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Formulation Development and Evaluation of Captopril Mouth Dissolving Films

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Abstract : Captopril is an oral drug belonging to the class of ACE inhibitors, the enzyme which is responsible for the conversion of Angiotensin I to Angiotensin II. Captopril is used in the treatment of Hypertension. The purpose of this was to develop mouth dissolving films of captopril (12.5mg). The Mouth Dissolving Films were prepared with different polymers like HPMC E_5, MC, PVP, PVA, and SCMC with super disintegrants like SSG, CCS and polyplasdone XL-10. The prepared films were evaluated for film mass, pH, thickness, folding endurance, % elongation and tensile strength, drug content , FTIR study and *in-vitro* drug release. The films readily dissolved in the dissolution medium. The release of captopril from the films was 100 percent in 15mins in the dissolution medium of pH 6.8 phosphate buffer. The release profiles of films were analyzed by using UV-visible spectrophotometer at 271nm. *In-vitro* parameters like thickness, disintegration, folding endurance, assay and weight of the films were evaluated. Preformulation studies of captopril like compatibility studies with polymers using FTIR, DSC studies were carried out. The drug and polymers were found to be compatible with each other. These results strongly suggested that the water soluble polymers were suitable for the formulation of mouth dissolving films of captopril.
Key words : captopril, oral drug delivery, mouth dissolving films.

Introduction

A wide range of research has been conducted to develop a number of dosage forms. Many extensive efforts have been put on delivery the drugs to a particular region of the body for a longer period of time (1). Among the numerous routes of drug delivery, oral route is the most preferred route and considered to be the most effective and acceptable form due to its better therapeutic efficacy (2). The advantages like ease of administration, avoidance of pain and various advantages over other dosage forms made it a promising route. Some drawbacks of oral dosage forms (tablets and capsules) like having difficulty in swallowing, resulting in patient incompliance particularly in pediatric, geriatric, bedridden and nauseous patients (3, 4). A recent advance in research activity has made an attempt to reformulate the existing drugs into new dosage forms to

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enhance the safety and efficacy of drug. One such attempt is the Oral Film (Oral strip), a thin film that is prepared using hydrophilic polymers that rapidly dissolves when placed on the tongue (5-7). Fundamentally thin films are excellent candidates for targeting sensitive sites that may not be possible with tablets or liquid formulations (8). Ideal thin films need to exhibit desirable features such as sufficient drug loading capacity, fast dissolution rate or long residence time at the site of administration and acceptable stability. Thin films are administered generally via buccal, sublingual, ocular and skin routes (9, 10). Among different routes, the use of thin films for delivering medicine into sublingual or buccal mucosa has drawn much interest in the recent years (11).

Various bio adhesive mucosal dosage forms have been developed which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery also known as Mouth Dissolving Films (12). Buccal delivery is suitable for administration of retentive dosage forms because of the excellent accessibility which occurs with the aid of the smooth muscle. It involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. A suitable buccal drug delivery system should possess good bio adhesive property so that it can be retained in the oral cavity for the desired time duration (13). Fast dissolving buccal film drug delivery systems have rapidly gained acceptance as an important new way of administration of drugs. They are generally used for pharmaceutical and nutraceutical products. It is the newest leading edge in drug delivery technology that provides a very convenient means of taking medications and supplements. Mouth dissolving films are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores or teething and also used where quick onset of action of drug is desired (14-16)

Experimental Methods

Materials used

The Drug used for the present study was a gift from Vijaya Scientifics limited, Hyderabad. HPMC E_5, MC was gifted from RA ChemPharma Limited, Hyderabad. All the other materials and reagents used were of analytical grade.

Preparation of mouth dissolving films:

The mouth dissolving films of Captopril was prepared by solvent evaporation method. Solution I is prepared by dissolving the drug in water. To this suitable amounts of plasticizers like PEG, Glycerin and sweetener like aspartame was added, to this citric acid was also added. Solution II is prepared by adding the film forming polymer in specific proportions in distilled water. The aqueous polymer solution was stirred for 10-15min to produce a clear solution and was kept aside for 30min to get a bubble free solution. The aqueous solution I and II were mixed and stirred for 15min and were poured on a glass petri plate. The plates were kept at room temperature for 24hours. The film was carefully removed from the petri plates and checked for any imperfections. The same procedure was repeated by using other polymers and the formed films were evaluated.

