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Research Article

DEVELOPMENT AND *IN VITRO* EVALUATION OF MOUTH DISSOLVING FILMS OF CAPTOPRIL

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ABSTRACT

Captopril is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I (AT I) to angiotensin II (AT II). Captopril may be used in the treatment of hypertension. Thus formulating Captopril into a fast dissolving dosage form would provide fast relief. The bitter taste of Captopril was masked with β-cyclodextrin. Inclusion complexes of drug β-cyclodextrin were prepared by kneading method in 1:1 molar ratios. The prepared inclusion complexes were characterized by FTIR spectroscopy suggesting no interaction. The oral fast dissolving films were prepared by using different polymers like HPMC, PVA, PVP and carbopol 934P with super disintegrants like micro crystalline cellulose (MCC) and croscarmellose sodium (CCS). The prepared films evaluated for folding endurance, swelling index, surface pH, in-vitro disintegration time, drug content, FTIR study, and in-vitro drug release. The physical appearance and folding endurance properties were found to be good with the films having clear, colorless and smooth surface without any scratches. The average folding endurance time was found within the range of 123 to 196 times. The drug content was found in the range of 92.21% to 98.97%. The in-vitro disintegration time was found to be in the range of 15 to 48 sec and the surface pH of the all formulations was in the range of 6.02 to 6.79. The in-vitro drug release showed 83.49 to 96.79% drug release within 10 minutes. The formulations F4, F5, F8 showed the highest amount of drug release as these formulations were having croscarmellose sodium as superdisintegrants.

Keywords: Captopril, β-cyclodextrin, Hydrophilic polymers, Superdisintegrants, oral fast dissolving films.

INTRODUCTION

For the last two decades, there has been an enhanced demand for more patient- complaint dosage form.[1] Recent developments in technology have presented viable dosage alternatives for patients who may have difficulty in swallowing of tablets or liquids. Conventionally oral solid dosage forms are administered with a glass of water may be inconvenient or impractical for some patient.[2] It is estimated that 25% of the population finds difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctor resulting in high incidence of non-compliance and ineffective therapy. It has been known for centuries that drug solutes are rapidly absorbed in to the reticulated vein by buccal and sublingual administration. It is probable that at least 90% of all drugs used to produce systemic effects are administered by oral route.[3] Among the different routes of administration, the oral route of administration continues to be most preferred route due to various advantages including ease of administration, avoidance of pain, versatility and most importantly patient compliance. 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. Recently, fast dissolving drug delivery system have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better compliance. These delivery systems either dissolve or disintegrate in mouth rapidly, without requiring any water to aid in swallowing.[4] However, there are a number of drugs which posses bitter taste and hence are difficult to take orally. For such kind of drugs different complexing agents are used to mask the taste. The complexing agent aid is masking the bitter taste of drug either by decreasing its oral solubility on ingestion or decreasing the number of drug particles exposed to the taste buds. Cyclodextrins are most widely used complexing agent for inclusion complex formation having lipophilic inner cavities and hydrophilic outer surfaces and are capable of interacting with a large cavity of guest molecules to form inclusion complexes.[5]

Captopril is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE), responsible for the conversion of angiotensin I (AT I) to angiotensin II (AT II). AT II regulates blood pressure and is a key component of the rennin-angiotensin- aldosterone system (RAAS). It is used for the treatment of essential or renovascular hypertension and also may be used to treat nephropathy, including diabetic nephropathy.

Hence in the present study an attempt was made to prepare and evaluate oral fast dissolving film of Captopril with the aim of improving its dissolution rate and bioavailability for the effective management of hypertension.

MATERIALS AND METHODS

Materials: Captopril was obtained as a gift sample from Karnataka Antibiotics Pvt. Ltd., Bangalore. HPMC, polyvinyl alcohol, polyvinyl pyrollidone, and croscarmellose sodium were purchased from SD Fine Chemicals Ltd., Mumbai. Carbopol934P was purchased from Rajesh Chemicals Co., Mumbai. All the other ingredients used were of analytical grade.

