUSION

The objective of the present investigation has been achieved by preparing fast-dissolving films of lisinopril for the effective management of hypertension and cardiac diseases. The present study also investigated the feasibility of the drug for sublingual delivery by formulating into fast-dissolving films using polymers for the purpose of improving their bioavailability and quick onset of drug action. The drug has a metallic taste and hence an attempt was made to mask the taste by adding the artificial sweetener sucralose. The method of preparation was found to be simple and required minimum excipients, thus making the product cost-effective. Finally, it can be concluded that this delivery system has the potential of overcoming the drawbacks associated with tablet formulations available in the market presently.

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