CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND *IN VITRO* EVALUATION OF GASTRORETENTIVE EXPANDABLE FILM OF ENALAPRIL MALEATE WITH DIFFERENT EUDRAGIT POLYMERS

Shreeya M S *, Mrs. Jyothi M, Dr.Chandrakala.V , Rashmi G
Department of Pharmaceutics, East Point college of pharmacy, Bidarahalli, Bengaluru-560049, Karnataka, India

Abstract:
The present study illustrates the formulation and in vitro evaluation of gastroretentive expandable film of Enalapril maleate. These films were prepared using Enalapril maleate, Eudragit RSPO and RL 100, HPMC, dichloromethane, ethanol and PEG 400 by solvent evaporation technique. Five different formulations were prepared with individual and combination of two Eudragit polymers. The evaluation parameters of the polymeric films comprising two different property Eudragit polymers were studied. These formulations were subjected to unfolding behavior which showed 10 to 15 mins.In-vitro drug release was studied to understand the drug release in these five formulations. Surface morphology and drug compatibility of this films were studied through Scanning electron microscopy and FTIR technique.

Keywords : *Enalapril maleate; Eudragit RSPO; Eudragit RL 100; Solvent evaporation technique; Scanning electron microscopy; Fourier transform infrared spectroscopy.*

Corresponding author:
Shreeya M S *,
Department of Pharmaceutics,
East Point college of pharmacy, Bidarahalli, Bengaluru-560049,
Karnataka, India
Email ID : shreeyams32@gmail.com
Telephone no: +91 7090779169

QR code

Please cite this article in press Shreeya M S et al, ***Formulation And In Vitro Evaluation Of Gastroretentive Expandable Film Of Enalapril Maleate With Different Eudragit Polymers****, Indo Am. J. P. Sci, 2023; 10 (08).*

1. INTRODUCTION:

Oral conventional drug delivery system has been a predominant route of drug delivery. Many innovations of oral route drug delivery system have been developed which releases the active substance over a defined period of time and a controlled rate.[1] But some of the drugs when orally administered shows poor bioavailability and are absorbed less. Increasing drug dosage can lead to undesirable side effects. Another major drawback of conventional dosage form is the less gastric residence time and non-specificity. Some of the drugs can only be absorbed in the specific site only.[2] To overcome these limitations, many approaches are come up to increase the gastric residence time of drug in the upper GIT. Gastroretentive dosage form prolongs the gastric residence time and targets the site specific drug release. GRDF increases the duration of drug release, improves bioavailability of drugs with narrow therapeutic window, patient compliance and extends the dosing interval.[3] Expandable drug delivery systems are the gastroretentive dosage forms designed for longer Gastric retention time through their volume and shape. Initially these systems were used for veterinary purpose and gradually their use extended to humans. These are also called "Plug-type system".[4] These systems are easily swallowed and swells or unfolds to reach a significantly larger size. This expansion mechanism prevents its exit from the pylorus. They remain logged for longer period of time at the pylorus sphincter. As a result , dosage form is retained in stomach for a longer period of time.[5] Expansion is achieved by either swelling through osmosis or unfolding through mechanical shape memory.[6] Gastroretentivity is improved through the combination of substantial dimensions with high rigidity of dosage form to withstand peristalsis and stomach contractility.[7]

2. MATERIALS AND METHODS:

The active ingredient Enalpril maleate and Eudragit polymers RSPO and RL 100 were obtained as gifted samples; HPMC and dichloromethane from SD Fine Chemicals Limited; Ethanol from Changshu Hongsheng Fine Chemicals Co.Ltd; PEG 400 plasticizer was obtained from Yucca Enterprises.

Enalapril maleate as Anti-hypertensive drug used for this formulation. HPMC as a swellable polymer, Eudragit RSPO & Eudragit RL 100 as film forming polymers, Ethanol & Dichloromethane as solvent, Polyethylene glycol 400 as plasticizer were used in the preparation of expandable polymeric films. The materials were obtained as mentioned in the Table.1

2.1. Standard Calibration curve of Enalapril maleate

100mg of Enalapril maleate was dissolved in 100ml of volumetric flask with 0.1N HCl. This solution was placed in ultrasonicator for 5 minutes to obtain the stock solution-1.From stock solution-1 , 10 ml was taken in 100 ml volumetric flask and made up to volume with 0.1N HCl. This gives stock solution -2 which was used to obtain 10µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml and 60 µg/ml concentration by taking 1ml, 2ml, 3ml, 4ml, 5ml and 6ml respectively diluting and making up volume to 10 ml in volumetric flask. Median concentration was used for determining the λmax by scanning with Double beam UV –Visible spectroscopy with a spectral range of 200nm to 400nm. The working dilutions were analysed by λmax using Double beam UV – Visible spectroscopy. By taking the concentration on x- axis and absorbance as y-axis, standard calibration was plotted.[8] The obtained results are as shown in Table.3