Weight Variation:

This test will let you know the uniformity of the formed film. Three small pieces were cut randomly each of 4cm^2 areas and the weight of each film strip was taken and then weight variation was observed

Thickness:

- The thickness of the drug loaded polymeric film was measured using a micrometer screw gauge at 5 different points (center and 4 corners) on the film to ensure the uniformity of the film thickness and the mean value was calculated(17).

Folding Endurance:

Folding endurance of the prepared films was calculated manually by repeatedly folding the film(2× 2cm) at the same place until it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance(18).

Drug Content/Assay:

This test was performed to ensure the drug loading into each film. This test was performed by dissolving a small area of the film i.e.; 4cm^{2}in a 50ml of pH 6.8 phosphate buffer with continuous stirring. This solution was filtered using a whatman filter paper and the obtained filtrate was adjusted to 100ml with the same buffer in a volumetric flask. This solution was analyzed using an UV-visible spectrophotometer.

***In vitro* Disintegration**

This test was performed using disintegration apparatus Electrolab Disintegration Tester ED-2L (USP). The test is done by taking 2ml of water in a petri plate with a film on the surface of water and the time taken for the disintegration of the film was calculated. This test is done in triplicates and the average value was taken as DT (19).

***In vitro* Dissolution study**

The *in vitro* release of fast dissolving MDF of captopril was carried out using basket type (USP Apparatus I) method (Lab India Model No: DISSO-2000) for this study. 300 ml of pH 6.8 phosphate buffer was taken which was maintained at 37±5°c. A 2×2 sample film is taken into the basket which was set at 75rpm; 5ml of sample were withdrawn at different time intervals and were replaced with fresh amounts of the same buffer. The samples withdrawn were filtered and analyzed using a UV spectrophotometer. The absorbance was measured at 227nm. A graph was plotted between time and percentage release was drawn in order to determine the maximum amount of drug release (19, 20)

Characterization studies

IR (Infra-red) spectroscopy analysis

The FT-IR spectroscopy (BRUKER Optics FTIR spectrophotometer Model Alpha 200218) was used as an analytical tool to know the drug-polymer interaction using the KBr disc method. FTIR spectra was scanned and recorded between 400 and 4000cm^{-1}

Differential scanning calorimetric studies

The Differential scanning calorimeter (DSC) study was done to determine the loss or gained of heat produced from physical or chemical change inside the sample as a function of heat. The DSC scans were performed for pure captopril powder and the physical mixture of polymer and the drug. The test was carried out by Differential scanning calorimeter at a heating rate of 10°C/min from 10-200°C in the nitrogen atmosphere.

Results and Discussion

In the present work, attempts have been made to prepare the mouth dissolving films of captopril using the water soluble polymers like HPMC E_5,MC, SCMC, PVP+PVA and HPMC E_5+MC using PEG 400 and glycerin as a plasticizer and aspartame was used as a sweetener in order to inhibit the bitter taste of the drug using the solvent evaporation method. The proper selection of polymers gave clear, uniform films with the desired thickness for the films of captopril. The captopril films which were prepared with a combination of polymers gave a better drug release compared with other polymers at 15min time point. The prepared films were evaluated for the different physicochemical characteristics such as thickness, weight variation, folding endurance, drug content and disintegration time. The *in-vitro* dissolution studies were carried out in pH 6.8 phosphate buffer.

The weight of the prepared films was determined using digital balance and the average weight of all the films is done. The thickness of the film was measured using screw gauge. The thickness was almost uniform in all the formulations and values ranged from 0.211±2.0817 to 0.318±3.0551mm. The folding endurance of the films is determined by repeatedly folding a small strip of the film at the same place until it broke. The folding endurance varied from 10 to 194 times. The surface pH of all the formulations was found to be in the range of

6.23 ±0.36 to 7.1±0.015. The drug content uniformity was done on all the formulations and the results indicated the proper mixing.

The *in-vitro* disintegration time is calculated by the time taken by the film to undergo complete disintegration.All the values of the above are given in the table 1.

The *in-vitro* drug release study of all the prepared formulations of captopril i.e. CAPT 1 to CAPT20 were performed. A plot of% cumulative drug releaseversus time(min) was plotted which was shown in the figures below.

Of all the formulations of captopril (CAPT 1 to CAPT 20) the formulations showed maximum amount of drug release with SSG as super disintegrant compared to other formulations. The lower the concentration of superdisintegrant, the better the release.

