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Formulation and Evaluation of Controlled Release Polymeric Microparticles of Eprosartan Mesylate

P. Palanisamy*, B.Jaykar, R.Margret Chandira, S. Thimya, K. Thirunavukarasu, V.N. *Sukanya, M.K. Thahir*
Department of Pharmaceutics, Vinayaka Mission's College of Pharmacy, Vinayaka Missions University, Salem (D.T), Tamil Nadu(State), India.

ABSTRACT

In the present research study focuses on formulate and evaluate Polymeric Microparticles of Eprosartan Mesylate aiming to increase the therapeutic efficacy, reduce the frequency of administration and to improve the patient compliance. Controlled release polymeric microparticles of Eprosartan Mesylate, were formulate by using different drug polymer ratios HPMC Phthalate and Eudragit S 100. The various formulations of controlled release Polymeric Microparticles of Eprosartan Mesylate were formulated by using various concentrations of different polymers HPMC Phthalate and Eudragit S 100 by fusion method. The Polymeric Microparticles were evaluated for pre compression and post compression parameters (Angle of repose, Tapped density & Percentage compressibility index) and *In-vitro* dissolution. The results indicated that the, physical parameters of microparticles were within the Pharmacopeial specifications. Among the different formulation, F4 showed controlled release of drug for 24 hours with 80.27% release. The kinetic drug release, the data was treated according to different model. The drug release data of F1-F5 fitted to Higuchi plots were best fit into Higuchi equation and diffusion mechanism. The result shows that, drug release rate for the F4 formulation follow the zero order mechanism. The selected formulation (F4) was subjected to stability studies for three months at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH and showed stability with respect to release pattern and all physical parameters. Thus, drug in Polymeric Microparticles with Eudragit S 100 were found to be effective in retarding the release of Eprosartan Mesylate.

Keywords: Eprosartan Mesylate, controlled release polymeric microparticles, HPMC phthalate, Eudragit S 100.

*Corresponding Author Email: palanisamy2907@gmail.com
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INTRODUCTION

Microparticles are a type of drug delivery systems where the particle size ranges from one micron (one thousandth of a mm) to few mm. This microencapsulation technology allows protection of drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste. Hence, they play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects.

Hypertension is defined as an elevated Blood Pressure (BP), which is a major risk factor that predisposes to cardiovascular disorders and is responsible for most of the morbidity and mortality[1-2]. Nowadays, patients are considered hypertensive if their BP reach or exceed 90/140mmHg[3]. High BP affects about 20% of the world's adult population and is a serious condition that can lead to coronary heart disease, heart failure, stroke, kidney failure and other health problems.

Polymeric Microparticle drug administration offers number of advantages in therapeutics, where the controlled releases of drug delivery as well as predictable and reproducible drug release of kinetics are important features of them.

The objectives of the present study were to develop and investigate controlled release Polymeric Microparticles of drug to improve the bioavailability, reduce the dose and frequency of drug administration.

Polymeric Microparticles of Eprosartan Mesylate to improve patient compliance by reducing the dosing frequency; To achieve site specific drug delivery and release for prolonged period; To achieve better therapeutic effect of short half life drugs; To study the statistical significance of evaluation parameters; To avoid gastric irritation because of controlled release; Evaluation of the prepared formulation and drug release profile; Analyses the drug release data for kinetic equations; To study the effect of temperature and relative humidity on microspheres.

Development of Polymeric Microparticles of Eprosartan Mesylate would be a significant advantage for patient compliance accompanied by minimization of the drug side effects and to achieve a controlled release in the GIT, which may result in enhanced absorption and thereby improved bioavailability.

MATERIALS AND METHOD

Eprosartan Mesylate was gifted by Ranboxy Pharmaceuticals, Mumbai, HPMC phthalate & Eudragit S 100 was gifted by Merck Limited, Bangalore.

UV Spectrophotometric Analysis[4]

Preparation of standard stock solution

100mg of Drug (Eprosartan Mesylate) transferred into 100ml volumetric flask. It was dissolved in methanol & Phosphate buffer pH 6.8 and volume was made up to the mark with methanol. This gives stock solution of concentration (1000mg/ml), from this 10ml was withdrawn and diluted to 100ml to get a concentration of (100mg/ml).