2.2. Preparation of enalapril maleate expandable dosage form

The expandable polymeric film was prepared by solvent evaporation technique. Polymeric dispersion for the film was prepared by using HPMC, Eudragit RSPO, Eudragit RL 100 and dissolving it in required amount of ethanol and dichloromethane which is in 1:1 ratio. Then weighed amount of drug (Enalapril maleate) is added to it and dissolved. As plasticizer, PEG 400 is used in optimum quantity and the dispersion is stirred vigorously. The formulations were prepared as per Table 2. Polymeric film was prepared by pouring the polymeric dispersion on the glass plate with the area 110 cm^2. The film was allowed to dry in the room temperature for 24 hours. The film was cut with dimensions 2cm * 4cm. The films cut are folded in zig-zag manner and then carefully inserted in empty 00 size hard gelatin capsule.[9]

2.3. Characterization of polymeric film of enalapril maleate

2.3.1. Drug content determination

Films was cut into pieces which contain the 20 mg of enalapril maleate were taken and placed in a 100ml of 0.1N HCl(pH1.2) buffer solution for up to 6 hrs for complete extraction of the drug. The above solution was filtered and diluted with 0.1N HCl solution and analysed by UV spectrophotometer at a wavelength of 216 nm. Drug content was determined from calibration curve for the drug.[10]

2.3.2. Unfolding behaviour of film

The prepared polymeric film was folded in a zigzag manner. Then film is inserted into 00 size capsule. The unfolding study was carried out in a 500ml of beaker which containing 0.1N HCl (pH1.2) at a constant temperature. The drug loaded polymeric film which is folded was placed in the beaker and the films are examined at several time intervals for their unfolding behaviour. [11]

2.3.3. In-vitro drug release study

The *in-vitro* dissolution study of the film of various batches were performed using USP paddle type II dissolution apparatus using 0.1N HCl buffer (pH 1.2) 900ml of dissolution medium with constant temperature maintained at 37 ±0.5C and 50 rpm till 8hrs. An aliquot of 5 ml was withdrawn at pre-determined time intervals analysed at 216nm using double beam UV- visible spectrophotometer. An equal volume of another 5ml of fresh 0.1N HCl buffer medium was replaced immediately after withdrawal of test sample. The *in-vitro* release profile was shown in Table 4. and Fig. 4. [12]

2.3.4. Fourier Transform Infrared (FT-IR) Spectroscopy

The chemical interaction between drug and polymer was studied by FT-IR spectroscopy. The IR spectrum of the drug, polymers and physical mixture was obtained using Fourier Transform Infrared spectrometry. Measurements was recorded at the scanning range 4000-600cm^{-1}. The FT-IR spectroscopy result was shown in Fig.06 [10]

2.3.5. Scanning electron microscopy (SEM)

The morphology of expandable film was studied by Scanning electron microscopy. The polymeric film was examined in a Scanning Electron Microscope equipped with a scanning image observation device. The SEM image were shown in Fig.07. [10]

Table 2: Enalapril film formulation table

INGREDIENTS	FORMULATION CODES				
	F1	**F2**	**F3**	**F4**	**F5**
Enalapril maleate	280 mg	280 mg	280 mg	280 mg	280 mg
HPMC	500 mg	550 mg	600 mg	600 mg	600 mg
Eudragit RSPO	400 mg	350 mg	300 mg	_	300 mg
Eudragit RL 100	400 mg	350 mg	300 mg	300 mg	_
Dichloromethane + Ethanol	1:1	1:1	1:1	1:1	1:1
PEG 400	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml

3. RESULTS AND DISCUSSIONS:

Physical Appearance:

The prepared films were qualified for color, flexibility and smoothness. The films are folded in zig-zag pattern and carefully inserted in the transparent hard gelatin capsule shell.

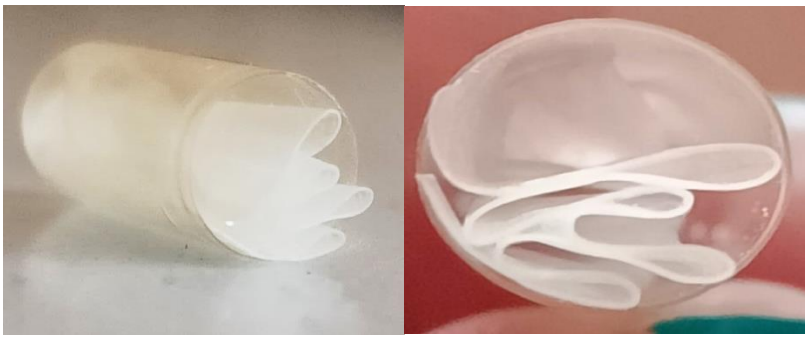


Fig 1 - Film folded in zig-zag pattern and inserted into a capsule shell

Unfolding behavior of film:

Expandable films were prepared in zig zag manner and were evaluated for understanding their *in- vitro* unfolding behavior. It was found out that the films folded in zig zag manner unfolded within 10-15 min *(*Fig.2*).* The main reason for the film to unfold is the mechanical shape memory. Polymers used had glass transition at room temperature might show shape memory. Film integrity of the films of F1 to F5 lasted for 10±0.5 hours. [11]

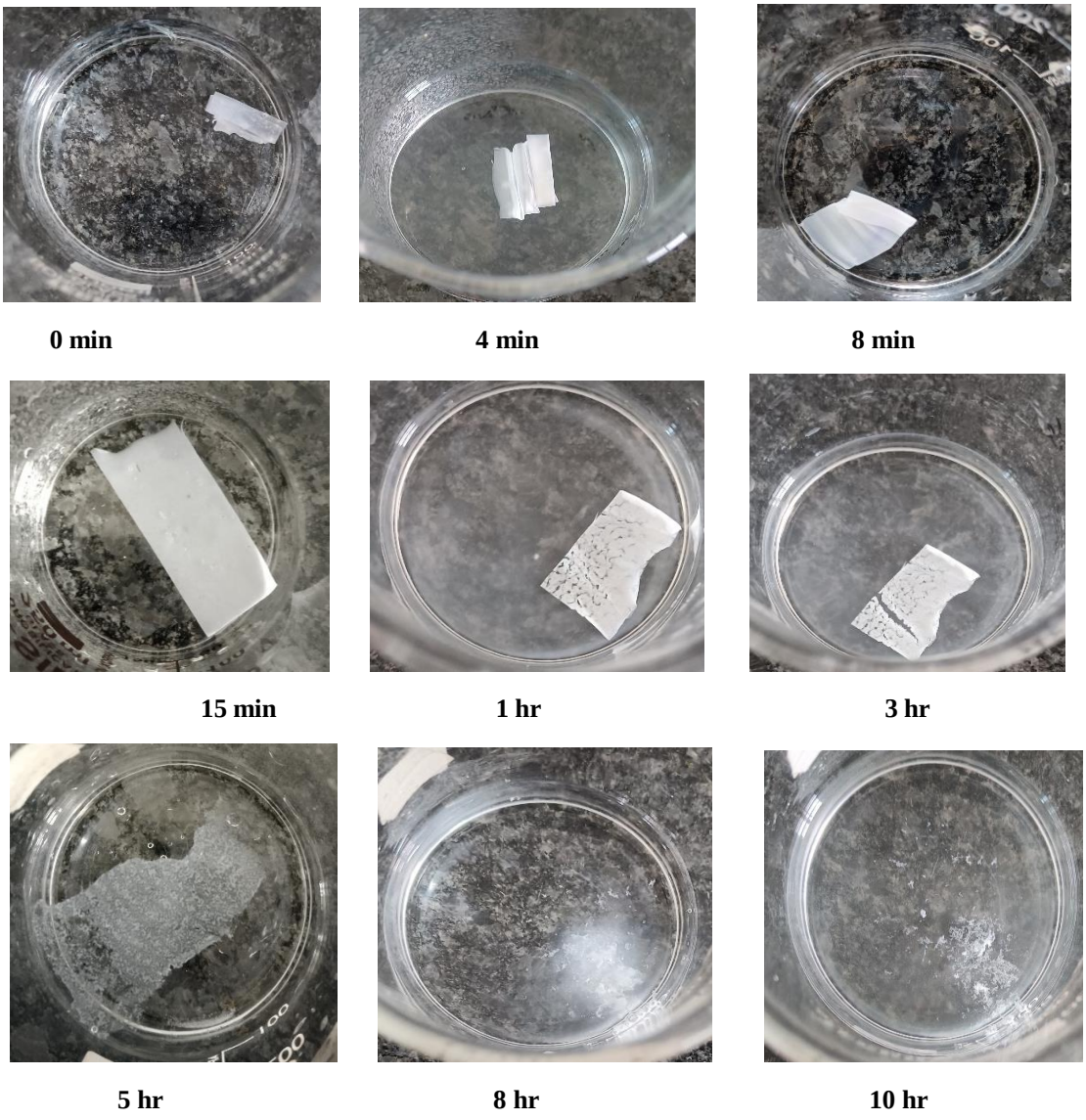


Fig 2 - Unfolding behavior of Enalapril maleate film at different time

Standard Calibration Curve:

Table 3 : Standard Calibration curve

Sl. No	CONCENTRATION (µg/ml)	ABSORBANCE (λ_{max})
1.	10	0.2934
2.	20	0.5306
3.	30	0.7764
4.	40	1.0212
5.	50	1.1941
6.	60	1.3255

