

FORMULATION AND EVALUATION OF CAPTOPRIL MOUTH DISSOLVING FILM

Abstract:

The aim of current study is to formulate captopril mouth dissolving films, and to investigate the effect of different formulation variables on the physical and mechanical properties of the prepared films, besides to the drug release behavior. Hydroxypropyl methyl cellulose (HPMC E15 and K4M) was used as the film forming polymer in different grades. Disintegration time showed by formulations was found to be in range of $(52 \pm 2.5$ to 125.6 ± 2.02 s). Formula F2 showed lowest in-vitro disintegration time (52 ± 2.5 s) and found to be suitable for film formation with desirable physicochemical properties, faster disintegration and optimum in-vitro release. It can be concluded that the mouth dissolving films of captopril can be made by solvent casting technique with an enhanced dissolution rate and better patient compliance.

Keywords: Captopril; HPMC; Disintegration time; Mechanical properties; Mouth dissolving film.

INTRODUCTION

The oral route of administration has always been preferred over the other routes of administration namely, parenteral, topical, rectal and vaginal by the medical practitioners, manufacturers due to patient acceptance (1, 2). Ease of administration, convenience and cost effectiveness has been the reason behind the popularity of this route among the patient population (1, 3). The oral cavity has unique environment that offers its potential as a site for drug delivery (2). There has been a lot of advancement in the oral solid drug delivery system, from conventional dosage forms such as tablets and capsules to modified release dosage forms and recently the fast dissolving dosage forms (Fig1.1). The limitation of difficulty in swallowing oral solid dosage forms has been the reason for the evolution of mouth dissolving drug delivery system.

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Advantages of Mouth dissolving films

- They are thin and elegant in appearance.
- Can be available in various shapes and sizes.
- Be taken without water so beneficial while travelling.
- Disintegrates and dissolves in mouth when placed on tongue so no risk of choking.
- Convenient and accurate dosing in comparison to liquid orals.
- Can be used for site specific local action in the oral cavity.

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Disadvantages of Mouth dissolving films

- High dose of the drug cannot be incorporated into the film^(1,4)
- Taste masking is essential if the drug is having a bitter taste
- Packaging needs special care and equipments⁽¹⁾
- The technical challenges in manufacture of films include achieving dose uniformity and uniformity in thickness of mouth dissolving film while casting of the film^(1,2).

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MATERIALS REQUIRED:

Captopril was purchased from Sun pharma, major excipient HPMC E₁₅, HPMC K_{4M} was also purchased from sun pharma, propylene glycol, carbopol, SSG and citric acid used were of analytical grade only

METHODS EMPLOYED

Preformulation studies for Captopril

- Solubility
- Determination of pH
- Moisture content
- Melting point
- Drug polymer compatibility studies

Solubility: The solubility of a drug may be expressed in number of ways. The U.S. pharmacopoeia and national formularies list the solubility of the drugs as the number of milli litres of solvent in which 1 gram of solute will dissolve (11)

Comment [nd5]: Last reference was 4 and then immediately it comes to 11

For substance whose solubility is not definitely known, the values are described in the pharmaceutical compendia by the use of certain general terms. One gm of Captopril was dispersed in the solvent and based on the following table solubility was determined. The solubility of the drug was determined in water, ethanol, methylene chloride, methanol, chloroform and acetone.

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Determination of pH:

pH of the drug solution was tested by using previously calibrated pH meter. 6.8 % w/v solution of Captopril was prepared using as a solvent and sonicated for 30 minutes. The glass electrode of the pH meter was immersed in the prepared solution and the pH of the solution was recorded.

Moisture content:

The moisture content was determined using Sartorius moisture determining apparatus. 50 mg of the pure Captopril was transferred to an aluminium plate and the moisture content was determined at 105°C

Melting point:

Melting point of the drug was determined by using Scientek digital melting point apparatus.

Drug polymer compatibility studies

Study was carried out using FT-IR spectrometer (Shimadzu). FT-IR Spectra of Captopril and polymers with Captopril were obtained. The spectrum was studied for specific peaks of drug and polymer. The spectra are shown in figure- 4, 5 and 6.

General method for the preparation of Oral thin films (OTF):

The current preferred manufacturing process for making this film is solvent casting method. Water-soluble polymers are completely soaked in water over night and dispersed to form a homogeneous viscous dispersion using a homogenizer. The active ingredient (if water insoluble) was dissolved in alcohol and to this propylene glycol was added. This solution was added to the polymeric dispersion with stirring. Other ingredients such as sweeteners etc were added by dissolving in small quantity of water and were added to the dispersion. The resulting bubble free dispersion was poured onto glass moulds and was kept in oven. Dried film was then cut into desired shape and size for the intended use. The formulae of the different films were given below.