Standard curve preparation of Eprosartan Mesylate

From this standard solution stock solution, aliquots 1 to 10ml were withdrawn and made up to 10ml methanol & Phosphate buffer pH 6.8 to give a concentration of 1 to 10mg/ml. Absorbance of these solution was measured 313 nm. The results were mentioned in the Table. No: 2 – 4.

Infra-Red Spectrophotometric Analysis[5]

The pellets were made with mixing 1gm of drug and 100gm of dried potassium bromide powder. Mixer was then compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The thin pallet was put on pellet disc to get IR Spectra. The results were mentioned in the Fig. No: 1 – 4.

Preformulation[6]

Pre-formulation is a branch of pharmaceutical sciences that utilizes biopharmaceutical principles in the determination of physicochemical properties of a drug substance. The goal of pre-formulation studies is to choose the correct form of the drug pre-requisite for formulation. Therefore, in pre-formulation substance, evaluate its physical properties and generate a thorough understanding of the material's stability under various conditions, leading to the optimal drug delivery system. The pre-formulation study focuses on the physicochemical parameters that could affect the development of efficacious dosage form. A thorough understanding of these properties may ultimately provide a rationale for formulation design. Also it will help in minimizing problems in later stages of drug development, reducing drug development costs and decreasing product's time to market.

FORMULATION STUDIES[6]

Formulation of Polymeric Microparticles

The Polymeric Microparticles of controlled release Eprosartan Mesylate were prepared by fusion method using different ratios of Polymers such as HPMC Phthalate and Eudragit S 100. The Polymers were melted by heating and then the drug was incorporated into it. The molten mass was poured into a tray which was coated with high-density polyethylene. After immediate solidification, the dispersion was passed through 88 µ size mesh. The prepared polymeric

microparticles were wrapped with aluminium foil and stored in a desiccator at room temperature for further evaluation. The different composition of F1 to F5 is given in Table: 1.

Table: 1 Composition of different formulations

Formulations	Ingredients	Ratio
F1	Eprosartan + HPMC Phthalate	1:1
F2	Eprosartan + HPMC Phthalate	1:2
F3	Eprosartan + Eudragit S 100	1:1
F4	Eprosartan + Eudragit S 100	1:2
F5	Eprosartan + HPMC Phthalate + Eudragit S 100	1:1:1

EVALUATION OF MICROPARTICLES[8-11]

Angle of repose, Tapped density, Compressibility index(Carr's index), Porosity & Percentage yield The results were mentioned in the Table 5

Content uniformity

Randomly samples were taken and weighed. The powdered Microparticle equivalent to 200 mg of Eprosartan Mesylate and was transferred into a 200ml flask containing suitable aqueous media. The flask was shaken for 24 hours and was kept for 12 hours. The solution is filtered through Whatmann filter paper. 10ml of this filtrate was taken and appropriate dilution was made. The samples were analyzed at 313nm using UV visible spectrophotometer. The drug content was determined from the standard curve prepared at λ max 313 nm

The results were mentioned in the Table. No: 6

***In-Vitro* release studies**[12-13]

The *in vitro* release study was carried out using a USP type-II (paddle) rotating dissolution test apparatus (Electrolab, EDT-08L) for the formulated Polymeric Microparticles (USP 2009). A weighed amount of Microparticles equivalent to 200 mg of Eprosartan Mesylate was placed in apparatus. The Phosphate buffer (pH 6.8) was used as dissolution medium (900 mL) and temperature was maintained at 37 ± 0.5°C at 50 rpm. Samples (10 mL) were withdrawn at predetermined time intervals (2, 4, 8, 12, 18 and 24 h) and replaced with an equal volume of fresh dissolution medium to maintain constant volume.

The absorbance of the withdrawn samples was measured at λ_{max}313nm using UV visible spectrophotometer.