Preparation of Captopril inclusion complexes: The inclusion complex of drug with β-cyclodextrin (β-CD) was prepared by wetting the physical mixture of Captopril: β-CD in the 1:1 molar

ratio in a mortar with water. Then the wet mixture is kneaded thoroughly to get paste like consistency. The paste was then dried under vacuum at room temperature, pulverized by passing through sieve no. 100 and stored in a desiccators till further use.

Preparation of fast dissolving oral film of Captopril: Oral fast dissolving film was prepared by solvent casting method. Aqueous solution I was prepared by dissolving film forming polymer, in specific proportion in distilled water and allowed to stirred for 3 hours and kept for 1 hour to remove all the air bubble entrapped. Aqueous solution II was prepared by dissolving the pure drug, sweetener, and plasticizer in specific proportion in distilled water. The aqueous solution I and II were mixed and stirred for 1 hour. The solutions were cast onto 9 cm diameter petridish and were dried in the oven at 45^0C for 12 hours. The film was carefully removed from surface of petridish and cut according to size required for testing (square film 1.5 cm length, 1.5cm width). The samples were stored in glass container maintained at a temperature 30^0C and relative humidity 60% ± 5% until further analysis.[6] The formulation details are given in table 1.
Calculation of dose for Captopril:

The dose of Captopril is 10 mg. Therefore amount of Captopril required in 3cm (1.5x1.5) is 10 mg.

- Area of film of 1.5X1.5 sq.cm is 2.25 sq.cm.
- Area of petridish of 6cm diameter is 28.26 sq.cm.
- Amount of drug present in 2.25 sq.cm of film is 10 mg.
- Amount of drug present in 28.26 sq.cm of petridish is 125.6 mg.

Therefore, 2.25 sq.cm of film should contain 10 mg of drug. It is fixed for all formulations.

Standard calibration curve of Captopril in 0.01N HCL and Phosphate buffer pH 7.4: Accurately weighed 100 mg of Captopril was dissolved in 100 ml 0.01N HCL and phosphate buffer pH 7.4, which gave the concentration of 1mg/ml standard solution. From the above stock solution, aliquots of 0.1, 0.2, 0.3, 0.4, 0.5 ml were pipette out into 10 ml volumetric flasks. The volume was made up to mark with 0.01N HCL. This dilution gave 10, 20, 30, 40, 50 mcg/ml concentration of Captopril. The absorbance was measured in UV spectrophotometer at 203 nm using 0.01N HCL and phosphate buffer pH 7.4 as blank. The concentration of Captopril and corresponding absorbance is given in figure 1 and 2.

Characterization of fast dissolving films by IR spectroscopy: The samples of fast dissolving films were prepared in the form of KBr pellets and subjected for scanning from 4000 cm^{-1} to 400 cm^{-1} using FT-IR spectrophotometer.[7]

Evaluation of fast dissolving films

Physical appearance and surface texture of the film: This parameter was checked by doing visual inspection of films[8] and texture of films is evaluated.

Thickness of film: The thicknesses of the drug-loaded polymeric films were measured at three different places[8] using a Vernier caliper and mean values were calculated.

Folding endurance: The folding endurance was measured manually for the prepared patches. The patches were repeatedly folded at the same place till it broke. The number of times the patches could be folded at the same place without breaking gave the value of folding endurance.[8]

Moisture uptake: The moisture uptake of the films are determined by exposing them to an environment of 40^0C with 75% relative humidity for 1 week.[9] The uptake of moisture by the films was calculated with percent increase in weight.

Uniformity of drug content: This parameter was determine by dissolving one film of dimension 1.5X1.5 cm containing 10 mg of Captopril by homogenization in 100 ml of pH 7.4 phosphate buffer for 30 minutes with continues shaking.[8]

Swelling index: The studies for swelling index of the film were conducted in pH 7.4 phosphate buffer solution.[6]

Surface pH of films: The surface pH was determined by using digital ph meter. Oral film was slightly wet using of water. The pH was measured by bringing the combined glass electrode in contact with surface of the films.[10]

In-vitro disintegration study: The in-vitro disintegration of the fast dissolving oral film was determined using disintegration test apparatus Electrolab Disintegration Tester ED-2L (USP).[10]

In-vitro dissolution study: The in-vitro release of fast dissolving oral film of Captopril was carried out using basket type electrolab tablet dissolution tester USPXXIII[10].