FORMULATION OF MOUTH DISSOLVING FILM:

Following processes are generally used to manufacture the mouth dissolving film: hot melt extrusion, solid dispersion extrusion, rolling, semisolid casting and solvent coating. The current preferred manufacturing process

for making this film is solvent casting method. Water-soluble polymers are completely dissolved in a mixing tank to form a homogeneous viscous solution. Other ingredients, including active ingredient are dissolved in a small portion of aqueous solvent using a high shear processor. The active mixture is then added to the viscous colloidal solution to form a homogeneous viscous solution. This viscous solution is degassed under vacuum. The resulting bubble free solutions poured on to glass mould and were kept in oven. Dried film is then cut into the desired shape and size for the intended application¹.

TABLE 1: FORMULATION OF CAPTOPRIL MOUTH DISSOLVING FILM

INGREDIENT	F1	F2	F3	F4	F5	F6	F7	F8	F9
DRUG	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
HPMC E15	80 mg	85mg	90mg	-	-	-	-	-	-
HPMC K4M	-	-	-	80 mg	85 mg	90 mg	-	-	-
CARBOPOL	-	-	-	-	-	-	80 mg	85 mg	90 mg
PVA	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
PROPYLENE GLYCOL	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg
SODIUM STARCH GLYCOLATE	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
ASPARTAME	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
CITRIC ACID	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg

ANALYTICAL METHODS:

There were many analytical methods that were used to determine the concentration of Captopril in pharmaceutical preparations such as spectrophotometric methods, HPLC methods etc.

In this project spectrophotometric technique (as per USFDA) was used to determine the concentration of Captopril in the prepared formulation (i.e. UV visible spectrophotometry)

Procedure For Calibration Of Captopril

Preparation Of Standard Solution:

50 mg of Captopril was accurately weighed and was transferred into 1000 ml volumetric flask. The drug was dissolved in a little quantity of 28.8 gm of disodium hydrogen phosphate and 11.54 gm of potassium dihydrogen phosphate (Stock A, 1mg/ml).

Scanning: From the prepared stock 10 µg/ ml solution was prepared and was scanned in the UV range of 200 – 400 nm and the absorption maxima (λ max) was found to 600 nm for further analysis.

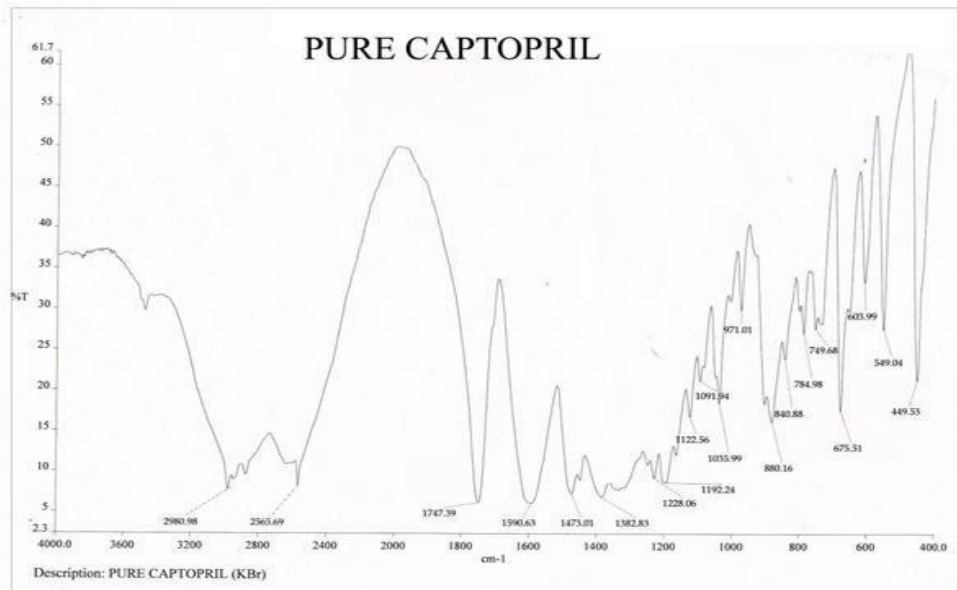


FIGURE 1: Absorbance Maxima Of Captopril

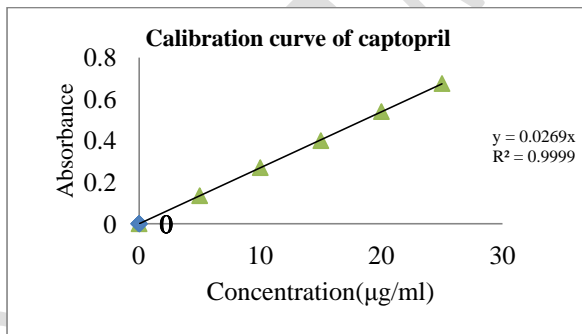


FIGURE 2: Standard graph of Captopril

DRUG – EXCIPIENT COMPATIBILITY STUDY:

Study was carried out using FTIR (BRUKER) where the spectra of the films were taken with and without the drug. The specific peaks of drug and the polymers were studied for the interactions.