Cumulative percentage of drug release was calculated using the equation obtained from a standard curve. The results were mentioned in the Table. No: 7

Kinetic modeling of drug release[14-15]

All the eight formulation of prepared matrix tablets of Ibrutinib were subjected to in-vitro release studies except batch B1 and B4 these studies were carried out using Electrolab TDT 08L dissolution apparatus (USP). The dissolution medium consisted of 900 ml of purified water for 12 hrs.

The results obtained in in-vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Log Cumulative percent drug released vs. square root of time (Higuchi's
4. Classical Diffusion Equation)
5. Log of cumulative % release Vs. log time (Peppas Exponential Equation)
6. (Percentage retained)$^{1/3}$ Vs. time (Hixson –Crowell Erosion Equation)

This model is widely used when the release mechanism is not well know or when more than one type of release phenomenon was involved. The 'n' values can be used to characterize diffusion release mechanism as

'n'	**Mechanism**
0.5	Fickian diffusion
0.5<n<1	Non- fickian diffusion
1	Class II transport

The results were mentioned in the Table: 8 – 9.

Stability studies[16-17]

Sustained release matrix tablets of Ibrutinib formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient temperature and humidity conditions at i.e. 25°C/60%RH, 30°C/65%RH, 40°C/75% RH for 3 months and analyzed after one month and three months for its drug content and in-vitro release.

The results were mentioned in the Table: 10.

RESULTS AND DISCUSSION

Determination of λ_{max}

The standard stock solution was prepared as per the method described in experimental section and scanned by UV spectrophotometer. The λ_{max} was found to be 313 nm.

Calibration curve

Table: 2 Standard calibration curve of Eprosartan Mesylate (Methanol)

S.No.	Concentration (mcg/ml)	Absorbance
1	1	0.082
2	2	0.151
3	3	0.239
4	4	0.33
5	5	0.401
6	6	0.480
7	7	0.550
8	8	0.638
9	9	0.710
10	10	0.803

*Mean±SD (n=6)

Table: 3 Standard calibration curve of Eprosartan

S.No.	Concentration (mcg/ml)	Absorbance
1	1	0.0680
2	2	0.1012
3	3	0.1418
4	4	0.1826
5	5	0.2415
6	6	0.2734
7	7	0.3142
8	8	0.3689
9	9	0.4203
10	10	0.4535

Mesylate (Phosphate buffer pH 6.8)

*Mean±SD (n=6)

Table: 4 Regression Analysis

Parameters	Value (Methanol)	Value (Phosphate buffer pH 6.8)
R^2	0.999	0.997
Slope	0.079	0.044
Intercept	0.000	0.009

On the basis of preliminary identification test it was concluded that the drug complied the preliminary identification. From scanning of drug in methanol dissolution media, it was also concluded that the drug had maximum wavelength of 313 nm.

From standard calibration curve of Eprosartan Mesylate in methanol & Phosphate buffer pH 6.8 dissolution media, it was observed that the drug obeys Beer-Lamberts law in concentration range of 1-10 µg/ml in the media.

Identification of drug (Eprosartan Mesylate) sample

The drug was identified and confirmed by FTIR spectrum. Fig. 1 – 4 shows the FT-IR spectrum of Eprosartan Mesylate. The characteristic absorption peaks of Eprosartan Mesylate are within the pharmacopeial limits.

Drug Excipients Compatibility study:

Compatibility of the drug with recipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the recipients. The samples were taken for FT-IR study.

