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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING BUCCAL FILM OF ENALAPRIL MALEATE

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ABSTRACT

In the development of buccal drug delivery system, mucoadhesion i.e.; the binding to mucin layer of biological membrane is the key element. Buccal film delivery system consist of at thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves, then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption. Here 5 Formulations of Enalapril Maleate oral films were formulated and produced by using solvent casting technique using the polymer hydroxyl propyl methyl cellulose based on various polymer excipients ratio and were evaluated. The infrared spectra showed stable and compatible character of the drug with the excipients and polymer. The F1 formulation was found to be the best formulation. The Formulation 1 with HPMC 250mg showed optimum swelling properties, maximum drug release and residence time.

Keywords: Buccal film, Preformulation, Compatibility, Drug release.

INTRODUCTION

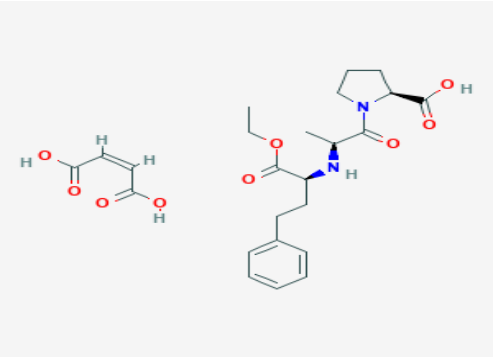
The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with a conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients.

A fast-dissolving buccal film drug delivery system, in most cases, is a film containing active ingredient that dissolves or disintegrates in the saliva remarkably fast, within a pharynx and esophagus as the saliva passes down into the stomach. [1]

ENALAPRIL MALEATE

Enalapril is used to treat high blood pressure. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. It is also used to treat heart failure and to help prevent people with a certain heart problem (left ventricular dysfunction) from developing heart failure.

Enalapril belongs to a class of drugs known as ACE inhibitors. It works by relaxing blood vessels so blood can flow more easily.[2]

Molecular Structure	
IUPAC name	(Z)-but-2-enedioic acid;(2S)-1-[(2S)-2-[[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]pyrrolidine-2-carboxylic acid
Molecular Formula	$C_{24}H_{32}N_2O_9$
Mol.Mass	492.525 g/mol
Trade names	Enalaprilet, vasotec
dose	2.5mg-5mg per day
storage	Store in air tight container

properties	Off white, crystalline powder.
bioavailability	60% oral
metabolism	hepatic
Half-life	11hrs
Excretion	renal
mp	143-144.5 °C
Water solubility	16400 mg/L (at 25 °C)
pH	pH (1% water) 2.6
pKa	2.97 (the carboxyl group) and 5.35 (the amine group) at 25°C [3]

MATERIALS AND METHODS

LIST OF MATERIALS USED

Chemicals and reagents like Enalapril maleate (Agila Pharmaceuticals, Bangaluru), Hydroxyl propyl methyl cellulose E15 (Otto chemicals), Citric Acid (Sara fine chemicals), Aspartame (Otto chemicals) Glycerin (Spectrum reagents), Potassium dihydrogen ortho phosphate (Nice chemicals), Sodium hydroxide (Nice chemicals) were used.

LIST OF INSTRUMENTS USED

Instruments such as Electronic balance (Bell electronics), Dissolution apparatus (Electro Lab), UV-Visible double beam spectrophotometer (Systonic India), Bath Ultasonicator (Ultrasonic cleaner C80-4, Confident equipments), FTIR (Shimadzu), Hot air oven (Serve well instrument), Dial Gauge (Baker Precision measuring instruments), Magnetic stirrer (2MLH) (Remi equipment Pvt Ltd.Mumbai), were used.

METHODOLOGY

ANALYTICAL METHOD DEVELOPMENT

Identification of λ_{max} for Enalapril Maleate

Construction of Standard curve

DRUG-POLYMER COMPACTIBILITY STUDIES

FABRICATION OF DOSAGE FORM

Product optimization was done after the evaluation of polymer and plasticizer combination and concentration by literature studies and drug compatibility studies. Following Table 3 shows the Compositions of the formulations.