Table 1: Evaluation of Mouth Dissolving Films of Captopril

Formulation Code	Percent Elongation	Tensile Strength	Film Mass(mg	pH	Thickness (µm)	Folding endurance	Drug content (%)	Disintegration Time (sec)
CAPT1	10.1±0.3055	18.2±0.159	120.6±0.577	6.23±0.36	224.6±0.5774	164.6±3.5119	98.03±1.516	91±0.4
CAPT2	10.2±0.6557	18.1±0.3605	127.3±3.464	6.35±1	228±1	150.3±2.5166	99.31±0.2498	97±1.35
CAPT3	10.5±0.4	18.5±0.2	128.2±0.264	6.33±0.3605	240.3±1.5275	144.6±3.5119	99.15±0.2025	98±0.26
CAPT4	10.1±0.0503	18.4±0.4509	127.1±0.763	6.78±0.3605	218.3±3.0551	161.3±3.5119	98.4±0.4743	98±0.264
CAPT5	11.5±0.3606	20.1±0.5059	226.9±0.5131	6.55±0.3605	311.3±5.5076	194±3.6056	99.51±0.2315	93±0.360
CAPT6	11.3±0.45	20.3±0.6557	229.4±1.3527	6.5±0.015	314.3±3.2146	189.6±4.1633	99.72±0.1504	97±1.352
CAPT7	11.3±0.0862	21.2±0.8621	237±0.568	6.45±0.513	315±3	192.6±4.7258	99.78±0.2950	98±0.265
CAPT8	11.5±0.2946	20.8±1.113	236.1±0.1527	6.5±0.513	318.3±3.0551	194.3±3.0551	98.16±0.1897	92±0.152
CAPT9	12.4±0.4041	19.2±0.3055	173.1±0.3605	7.05±0.513	232.6±1.5725	164.6±3.5119	99.2±0.1493	95±0.305
CAPT10	12.2±0.1504	19.3±1.645	174±0.8	6.95±0.513	231.6±2.0817	165±4	99.1±0.1025	98±0.264
CAPT11	12.3±0.195	19.1±2.516	178.2±0.8185	6.85±0.513	240.3±0.1155	174.6±3.5119	99.5±0.2743	95±0.818
CAPT12	12.3±0.1997	19.3±1.605	177.2±1.1590	7.02±0.015	231.6±0.8083	175±4	99.3±0.2315	93±1.15
CAPT13	10.2±0.1493	22.4±3.511	121.2±0.3605	7.1±0.015	215.6±3.0551	181.3±1.5275	98.1±0.2041	93±0.360
CAPT14	10.3±0.2026	22.4±2.645	124.1±0.4	7.01±0.015	214±3.6056	184±2.6458	99.34±0.4041	91±0.414
CAPT15	10.3±0.4744	22.3±4.163	123.7±0.4509	6.98±0.015	214.3±4.0415	183.6±2.5166	99.8±3.511	91±0.401
CAPT16	10.3±0.2316	22.4±2.516	123.3±0.5859	7.02±0.015	211.6±2.0817	182±3.6056	99.87±2	98±0.265
CAPT17	12.4±0.4041	20.8±0.419	120.2±0.6557	7.15±0.015	219.3±1.5275	154.6±3.5119	99.05±0.6275	98±0.263
CAPT18	12.5±0.4041	21.3±0.202	118.5±0.8621	7.1±0.015	222.6±2.5166	152±2.6458	98.9±2.645	96±0.862
CAPT19	12.8±0.4041	22.8±0.474	117.3±0.8621	7.15±1	227±2	149.6±4.1633	99.2±1.5166	91±0.4
CAPT20	12.3±0.195	22.7±0.231	120.8±0.3055	7.25±1	214.6±3.0551	152.6±2.5166	98.63±2.4055	95±0.819