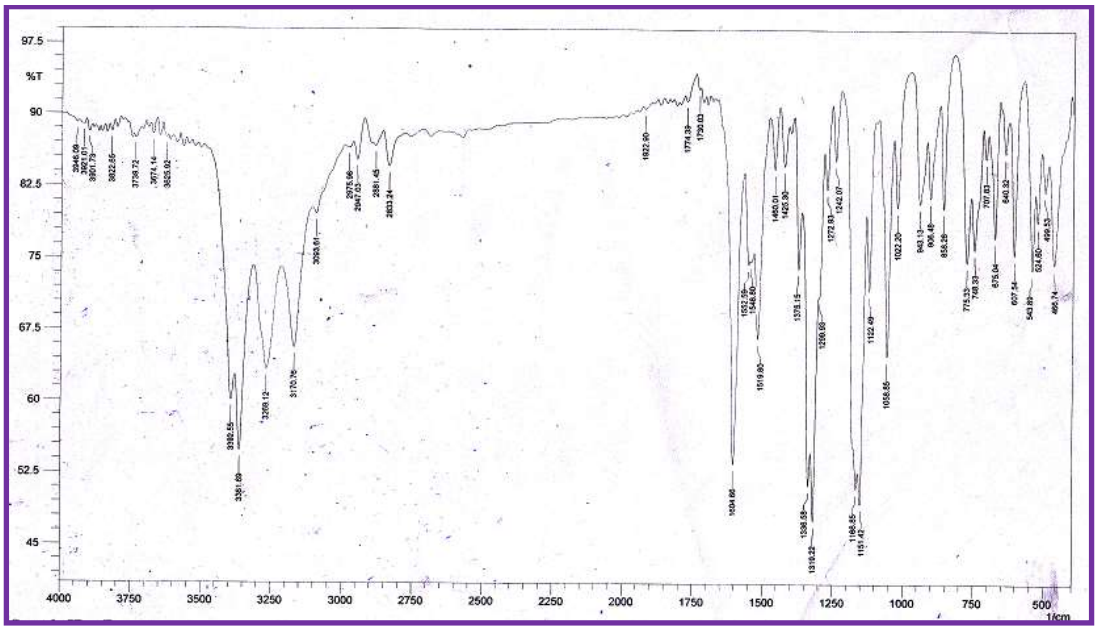

Figure 1: FT-IR Spectrum of Pure Drug (Eprosartan Mesylate)