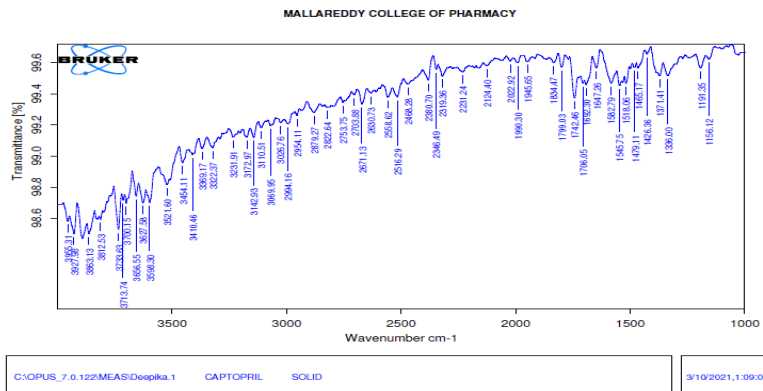


FIGURE 3:FTIR spectrum of pure Captopril

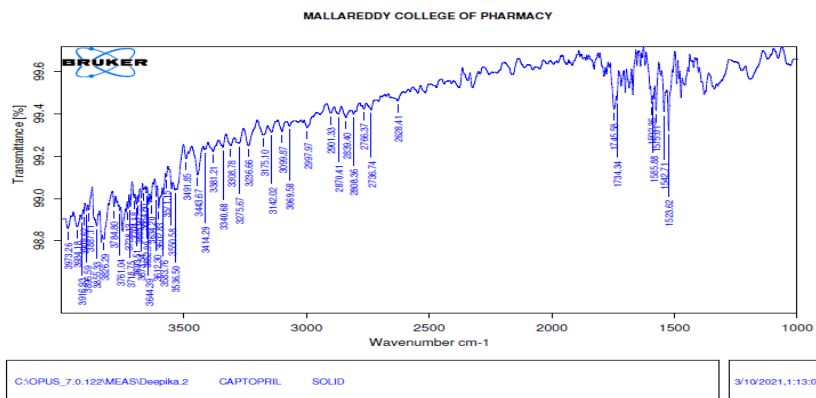


FIGURE 4:FTIR spectrum of Captopril film

RESULTS AND DISCUSSION:

Weight variation of the films:

Mouthdissolvingfilmswerepreparedbycastingmethod.FiveFilmseachofonesquare inch were cut at five different places from casted films and weight variation was measured. Weight variation varies from 89.28± 0.5450 to 96.78± 0.1021 mg. The results of weight variations are shown in the Table-2.0

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Thickness of the film:

The thickness of the drug loaded films were measured with the help of screw gauge by combining of five films of film F1 to F9 formulations, as it was difficult to measure the thickness of the single film, thickness varies from 0.313± 0.0358 to 0.373± 0.0183 mm. The results were reported in the Table-2.0

Tensile strength of the films:

The film of 3 inch X 10 mm was taken for the studies. From the results it is clear that when the concentration of the polymer increases, the tensile strength of the film also increases. The formulation F III shows the maximum tensile strength, percentage elongation and folding endurance. Presence of glycerine as a plasticizer imparts the flexibility to the polymers. Tensile strength measures the ability of the film to withstand rupture. The formulation F2 shows the maximum value of tensile strength 1.513 ± 0.0465 , percentage elongation 23.85 ± 0.6234 and folding endurance was 183 (no. of folds) as shown in the table-2.0. This might be due to the formation of strong hydrogen bonds between polymer and plasticizer there by imparting flexibility to withstand rupture. Tensile strength of the films was recorded in the Table-2.0.

Comment [nd8]: What is FIII?

Comment [nd9]: Same statement for FII. But as table F 3 is not showing the maximum value.

Percentage elongation of the films:

The film of 03 inch X 10 mm was taken for the studies. Percentage elongation was found to increase with increase in concentration of polymer in the film. Data are reported in the Table-2.0.

Folding endurance of the films:

The folding endurance was measured manually. A strip of film 4 square cm was cut and subjected for the folding endurance studies until it broke at the same place. Folding endurance increases with increase in polymer concentration. The number of times the film fold until it broke was reported in the Table-2.0.