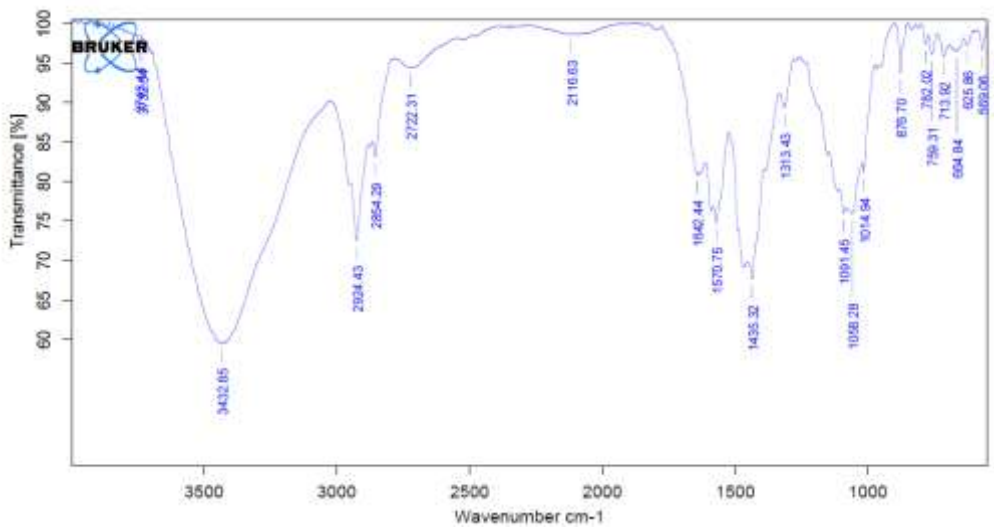

Figure 1: FT-IR spectra of pure drug

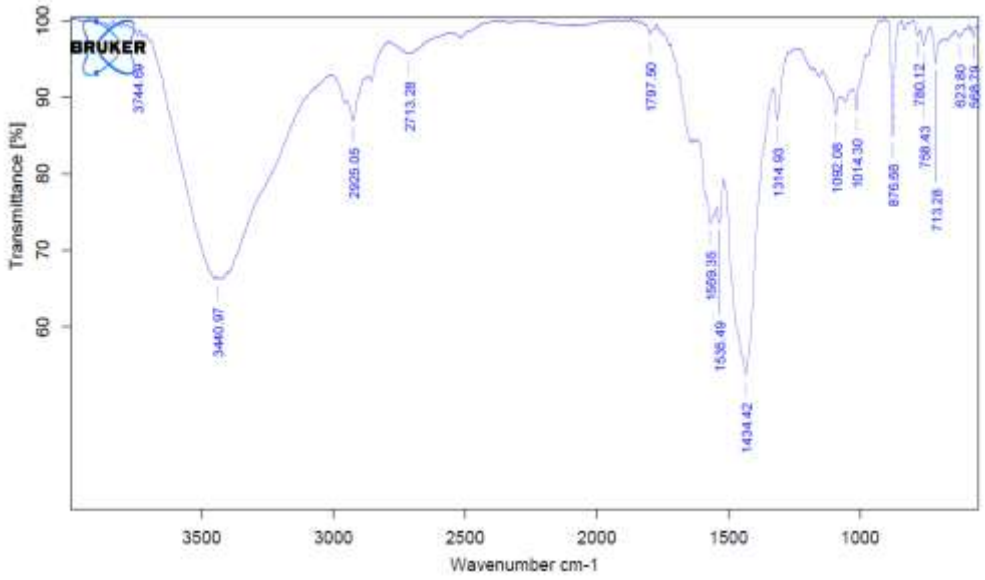

Figure 2: FT-IR spectra of drug and polymer

The FTIR spectrum of captopril drug and the drug polymer mixture was performed and they indicated that there is no interaction between the drug and the polymers used in the formulation.