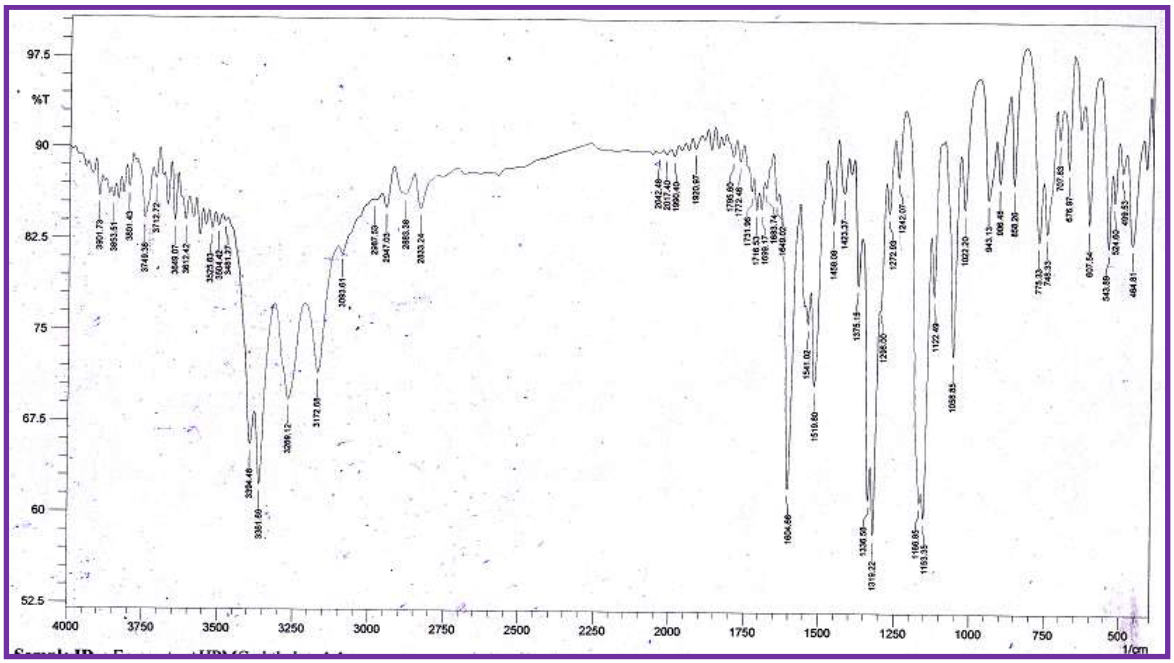

Figure 2: FT-IR Spectrum of Eprosartan Mesylate + HPMC Phthalate

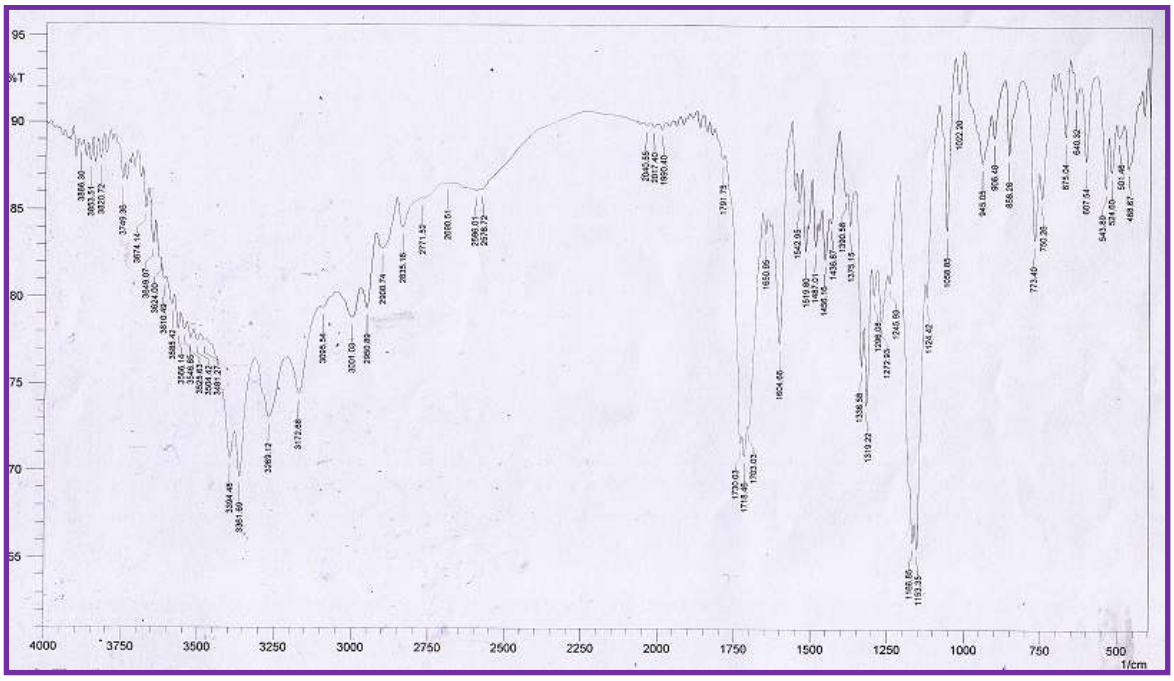

Figure 3: FT-IR Spectrum of Eprosartan Mesylate + Eduragit S 100

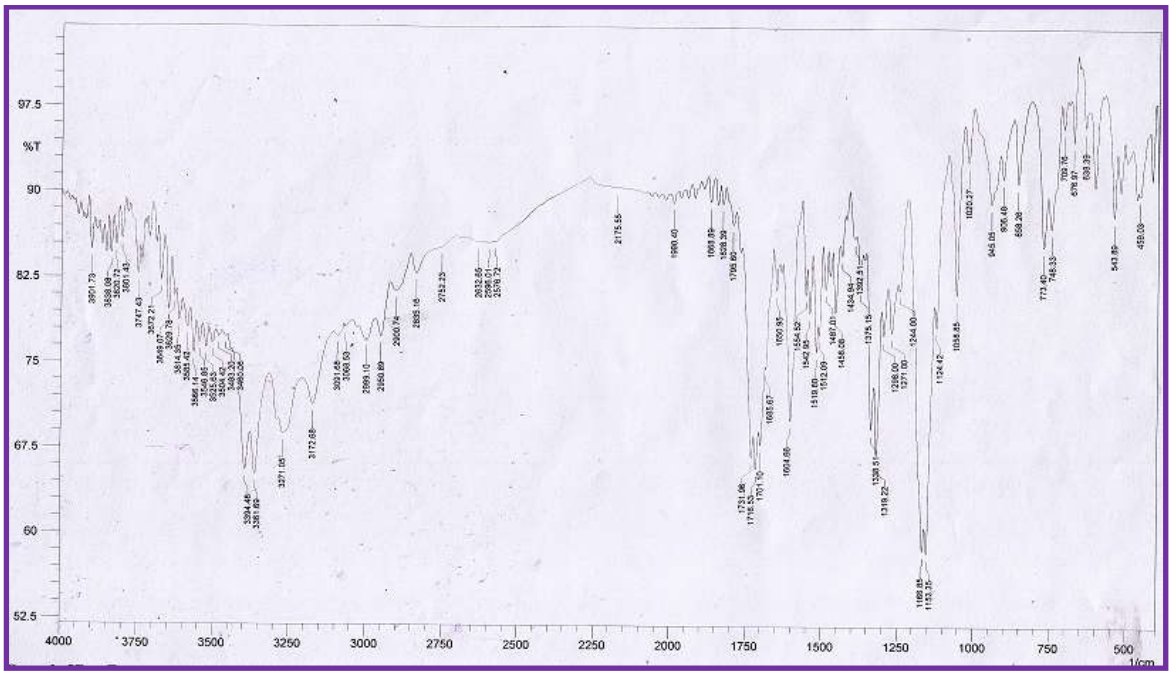

Figure 4: FT-IR Spectrum of Eprosartan Mesylate Microparticle (Optimized formulation) F4

Preformulation studies:

The preformulation studies of the pure drug (Eprosartan Mesylate) were analyzed and various parameters-angles of repose (25º.09´), tapped density (0.39), porosity (13.79 %) and Carr's index (12.82 %) were determined.

EVALUATION OF MICROPARTICLES:

Table: 5 Physico-chemical parameter of different batches of Polymeric Microparticles

S.no	Formulation code	Angle of repose(º)	Tapped density(g/cm^3)	Percentage compressibility index (%)
1	F1	36º22	0.38	20.5
2	F2	32º38	0.42	26.4
3	F3	25º61	0.51	27.03
4	F4	38º12	0.59	31.89
5	F5	31º60	0.47	28.42

*Mean±SD (n=6)

Table: 6 Percentage Yield, Drug content and content uniformity of different batches of Polymeric Microparticles.

S.no	Formulation code	Percentage Yield	Drug content	Content uniformity