Preparation of films

Buccal films of Enalapril Maleate were prepared by solvent casting method, using film forming muccoadhesive polymer HPMC-E 15. The formulation code and their respective composition are given in the table. HPMC was weighed accurately and is soaked in double distilled water with continuous stirring for 1hr for the swelling of the polymer solution. Enalapril Maleate was accurately weighed (10mg) and was dissolved in the polymer solution. Specified quantity of plasticizer glycerine (65mg), Sweetening agent Aspatame (40mg), Saliva stimulating agent citric acid (50mg) were added to drug polymeric solution and mixed thoroughly with the help of a magnetic stirrer .Whole solution was poured into the glass petridish(8cm diameter)placed over a flat surface, and is dried at 50 degree Celsius for 5hrs in a hot air oven.After drying the films were observed and checked for possible imperfections upon their removal from the moulds.They were covered with wax paper and preserved in desiccators' till the evaluation test were performed.[4]

Table 1 COMPOSITION OF INGREDIENTS

INGREDIENTS	FORMULATION CODE				
	F1	F2	F3	F4	F5
Enalapril Maleate	35.5g	35.5g	35.5g	35.5g	35.5g
HPMC-E15	250mg	300mg	400mg	500mg	600mg
Glycerin	46mg	98mg	73mg	90mg	84mg
Citric acid	50mg	50mg	50mg	50mg	50mg
Aspartame	40mg	40mg	40mg	40mg	40mg
Distilled water	10ml	10ml	10ml	10ml	10ml

RESULTS AND DISCUSSION

ANALYTICAL METHOD DEVELOPMENT

Identification of λ_{max} for Enalapril Maleate

The λ_{max} of Enalapril Maleate was found to be 206nm.

Construction of standard curve for Enalapril Maleate

The wavelength of maximum absorbance of drug was found to be 206nm and the drug solution was found to obey Beer's Law in the range of 5-25µg/ml at 206nm against 6.6pH buffer as blank. The values are given in table 4 and standard graphs in figure.

Table 2 Standard Curve of Enalapril Maleate Absorbance of Enalapril Maleate at 206nm in pH 6.6

Sl no	Concentration (µg/ml)	Absorbance at 206nm
1	0	0
2	5	0.311
3	10	0.446
4	15	0.611
5	20	0.847
6	25	0.963

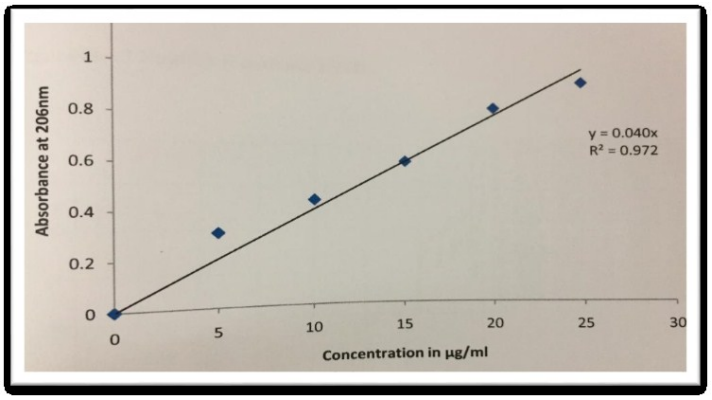


Figure 1: Calibration curve for Enalapril maleate pH 6.6 Phophate buffer at 206.