Disintegration time:

Disintegration time of the film was done by using tablet disintegration test apparatus. A size of one square inch film was subjected for this study. Mouth dissolving time and disintegration time of the films were found to be increased with increase in the concentration of the polymer. The formulation F2 shows 52 Sec (disintegration time) and 45 Sec (mouth dissolving time) as shown in the table-2.0.

Comment [nd10]: There is no data of mouth dissolving in Table 2

Comment [nd11]: Results are written in disintegration time

Mouth dissolving time:

The mouth dissolving time was determined by using beaker containing 6.8-pH phosphate buffer. A size of one square inch film was subjected for this study. The mouth dissolving time of the film was reported in the Table-2.0.

Drug content uniformity of films:

The prepared film formulations were analyzed for drug content and it was observed that all the formulation found to contain almost uniform quantity of drug as per content uniformity studies indicating reproducible technique. F2 formulation shows 99 percent of drug content. The data is reported in the table-2.0.

Table no. 2.0: Evaluation of oral thin film (mouth dissolving films) for various parameters

FC	Average weight of the 1 inch square film in mg	Elongation at break (%)	Average thickness in mm	Tensile strength in kgs	Folding Endurance	Disintegration time in Sec	Drug content in mg
F1	92.42± 0.4020	25.73± 0.9415	0.309± 0.0003	1.216± 0.0541	92.13± 6.0147	56.1±1.112	97.00±1.732
F2	96.78± 0.1021	23.85± 0.6234	0.383± 0.0163	1.513± 0.046	102.0± 10.1421	52 ± 2.528	99.00± 1.528
F3	93.28± 0.5450	26.32± 0.5128	0.313± 0.0358	1.321± 0.1210	154.13± 5.0242	125.6± 2.024	95.00±3.000
F4	94.54± 0.3118	30.74± 0.8742	0.335± 0.0128	1.246± 0.0745	124.3± 10.2813	96.0± 3.001	95.00±3.000
F5	96.42± 0.4070	22.73± 0.9335	0.356± 0.0163	1.187± 0.0524	91.34± 6.0157	55.6±1.134	94.00±1.732
F6	90.18± 0.2241	25.85± 0.6744	0.373± 0.0183	1.391± 0.044	105.1± 106.148	91 ± 2.514	96.00± 1.528
F7	89.28± 0.5450	24.52± 0.5228	0.343± 0.7148	1.316± 0.1021	161.33± 5.0352	120.6± 2.004	94.00±3.000
F8	93.14± 0.3138	27.74± 0.8112	0.325± 0.0148	1.324± 0.0748	180.1± 10.213	96.0± 3.120	96.00±3.000
F9	94.44± 0.3618	31.75± 0.8252	0.315± 0.0208	1.472± 0.0714	178.3± 10.233	92.0± 3.230	98.00±3.000

Invitro dissolution studies:

Dissolution profiles of the mouth dissolving films containing Captopril formulations were compared with pure drug. No significant differences were observed from Invitro dissolution studies for the film F1 to F9 and pure drug due to film instantly get wet by dissolution medium and disintegrate. Percentage of drug release at different time intervals are shown in the table-3.0. And F2 formulation showed the best percentage of drug release at 90 minutes i.e. 85.99 % and 98.90 at 120 minutes.

Comment [nd12]: In table the time in mins is totally different as per the result. Kindly justify.

TABLE 3: Comparative evaluation of *Invitro* dissolution profiles of mouth dissolving Captopril films

Time in mins	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	7.23	7.54	5.89	6.53	6.75	5.15	5.19	4.52	5.35
4	14.68	15.29	12.50	14.78	15.48	15.45	16.42	7.83	9.62
6	33.51	32.68	25.63	20.30	27.85	35.23	32.92	18.66	22.16
8	45.10	47.19	39.50	35.61	45.13	40.81	46.8	44.26	44.30
10	75.93	85.99	74.79	79.23	73.46	70.87	75.10	62.93	61.83
12	96.51	98.90	96.13	95.62	95.30	90.17	94.57	89.29	84.52

CONCLUSION:

Fast dissolving films are the novel approach in oral drug delivery systems. It promises patient compliance especially in case of pediatrics and geriatrics patients. They can also be used when quick action is required. On the basis of obtained results, one can conclude that HPMC E15 and HPMC K4M are better for the formulation of oral film of captopril. The release of F2 formula show higher drug release, also F2 Show *in-vitro* disintegration time of 52 s. On the basis of data obtained from *in-vitro* dissolution that F2 is promising formulation suitable for the fast release of captopril for systemic use since they exhibited maximum drug release.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Comment [nd13]: References are not as per guidelines to author(s)

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