1	F1	59.83	60.54	59.01
2	F2	61.03	62.86	62.20
3	F3	61.23	53.25	61.01
4	F4	64.54	63.25	65.70
5	F5	62.43	61.56	58.58

*Mean±SD (n=6)

***In Vitro* drug release study:**

Table 7: *In Vitro* drug release of different batches of Polymeric Microparticles of Eprosartan Mesylate.

Time(hrs)	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	22.20	28.48	9.83	10.43	18.2
4	43.93	41.90	16.23	19.38	28.61
8	57.41	53.92	24.04	37.43	46.72
12	68.04	61.32	41.39	51.88	58.25
18	65.78	63.55	58.82	63.24	63.07
24	69.11	64.05	68.24	80.27	63.12

Kinetic Studies

Table: 8 *In Vitro* kinetic release profiles of Polymeric Microparticles of Eprosartan Mesylate of F4 formulation

Time (Hrs.)	SquareRoot T	Log T	Cum% drug release	Cum% drug retained	Log Cum % drug release	Log Cum % drug retained	Cube root of % retained)
0	0	0	0	100	0	2	4.6415
1	1.4142	0.301	10.43	89.57	1.0182	1.9522	4.4742
2	2	0.602	19.38	80.62	1.2874	1.9064	4.3199
3	2.8284	0.903	37.43	62.57	1.5732	1.7964	3.9699
4	3.4641	1.0792	51.88	48.12	1.7149	1.6823	3.6372
5	4.2426	1.2552	63.24	36.76	1.8009	1.5654	3.325
6	4.8989	1.3802	80.27	19.73	1.9046	1.2951	2.7021