DRUG-POLYMER COMPATIBILITY STUDY

FTIR analysis for drug, polymers and the Drug polymer mixtures were done. The reports were given as figures;

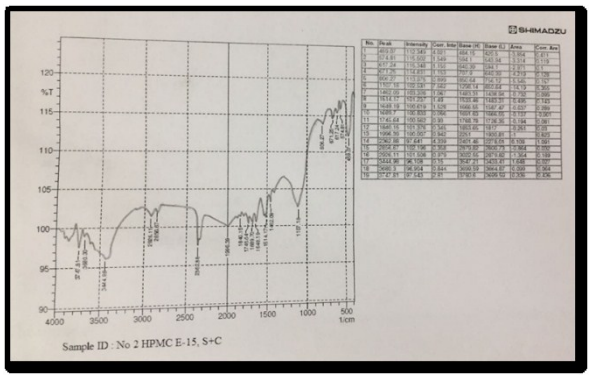


Figure 2 Enalapril maleate FTIR

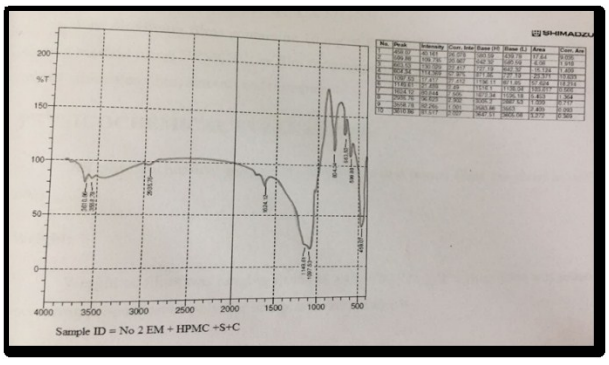


Figure 3 FTIR studies of drug with excipients

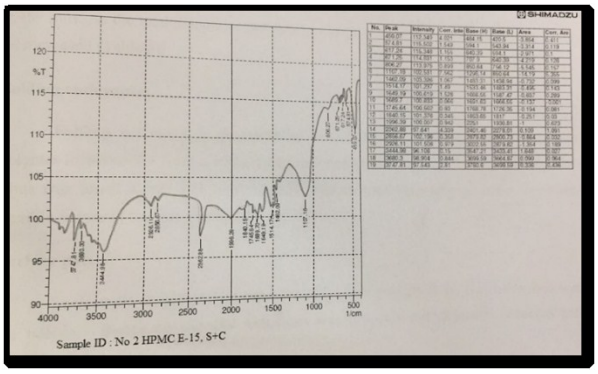


Figure 4 FTIR study of drug with excipients

The results of FTIR showed that there was no interaction between the excipients an drug as all individual peaks for the drug and polymers were obtained in the mixture.

DEVELOPMENT OF FORMULATIONS

Fast dissolving films containing 10mg of Enalapril maleate were prepared by solvent casting method using HPMC E_{15} as film forming polymer and glycerine as plasticizer. All the casted films were thin, smooth and transparent.

PHYSICOCHEMICAL EVALUATIONS

All physicochemical Parameters of the prepared buccal films are given in the table 5.

Table 3: Physicochemical Evaluations of buccal films.

Batch no	Weight(mg) (n=3)	Thickness (mm) (n=3)	Folding endurance (n=3)	Surface pH	Invitro dissolving time (sec)	Drug content (mg)	Swelling index
F1	148.14± 0.3	0.281± 0.10	216 ±1	6	20	9.88± 0.01	25± 0.10
F2	176.31± 0.6	0.334± 0.13	324± 2	6	51	9.96 ±0.03	29± 0.13
F3	219.42± 0.3	0.397 ±0.19	469± 5	6	71	10.11 ±0.002	32 ±0.19
F4	256.11 ±0.7	0.437 ±0.27	558 ±3	6	98	9.99± 0.01	35 ±0.27
F5	287.75 ±0.8	0.489± 0.14	681 ±4	6	138	10.02± 0.03	42± 0.14