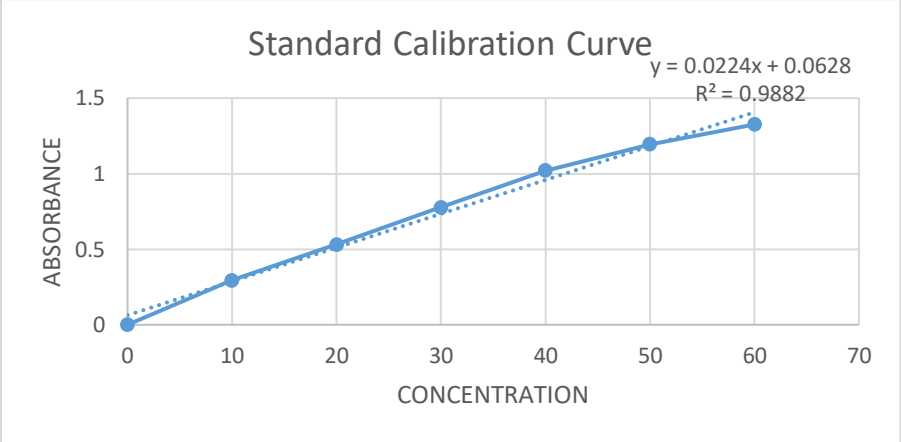


Fig 3 – Standard Calibration curve graph of Enalapril maleate

In-vitro Drug Release:

In-vitro drug dissolution study was carried out for all the 5 formulations i.e., F1, F2, F3, F4 and F5 and recorded as seen in Table.4 . Among these formulation, F1 to F3 had varying concentration of polymers whereas F4 and F5 had different grades of Eudragit polymers. F1 showed the minimum percentage of drug release of 80.88% followed by formulation F2 and F3 with release of 82.48% and 87.32% respectively for over 8 hours. Formulation F4 with Eudragit RL 100 showed drug release of 90.99% and Formulation F5 with Eudragit RSPO showed 75.91% release. F5 with Eudragit RSPO showed decreased drug release in the media whereas F4 with Eudragit RL 100 showed maximum drug release. Formulations of F1, F2 and F3 with the combinations of both the polymers Eudragit RSPO and RL 100 showed sustained drug release from the polymeric film over the period of time. [11] [13]

Table 4 : *In vitro* dissolution study

SL.NO	TIME	F1 %CDR	F2 %CDR	F3% CDR	F4 %CDR	F5 %CDR
1.	0	0	0	0	0	0
2.	1	33.8067	33.18866	41.9112	46.65036	32.47837
3.	2	48.1721	46.53627	54.3857	57.84252	49.94725
4.	3	53.2958	50.59467	59.4908	69.68096	56.27625
5.	4	63.4473	54.74325	65.9134	78.25049	63.11188
6.	5	69.6245	61.91309	71.3478	81.46406	71.23193
7.	6	72.2581	69.08292	76.9881	86.94856	73.05735
8.	7	75.1312	77.9663	82.1756	88.6946	75.66647
9.	8	80.8774	82.47563	87.3218	90.99766	75.91658