Table 9: Kinetic Data of Formulations F4

Code	Zero-order		First order		Higuchi		Hixson Crowell		Peppas	
	R^2	Slope	R^2	Slope	R^2	slope	R^2	slope	R^2	N
F4	0.974	5.640	0.985	2.015	0.966	-8.295	0.994	4.628	0.888	0.363

DISCUSSION

As per the results shown in table 16, the batch F4 had appreciable correlation with zero order plot (R^2=0.974) and simultaneously apparent to Higuchi drug release profile (R^2=0.966) presented a controlled drug release microparticles. As per data fitting with Korsmeyer Peppas model, value of n for each batch was calculated and for batch F4, then value was 0.363 describing Non-Fickian drug release mechanism.

All the formulations exhibited anomalous (Non - Fickian transport) diffusion mechanism and followed zero order kinetics. Based on the found data of *in vitro* drug release and kinetic data modeling, formulation F4 was selected for the stability studies.

Stability studies

Table: 10 *In Vitro* drug release Polymeric Microparticles of Optimized formulation (F4) accelerated stability data (40ºC±2ºC/75%RH±5%RH)

Time(hrs)	0 day	After 1 month	After 3 month
0	0	0	0
2	10.43	10.03	10.00
4	19.38	19.01	18.91
8	37.43	36.83	36.03
12	51.88	51.21	50.81
18	63.24	62.40	62.04
24	80.27	80.10	79.73

*Mean±SD (n=6)

SUMMARY AND CONCLUSION

In the present research work an attempt was made to formulate and evaluate Polymeric Microparticles of Eprosartan Mesylate by using different polymers, which are having release rate controlling ability, permeable, non-toxicity, non-irritancy, stable in stomach pH, polymers namely HPMC Phthalate and Eudragit S 100, have been chosen as carriers for the preparation of controlled release Polymeric Microparticles. The drug λ_{max} was found to be 313 nm by using UV spectrophotometer. Drug polymer interaction studies were carried out by using FTIR analysis which confirmed that there were no interactions between the drug and selected polymers. The Angle of Repose, Tapped Density and Percentage compressibility index of each formulation was calculated. The results indicated that all formulations were within the Pharmacopeial

specifications. The various formulations of controlled release Polymeric Microparticles of Eprosartan Mesylate were formulated by using various concentration of different polymers HPMC Phthalate and Eudragit S 100 by fusion method. The Polymeric Microparticles were evaluated for pre compression and post compression parameters (Angle of repose, Tapped density & Percentage compressibility index) and *In-vitro* dissolution. The results indicated that the, physical parameters of microparticles were within the Pharmacopeial specifications. There has been considerable interest in using different grades of HPMC phthalate & Eudragit S 100 both controlled release drug delivery system due to their hydrophilic nature and fast hydration. It has been reported that polymers of different viscosity grades can yield different drug absorption.

In the present study *in-vitro* release profile could be expressed by Higuchi for all formulation showed good linearity indicates that diffusion is dominant mechanism of drug release with these formulations. From results of *in- vitro* drug release studies; it concludes that F4 had better-controlled release than the other formulation (F1, F2, F3 & F5). To know the kinetic drug release, the data was treated according to different model. The drug release data of F1-F5 fitted to Higuchi plots were best fit into Higuchi equation and diffusion mechanism. The diffusion is related to the transport of drug from the dosage form into *in-vitro* fluid depending upon concentration of the gradient varies the drug release the distance for diffusion increases. The zero order plots for all formulation were found linear. The result shows that, drug release rate for the F4 formulation follow the zero order mechanism. From the above studies; it was concluded that the Polymeric Microparticles of optimized formulation F4 containing Drug : Polymer (1:2) Eudragit S 100 showed the best ability in stimulated gastric fluids as compared with other formulations. The accelerated stability studies of selected formulation (F4) showed that there were no significant changes observed in the drug content and *in vitro* drug release during and at the end of the accelerated stability study period.