- **Weight** of films was found to be increasing proportion of polymer and plasticizer.
- As the total amount of polymer increases the t**hickness** of the films were found to be increased.
- All patches exhibited **folding endurance** proving the flexible nature of the film.
- **Surface pH** for all batches was 6.0 which was due to pH of the drug solution as well as the polymer, hence no mucosal irritations was expected and ultimately achieves patient compliance.
- **Drug content studies** indicate that there is no loss of drug during preparation of the films. All the batches of the films exhibit drug content within limit which is within the desirable range due to the equal distribution of the drug in the solution.
- The **dissolution time** for the film was varying from 20-138 sec, which increases with increasing polymer concentration.
- The formulation F_1 showed optimum **swelling index**, and performed fast drug release with respect to time. The other formulation $F_2 – F_5$ showed swelling index in the range of 29,32, 35. And 42 and their drug release was delayed, this may be due to increase swelling of polymer which in turn causes decrease in drug release.
- The *in vitro* drug release studies were done for all the batches in phosphate buffer pH 6.6 using electro lab 08L dissolution apparatus. The release data are given in table 7, release pattern of the formulation was found to be increasing. After 30min the release was found to be in the range of 98.1-99%. The rank order of drug release after 30min was found to be 99.8,99.9,92.5,99.4 and 98.1% for F_1 F_2 F_3 F_4 and F_5 respectively. The drug release was found to be decreasing with increasing polymer content which may be due to increase in thickness of the film.

Table 4; *in-vitro* drug release of Enalapril maleate from formulation

Time (min)	Cumulative drug release %				
	F1	**F2**	**F3**	**F4**	**F5**
2	81.8	74.1	68.3	63.1	62.8
5	93.4	86.6	76.4	69.9	70.2
10	99.8	92.3	87.2	75.8	76.1
15	-	98.0	92.5	82.7	81.6
20	-	99.9	96.9	90.8	88.3
25	-	-	99.8	95.1	92.6
30	-	-	-	99.4	98.1

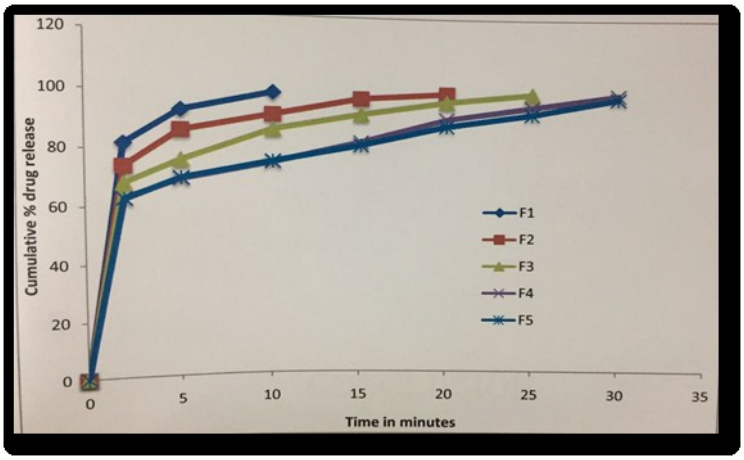


Figure 5; *in-vitro* drug release of Enalapril maleate from formulation.

CONCLUSION

The aim of the work was to develop the formulation of fast dissolving films of Enalapril maleate using hydroxyl propyl methyl cellulose as polymer and evaluation of formulated films for various characteristics and properties. The evaluation parameters prove that HPMC 250mg showed optimum swelling properties for maximum release, residence time as well as promising drug release. Therefore it can be concluded that F_1 (HPMC-250mg) can be used for the preparation of commercial batches of buccal films to attain fast onset of action. It was observed that during dissolution the release pattern of Enalapril maleate depends on time. The formulation F_1 (250mg) showed its maximum release 99.8% after 10min, but the other formulation F_2 99.9% at 20min and F_3 99.8% at 25min and F_4 at 30min, finally F_5 98.1% at 30min. The drug release was found to be delayed with time may be due to the increase in the thickness of the film (F_2-F_5). Therefore it can be concluded that F_1 attains maximum bioavailability within a short time (10 min) and therefore it was selected as best formulation.

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