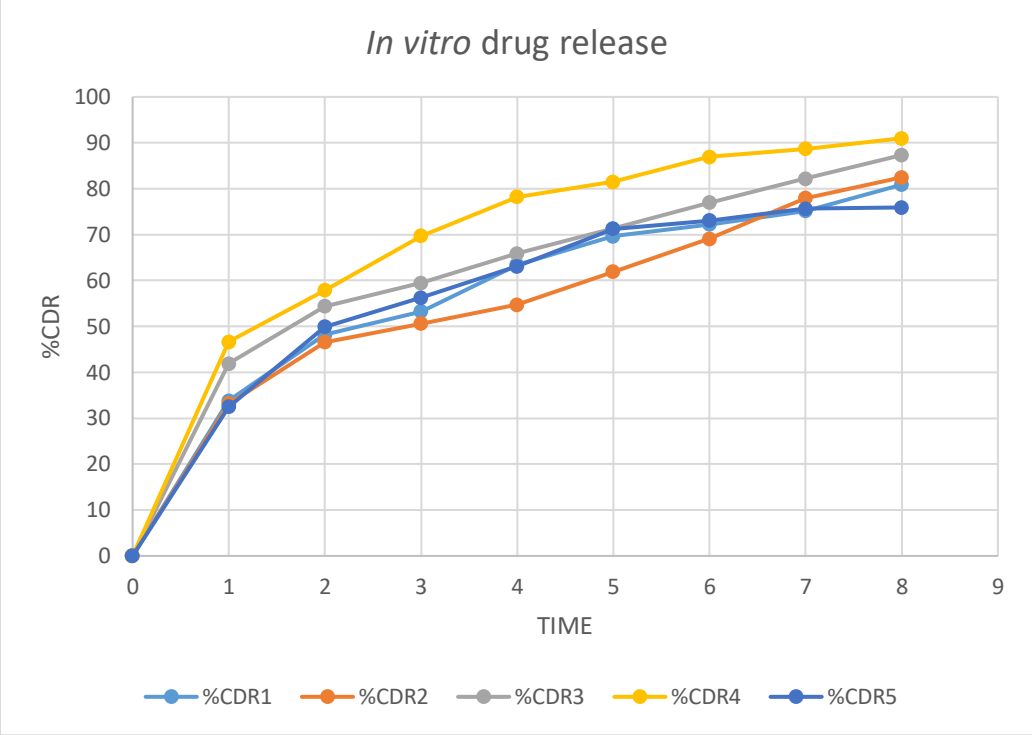
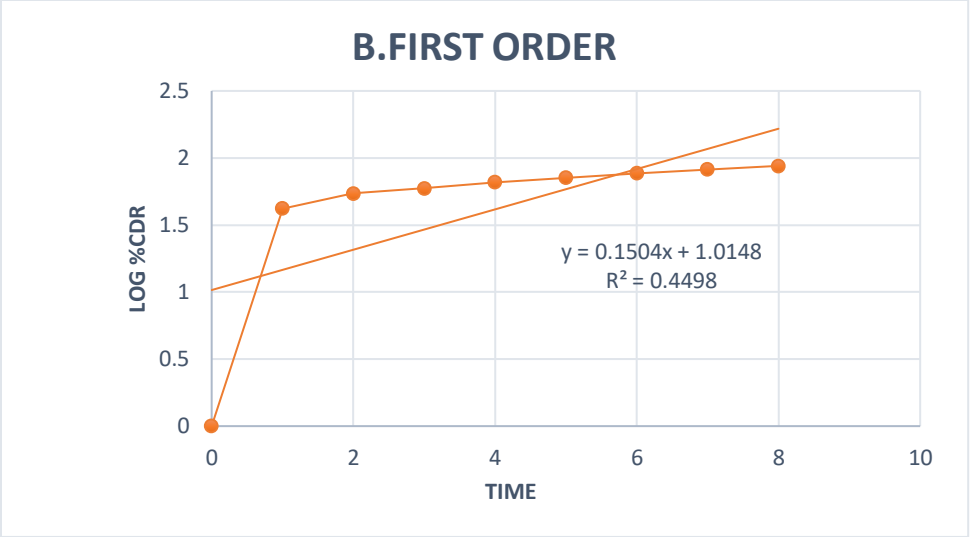
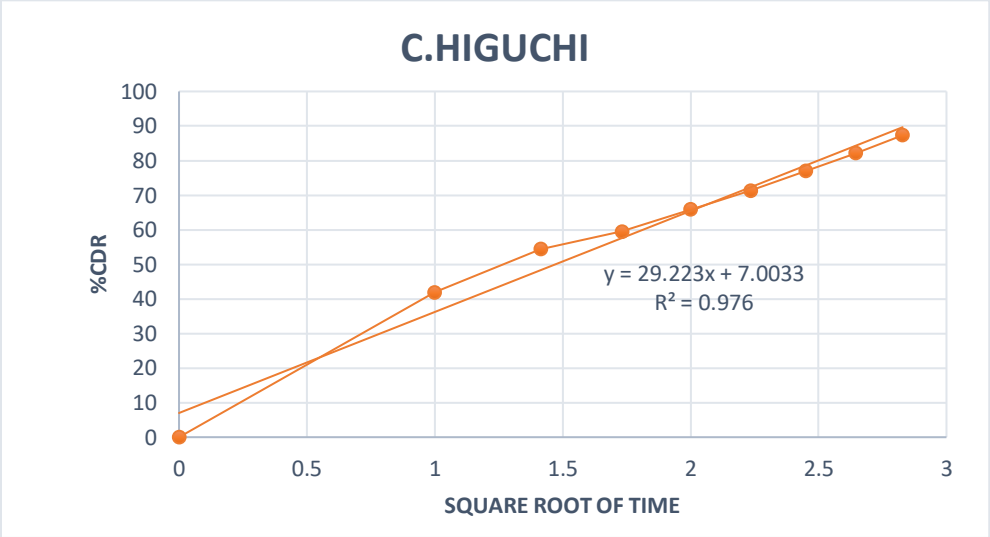


Fig 4 – In-vitro drug release graph for Enalapril maleate

Drug Release Kinetics

The *In vitro* release of Enalapril maleate from the expandable film F3 was fitted to zero order, first order, Higuchi, Koresmeyer - Peppas and Hixson- Crowell models as shown in Fig.5 The F3 fits best with the zero order kinetic model. The release component value (n) which was obtained from Koresmeyer – Peppas model depicts that the F3 follows Fickian release pattern. Hence it shows the diffusion mechanism.