In-vitro drug release studies details: USP XXIII dissolution test apparatus was employed for the study in pH 7.4 phosphate buffer solution, volume 300 ml and maintained at temperature of 37±0.5^0C. The absorbance was measured at 203 nm.

Stability studies: Stability studies for selected formulations were carried out by storing in amber colors bottle tightly plugged with cotton and capped at 40 ± 0.5^0C and 75 ± 5% RH for 3 month.[9] The formulations were evaluated for physical appearance, drug content and in-vitro dispersion time at1month interval time.

RESULTS & DISCUSSIONS

In preformulation studies, it was found that, the λmax of Captopril by UV spectroscopic method was found at 203 nm in 0.01N HCL and phosphate buffer pH 7.4. Captopril was found to be freely soluble in water, ethanol, methanol, phosphate buffer solution (PBS) pH 7.4 and 0.01N HCL. The results are given in table 2. The Captopril inclusion complexes were characterized by FTIR spectroscopy for drug interaction with β-cyclodextrin. Captopril contains number of –CH peaks at 1450 cm^{-1} 1700 cm^{-1}. These peaks were unaltered when the inclusion complex were mixed with different excipients used in the formulation. Thus, indicating that the mixture prepared was physical in nature. The IR spectrum is shown in figure 3.

The weight of the prepared films was determined using digital balance and the average weight of the all the films was given in table 3.

All the films are free from the moisture uptake and there is no evidence of moisture attack in the prepared films.

The thickness of the film was measured using screw gauge micrometer. The thickness was almost uniform in all the formulations and values ranges from 0.6 ± 0.087 mm to 1.1 ± 0.035 mm. The standard deviation values indicated that all the formulations were within the range. The results of thickness for films were shown in table 3.

The folding endurance of the films was determined by repeatedly folding a small strip of films at the same place till it breaks and the folding endurance data of all the films is given in table 10.

The swelling index study was carried out in pH 7.4 phosphate buffer

solution and the results are tabulated in table 3. The formulations containing super disintegrants showed high swelling index due to the more water absorption as compared to the other formulations.

The surface pH of the all formulations was found to be in the range of 6.02 ± 0.153 to 6.79 ± 0.100 which is in the official range of salivary pH and results are shown in table 4.

The drug content uniformity was performed for all the formulations and results are shown in table 4. The results were within the range and that indicated uniformity of mixing.

The in-vitro disintegration time is calculated by the time taken by film to undergo complete disintegration. The in-vitro disintegration time of all the formulations fulfills the official requirements and the data is tabulated in table 4. As the concentration of the super disintegrants increases the in-vitro disintegration time of the film also decreases.

The in-vitro drug release study of fast dissolving film from each batch of F1 to F9 was carried out. The plot of % cumulative drug release v/s time plotted and depicted as shown in figure 4.

Moreover formulations from F13 to F18 showed maximum % drug release which contains croscarmellose sodium as super disintegrant than the formulations from F1 to F3.

The selected formulations was evaluated for short term stability studies which was stored at 40^0C at 75% RH tested for 3 month and were analyzed periodically for their physical parameters, in-vitro dispersion time and drug content at 30 days interval. The residual drug contents of formulations were found to be within the permissible limits and the values were shown in the table 5.

Table 1: Formulation details of fast dissolving films of Captopril

Ingredients (%w/v)	F1	F2	F3	F4	F5	F6	F7	F8	F9
β- CD + Captopril complex(gm)	4.34	4.34	4.34	4.34	4.34	4.34	4.34	4.34	4.34
HPMC	2.25	2.25	2.25	2.25	2.25	2.25	-	-	-
PVA	-	-	-	-	-	-	2.25	2.25	2.25
PVP	-	0.25	-	-	-	-	-	0.25	-
Carbopol	-	-	0.25	-	-	0.25	-	-	0.25
MCC (%w/w)	2	2	2	-	-	-	-	-	-
CCS (%w/w)	-	-	-	2	2	2	2	2	2
Propylene glycol	2	2	2	2	2	2	2	2	2
Glycerol	1	1	1	1	1	1	1	1	1
Water up to (ml)	100	100	100	100	100	100	100	100	100

Table 2: Solubility Profile of Captopril

Solvents	Solubility
Distilled Water	+++
Methanol	++
Ethanol	++
0.01 N HCL	++
PBS (pH 7.4)	++