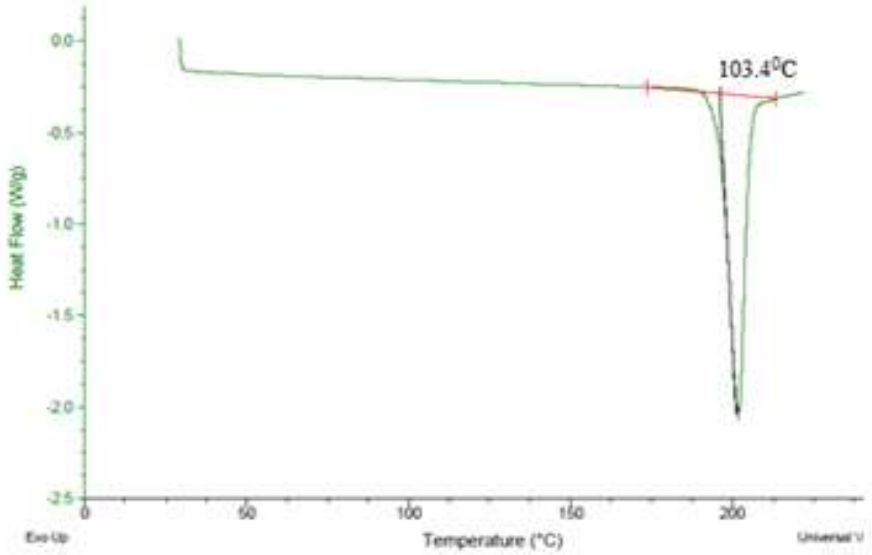

Figure 3: DSC study of pure drug captopril

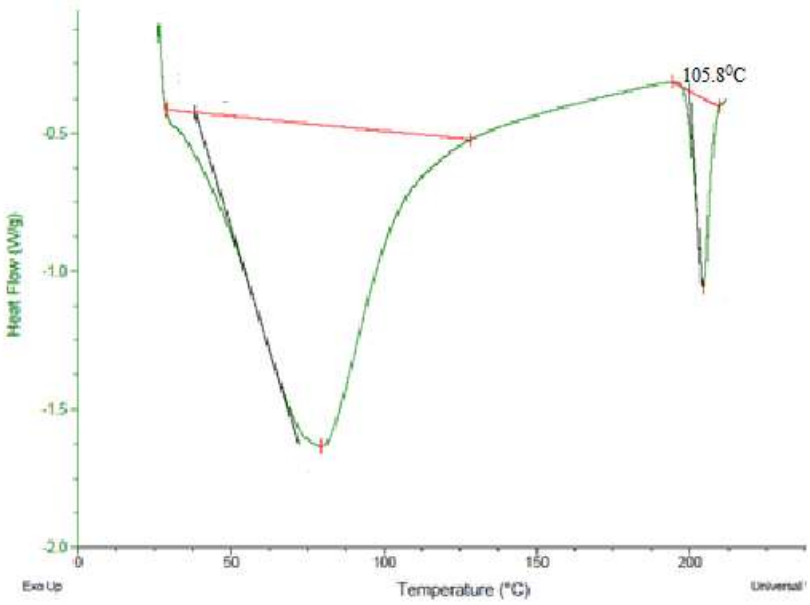

Figure 4: DSC study of physical mixture of captopril, HPMC E_5, MC

On observation of Figure 4, the DSC thermogram of drug displayed the characteristic endotherm at 103^0C, corresponding to its melting point. The endotherm is observed in the drug-HPMC E_5capt physical mixture there by indicating the absence of drug-polymer interaction.