B.FIRST ORDER
LOG %CDR
TIME
y = 0.1504x + 1.0148
R² = 0.4498
2.5
2
1.5
1
0.5
0
0
2
4
6
8
10


C.HIGUCHI
%CDR
SQUARE ROOT OF TIME
y = 29.223x + 7.0033
R² = 0.976
100
90
80
70
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3

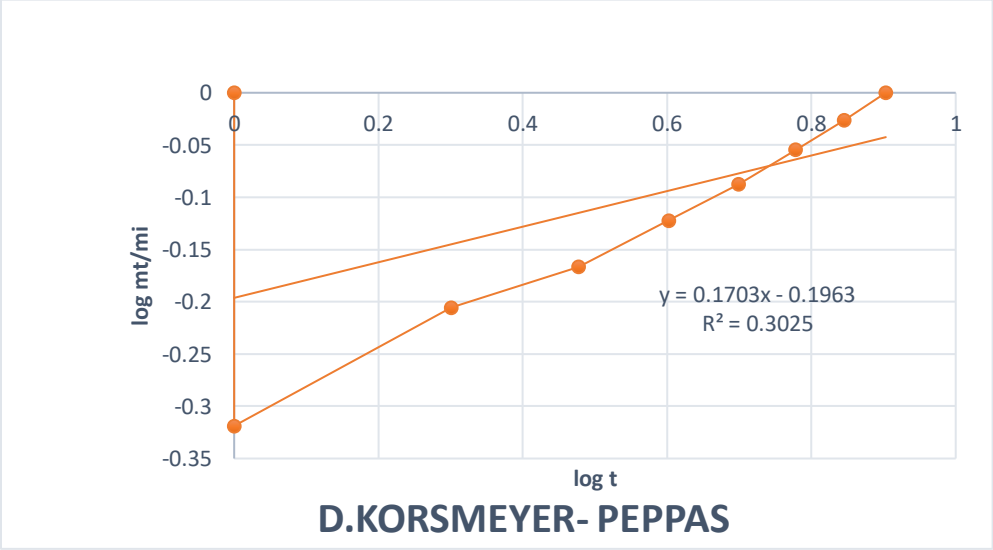

log mt/mi
log t
y = 0.1703x - 0.1963
R² = 0.3025
0
-0.05
-0.1
-0.15
-0.2
-0.25
-0.3
-0.35
0
0.2
0.4
0.6
0.8
1
D.KORSMEYER- PEPPAS

Fig 5– A) Zero Order B) First order C)Higuchi D) Korsmeyer-Peppas release kinetics of Formulation 3 of expandable film of Enalapril maleate

Formulation	Zero order	First order	Higuchi mattrix	Peppas plot	
				r^2 value	n value
F3	0.8198	0.4498	0.976	0.3025	0.1963

Fourier Transform Infrared Spectroscopy (FTIR)

FT-IR spectroscopy was conducted for the drug, polymers and physical mixture of drug and polymers. The absorption range (2850 - 2975 cm^{-1}) in the infrared spectroscopy represents the C−H alkane group. The absorption regions 1640 – 1680 cm^{-1} shows the presence of alkene group. 1735 – 1750 cm^{-1} absorption range regions represent the ester group (RCOOR). The absorption region 1700 – 1725 cm^{-1} represents the presence of carboxylic acid group (RCOOH). The regions (1650 – 2000 cm^{-1}) is associated with the presence of aromatic group. The peaks in the infrared spectra for functional groups are similar to both IR spectra of the drug and physical mixture of the drug and polymer. There were no major shifts between the peaks. So it can be deduced that drug and polymer are compatible.