Table 3: Evaluation of oral fast dissolving film of Captopril

Formulation Code	Weight (mg)	Thickness (mm)	Folding endurance
F1	56.25 ± 0.362	0.6 ± 0.087	123 ± 2.107
F2	57.45 ± 0.220	0.8 ± 0.042	138 ± 3.456
F3	60.29 ± 1.210	1.1 ± 0.036	168 ± 2.989
F4	50.12 ± 0.320	0.7 ± 0.054	127 ± 4.513
F5	51.12 ± 0.336	0.8 ± 0.023	141 ± 4.025
F6	52.29 ± 0.385	1.1 ± 0.090	172 ± 3.197
F7	43.70 ± 0.772	0.9 ± 0.147	196 ± 2.874
F8	57.11 ±0.210	0.8 ± 0.101	195 ± 3.950
F9	60.77 ± 1.110	1.1 ±0.035	174 ± 2.517

Table 4: Evaluation of oral fast dissolving film of Captopril

Formulation code	Drug content Uniformity (%)	In vitro disintegration (sec)	Swelling index	Surface pH
F1	95.06 ± 0.027	23 ± 1.058	59.14 ± 2.523	6.23 ± 0.152
F2	94.55 ± 0.025	24 ± 2.699	62.78 ± 3.222	6.66 ± 0.152
F3	92.21 ± 0.027	22 ± 2.531	57.77 ± 3.258	6.02± 0.153
F4	95.84 ± 0.015	20 ± 4.077	64.49 ± 3.147	6.76 ± 0.152
F5	97.85 ± 0.041	15 ± 1.002	69.08 ± 3.608	6.79 ± 0.100
F6	98.97 ± 0.034	25 ± 1.802	64.76 ± 3.852	6.30 ± 0.173
F7	96.32 ± 0.021	22 ± 3.881	60.32 ± 2.456	6.63 ± 0.152
F8	95.47 ± 0.045	18 ±2.551	67.65 ± 1.753	6.45 ± 0.152
F9	94.66 ± 0.014	28±1.237	58.21 ± 1.159	6.61 ± 0.100

Table 5: Stability data of oral fast dissolving film of Captopril

Formulation stored at 40 ^{0}C/75%RH	Time in Months	Physical Appearance	In vitro disintegration Time (sec)	% Drug Content
F4	1	+++	20	95.84
	2	+++	21	95.69
	3	++	23	95.23
F5	1	+++	15	97.85
	2	+++	16	97.50
	3	++	18	97.10
F6	1	+++	18	98.68
	2	+++	20	98.45
	3	++	21	98.18