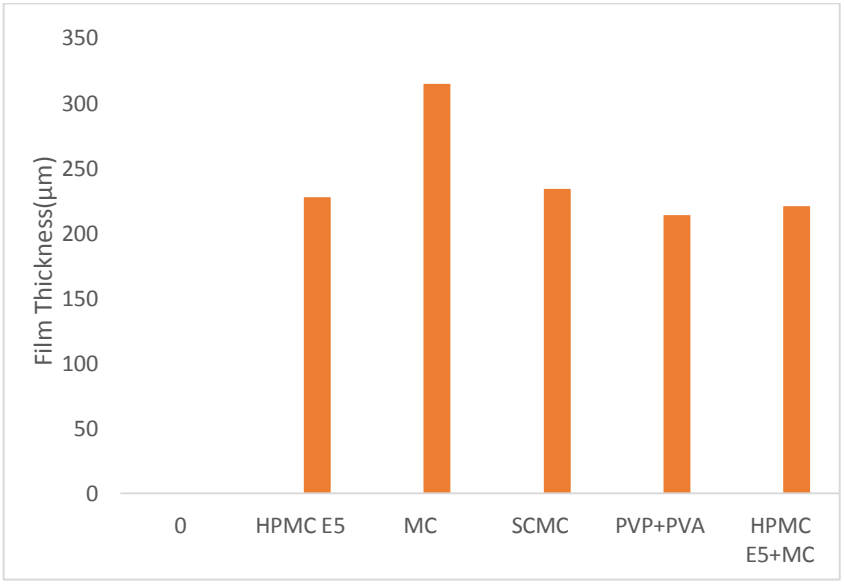

Fig 5: Thickness of CAPT mouth dissolving films

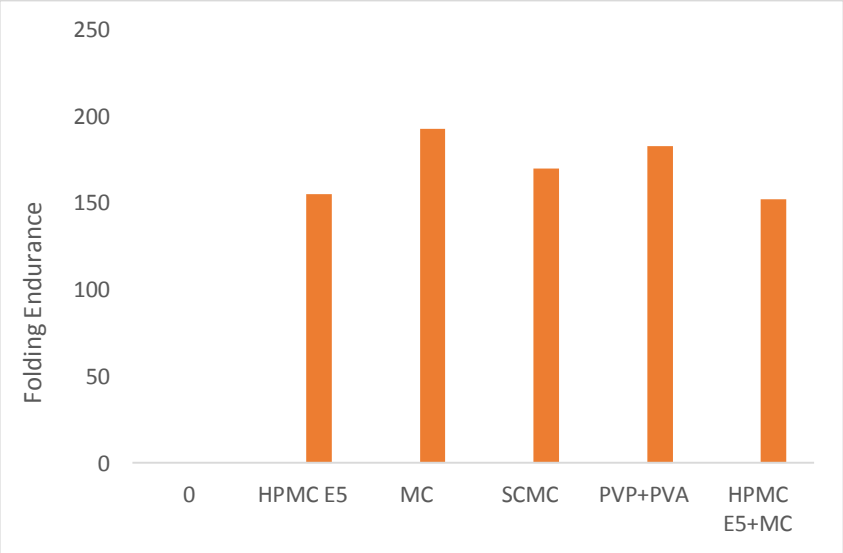

Fig 6: Folding endurance of CAPT mouth dissolving films

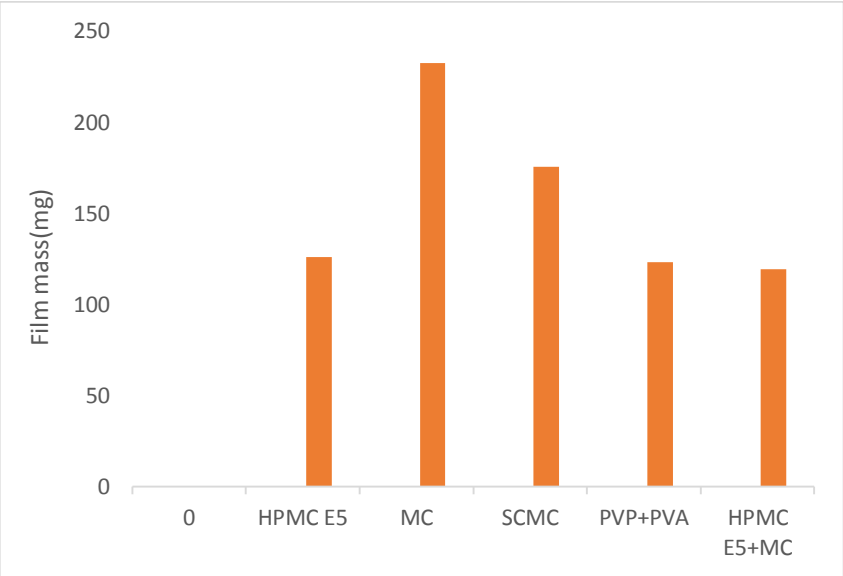

Figure 7: Weight variation of CAPT mouth dissolving films

Standard curve of the drug was prepared to set up a standard analytical method of drug by U.V. spectroscopy. The absorbance versus concentration was plotted. The curve was linear showing R^2 value 0.999.