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REFERENCES

1. Kannel, W. B. "Elevated systolic blood pressure as a cardiovascular risk factor", Am. J. Cardiol., Vol. 85, No. 2, pp. 251-255, 2000.
2. Kannel, W. B. "Hypertensive risk assessment: Cardiovascular risk factors and hypertension", J. Clin. Hypertens., Vol. 6, No. 7, pp. 393-399, 2004.

3. European Society of Hypertension. "European Society of Cardiology guidelines for the management of arterial hypertension", J. Hypertens., Vol. 21, No. 6, pp. 1011-1053, 2003.
4. Surapaneni MS, Das SK and Das NG," The effect of excipients and processing variables on adhesive properties and release profile of pentoxifylline from mucoadhesive tablets", Idaho state university, Procatello, USA.
5. Palanisamy. P, Jaykar. B, Margret Chandira. R, B.S.Venkateswarlu, "Formulation and Charaterization of Pulsatile Drug Delivery System Containing Antiasthmatic Drug" IJDDT, Vol.3 No.1 January-June 2013, pp. 1-16.
6. Palanisamy. P, R. Margret Chandira, B. Jaykar, A.Pasupathi, B. S. Venkateshwarlu, M. Kumar, M. V. Kumudhavalli, "Formulation and evaluation of inlay tablet of metformin hydrochloride as sustained release and pioglitazone with glibenclamide as immediate release" , Journal of Pharmacy Research, 2014,8(11),Page. No: 1592-1607.
7. Palanisamy. P and B. Jaykar "Formulation and evaluation of controlled release mucoadhesive matrix tablet of nadolol", world journal of pharmaceutical research, 2015, Volume 4, Issue 8, 1223-1232.
8. R.Margret Chandira, P.Palanisamy, B. Jayakar "Design And Development Of Controlled Release Mucoadhesive Oral Tablet Of Clarithromycin", International Journal of Pharma Recent Research, 2009, 1(1), Page. No: 59-66
9. R.Margret Chandira, P.Palanisamy, B. Jayakar "Formulation and Evaluation of Effervescent Tablets of Aceclofenac", International Research Journal of Pharmacy, December--2011; Volume.no:2, Issue (12), Page. no: 185-190.
10. R. Margret Chandira, P.Palanisamy, B. Jayakar "Formulation and Evaluation of Isoniazid and Ethambutol Hydrochloride Combination Tablets", International Research Journal of Pharmacy (IRJP), February-2012; Volume.no:3, Issue (2), Page. no: (90-97).
11. R .Margret Chandira, P.Palanisamy, B. Jayakar "Formulation and Evaluation of Bilayered Floated Tablets of Metformin Hydrochloride", International Research Journal of Pharmacy (IRJP), February-2012; Volume.no:3, Issue (2), Page. no: (257-266).
12. LV Allen and PE Luner, Magnesium Stearate, in "Handbook of Pharmaceutical Excipients" IInd edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington D.C. Published by Pharmaceutical Press, London, UK, 305-308.

13. E Morefield, Colloidal Silicon dioxide, in "Handbook of Pharmaceutical Excipients" IInd edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington D.C. Published by Pharmaceutical Press, London, UK, 143-145.
14. Haung Y., Khanvilkar KH, Moore AD, Hilliard Lott M. in "Drug Development and Industrial Pharmacy", 2003, 29 (1) 79- 88.
15. Pandey VP, Manavalan R, Sunder Rajan T, Ganesh KS, in "Indian Journal of Pharmaceutical Science", 2003, 65 (1), 44-48.
16. Ahlneck, C., and Zografi. 1990. The molecular Basis of moisture effects on the physical and chemical stability of drugs in the solid state, Int. J. Pharm. 62: 87-85.
17. ICH Guideline Published by Europian Medicines agency CAMP /ICH/ 2736/99 August 2003.