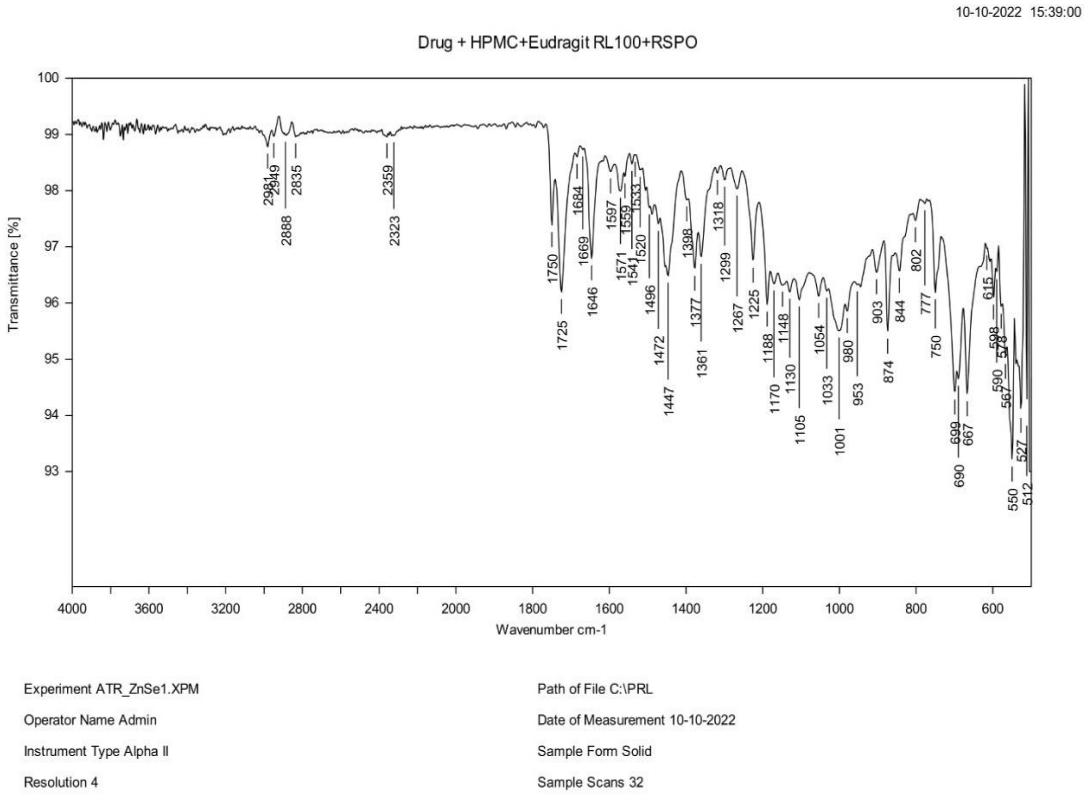


Fig 6 – FTIR of Physical mixture of drug & polymer

Scanning Electron Microscopy (SEM)

Formulation 3 was subjected to the scanning electron microscopy to understand the morphology of the expandable films. F3 was examined using Hitachi S3400 scanning electron microscope at the voltage of 10.0kV with different magnifications. The film surface shown were found to be non-porous and integrated.

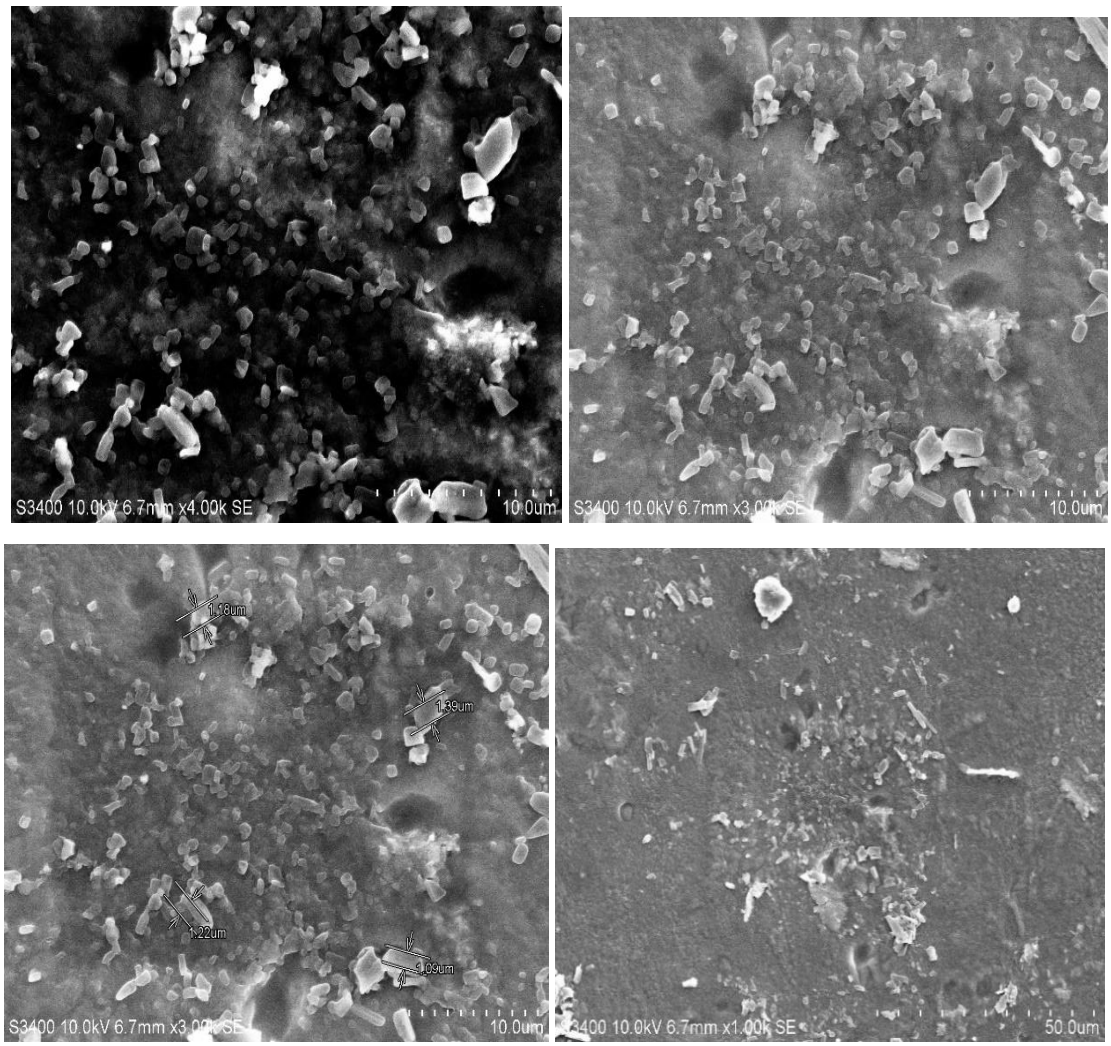


Fig 7 – Scanning electron micrographs of GRDF of F3.