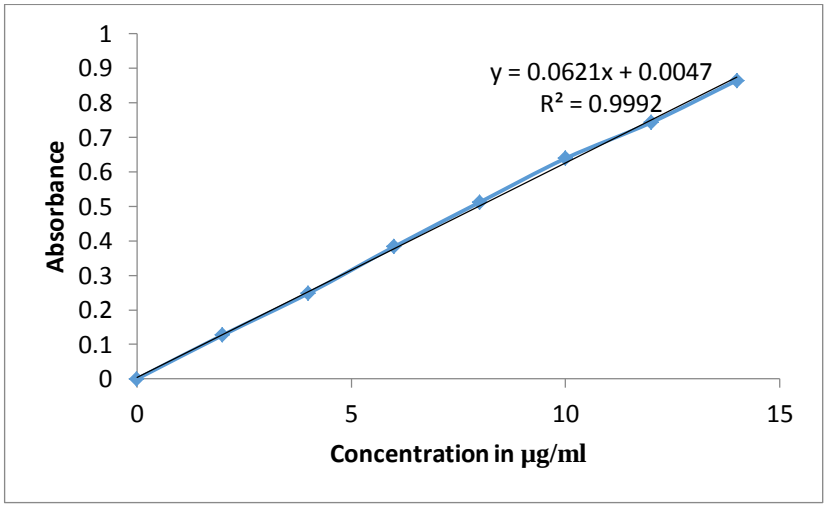

Figure 8: Standard Calibration curve of Captopril in phosphate buffer pH 6.8

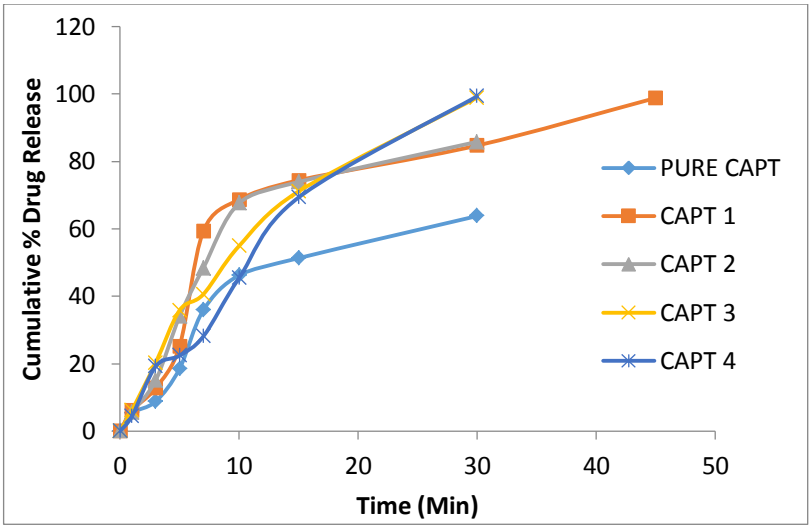

Fig 9:*In vitro* drug release from films containing CAPT and HPMC E_5

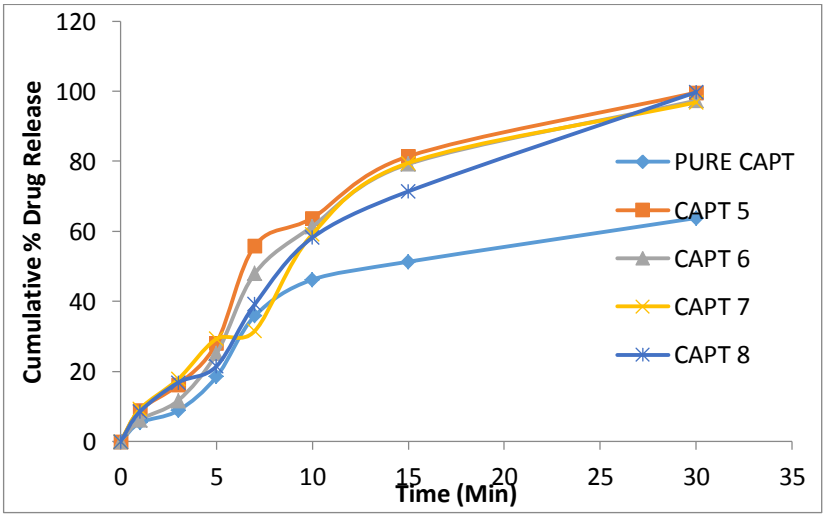

Fig 10: *In vitro* drug release from films containing CAPT and MC

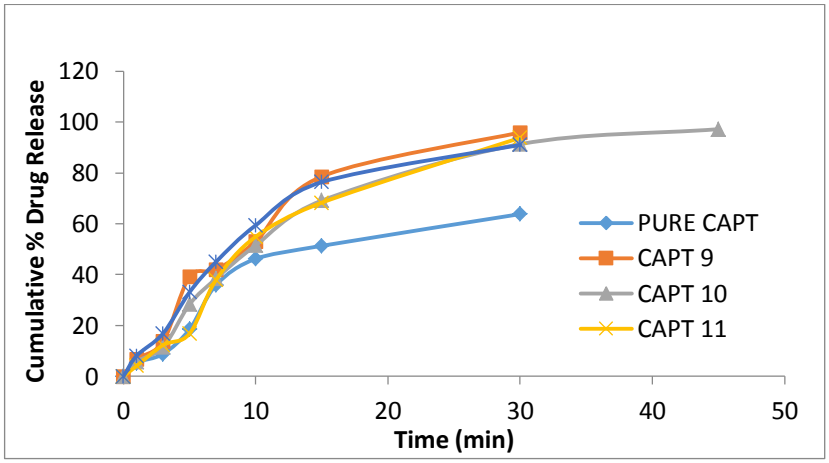

Fig11: *In vitro* drug release from the films containing CAPT and SCMC

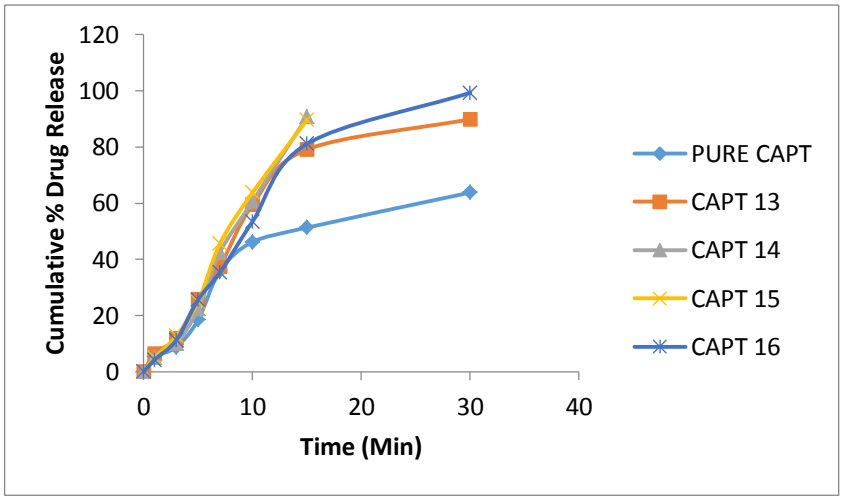

Fig 12: *In vitro* drug release from films containing CAPT and (PVP+PVA)

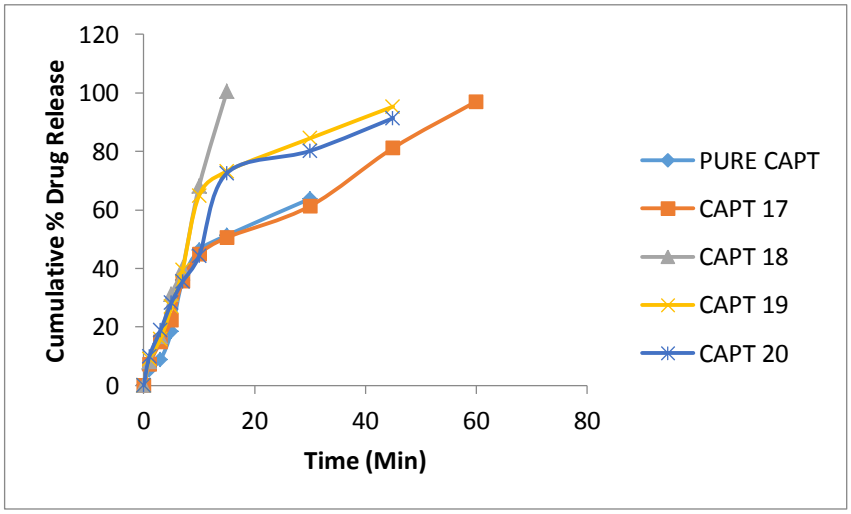

Fig 13:*In vitro* drug release from films containing CAPT and (HPMC E5+MC)

Conclusion

The captopril mouth dissolving films were successfully formulated using different polymers such as HPMC E5, SCMC, MC and combination of polymers like HPMC E5+MC and PVP+PVA. From the results pertaining to evaluation studies it was found that all the formulations of mouth dissolving films showed satisfactory results based on the integrity and dispersion of drug. The evaluation parameters such as thickness, folding endurance, weight variation, and pH and disintegration time were optimum and found to be satisfactory. The films which were prepared with combination of polymers showed promising results than others. Among all the formulations, the formulation CAPT 18 containing drug with low concentration of SSG was concluded as an optimized formulation which produced 100% drug release in 15minutes.

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