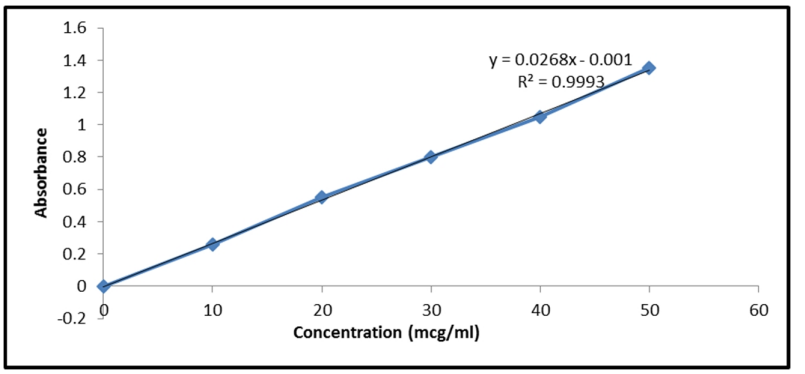

Figure 1: Standard Caliberation curve of Captopril in 0.01N HCL

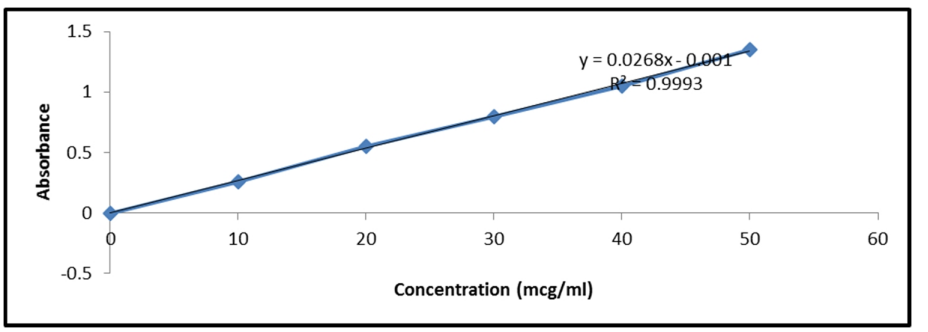

Figure 2: Standard Caliberation curve of Captopril in phosphate buffer pH 7.4

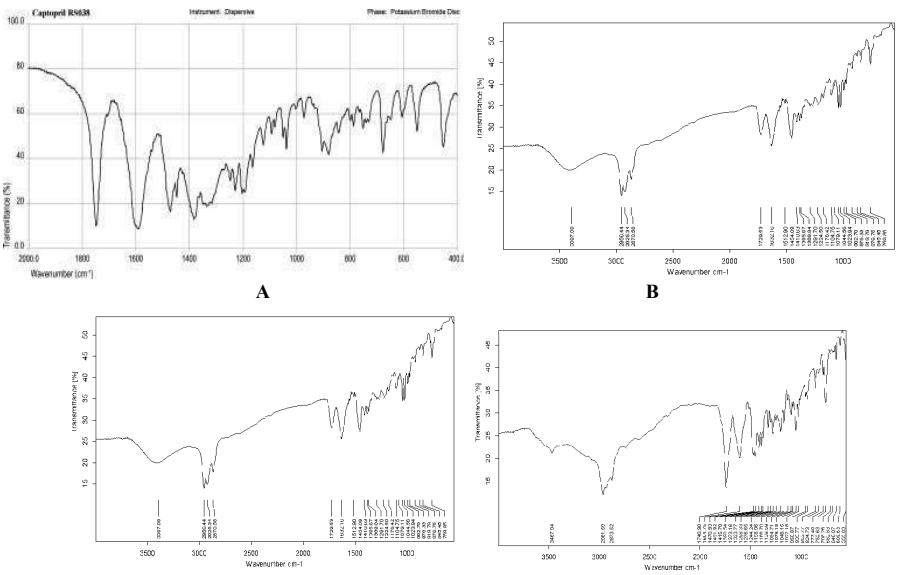

Figure 3: IR spectrum of (A) Captopril (B) Captopril + CCS (C) Captopril + Mannitol (D) Captopril + MCC

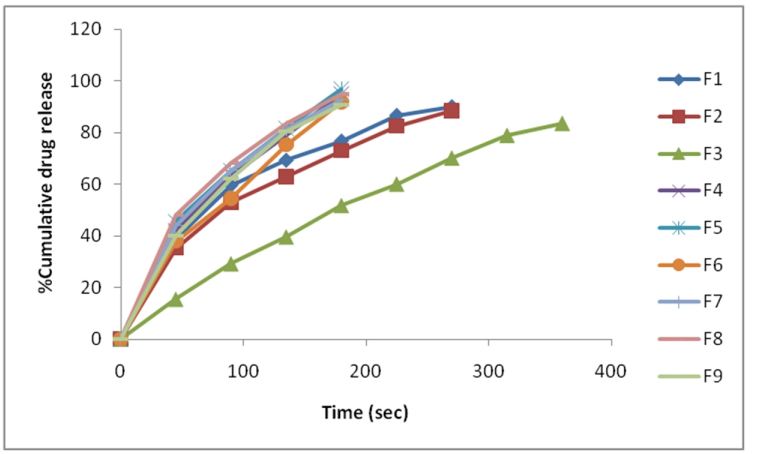

Figure 4: % cumulative drug release of formulations F1 – F9

CONCLUSION

In the present study oral fast dissolving drug delivery system of Captopril was successfully developed which offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increase in patient compliance. The drug and β- cyclodextrin inclusion complexes were developed successfully to mask the bitter taste of Captopril and prepared complexes were evaluated in-vitro. The results were positive in developing a novel oral fast dissolving film of Captopril however; there is scope for an extensive pharmacokinetic and pharmacodynamic evaluation.

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