4. CONCLUSION:

The present research work involves the preparation, formulation and *in-vitro* evaluation of Gastroretentive expandable film of Enalapril maleate. Under this study, the active pharmaceutical ingredient Enalapril maleate and characterization of the formulations were carried out. In this study, the effect of varying concentration of polymers and absence of the one of polymers on the polymer film is studies. The formulation with the combination of Eudragit RSPO and RL 100 showed the maximum drug release of 87.32%. It was concluded that using combination polymers rather than individual polymer is more appealable, and their permeability issues of individual polymers can be resolved using combination polymers whose permeability lie between high and low. The combination polymers of Eudragit are used to tailor the desired dosage forms for sustained release. Hence, Enalapril maleate expandable gastroretentive films were successfully formulated and their evaluation reports were within the limits.

Conflicts of interest

We authors have no potential conflict of interest towards it.

LIST OF ABBREVIATIONS USED

Symbols/Abbreviations	Elucidations
%	Percentage
ACE	Angiotensin converting enzyme
℃	Degree centigrade
CDR	Cumulative Drug Release
cm	Centimeter
DCM	Dichloromethane
F	Formulation
Fig.	Figure
FTIR	Fourier Transform Infrared Spectroscopy
g/mol	Gram per mole
GIT	Gastrointestinal tract
GR patch	Gastroretentive patch
GRDDS	Gastroretentive drug delivery system
GRDF	Gastroretentive dosage form
HPMC	Hydroxy propyl methyl cellulose
hr	Hour
IUPAC	International Union of Pure and Applied Chemistry
kg	Kilogram
mg	Milligram
min	Minute
ml	Millilitre
nm	Nanometer
PEG	Polyethylene glycol
pH	Negative logarithm of hydrogen ion concentration
rpm	Rounds per minute
SEM	Scanning electron microscopy
UV	Ultraviolet
λmax	Maximum absorbance
µg/ml	Micrograms per milliliter

Table 1: List of Abbreviation

REFERENCES:

1. Jassal M, Nautiyal U, Kundlas J, Singh D. A review: Gastroretentive drug delivery system (grdds). *International Journal Of Pharmaceutical and Biological Research.* 31Mar.2015;3(01):82.
2. Pant, S., Badola, A., & Kothiyal, P. A review on gastroretentive drug delivery system. *International Journal Of Pharmaceutical Research.* 30Mar.2016;3(02):0-01.
3. More, S.M., Gavali, K.V., Doke, O., & Kasgawade, P. Gastroretentive drug delivery system. *Journal of Drug Delivery and Therapeutics.*12Dec.2022;8(04):5-24.
4. Tripathi, J., Thapa, P., Maharjan, R., & Jeong, S. H. Current state and future perspectives on gastroretentive drug delivery systems. *Pharmaceutics.* .Apr.2019;11(4):193.
5. Mahor, Alok & Gupta, Rishikesh. Recent advances in gastro retentive drug delivery systems and its application on treatment of H. Pylori infections. *Journal of Analytical & Pharmaceutical Research.*2018;7(4):404-10.
6. Awar, V. K., Kansal, S., Garg, G., Awasthi, R., Singodia, D., & Kulkarni, G. T. . Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. *Drug Delivery*.2011;18(2):97-110.

7. Nayak, A.K., Maji, R., & Das, B. Gastroretentive drug delivery systems: a review.*Asian Journal of Pharmaceutical and Clinical Research.*2010;3(01):2-10.
8. Sireesha Reddy Pilaka et al., "Formulation and In vitro evaluation of Enalapril maleate Gastro-retentive Effervescent Floating Tablets with the combination of Natural and Synthetic polymers," *International Journal of Chemical and Life Sciences.* 2022;11(1):2286-97.
9. Ullah, Md & Karim, Md & Alam, Md & Hassan, Rajib & Bhuiyan, Mohiuddin & Rana, Md. Formulation and *In vitro* Evaluation of Unfolding Type Expandable Gastroretentive Film of Enalapril Maleate. *Bangladesh Pharmaceutical Journal*. 2017;20: 148-56.
10. S. Sivaneswari, E. Karthikeyan, P.J. Chandana, Novel expandable gastro retentive system by unfolding mechanism of levetiracetam using simple lattice design – Formulation optimization and in vitro evaluation, *Bulletin of Faculty of Pharmacy, Cairo University*.2017;15(1): 63-72.
11. Sathish Dharani, Himabindu Subedari, Kumar Pavan Panakanti and Rao M. Yamsani, Preparation and evaluation of novel expandable drug delivery system with captopril, *Current Drug Therapy*. 2013;8(3):43-8
12. Chittam S, Bhosale A. Development and evaluation of floating and expanding gastroretentive film of furosemide. *International Journal of Pharmaceutical Investigation.* 8Jun.2020;10(2):179-83.
13. C. E. Jones, "Preparation and characterization of polymer films for the release of Metronidazole," ProQuest, United States. 2017;