

How to Cite:

Vantimita, S. R., & Jeganath, S. (2022). Formulation and evaluation of gastroretentive drug delivery system of eprosartanmesylate. *International Journal of Health Sciences*, 6(S1), 2914–2926.
<https://doi.org/10.53730/ijhs.v6nS1.5364>

Formulation and Evaluation of Gastroretentive Drug Delivery System of Eprosartanmesylate

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Abstract---It had become a challenging experience and effort for a formulator to develop and innovate a drug with maximum bioavailability. Objective: In the present study the focus of research is in the treatment of Hypertension, which is one of the most prevalent cardiovascular diseases in the world, affecting a big proportion of the adult and old age population. Eprosartan mesylate(EPM) is angiotensin-II receptor antagonist used for the treatment of high blood pressure. The drug has poor bioavailability due to limited oral absorption and maximum absorption at proximal intestine. This warrants and offers the use of Gastro Retentive Drug Delivery System (GRDDS) for sustained release formulation in order to achieve prolonged action and to improve patients compliance. Method: Wet granulation technique was selected for preparation of tablets and the drug is formulated with hydroxyl propyl methyl cellulose K100m, hydroxyl propyl methyl cellulose K15m, polyox WSR coagulant, polyox WSR301, polyox WSR N80, Lactose Monohydrate, Micro crystalline cellulose(Avicel), magnesium stearate, ethylcellulose, sodium bicarbonate, tromethamine, etc. Results: For around twenty formulations were made and evaluated for General appearance, Thickness, Hardness or Crushing strength Test, Friability Test, Estimation of drug content, *In-vitro* buoyancy studies and *In-vitro* drug release and the results obtained for the performed tests were found within the range of specified limits. Conclusion: Among all the formulations prepared, F-X (Polyox WSR Coagulant 30mg and HPMC K100M 30mg) holds the promise for the present study.

Keywords---Eprosartan mesylate HPMC K100M, HPMC15M, *In-vitro* buoyancy studies, *In-vitro* drug release.

Introduction

Controlled release dosage forms are the most and favorable convenient means to obtain a reduction and mitigation of daily administration of drugs with rapid absorption and elimination. Numerous controlled release systems have been developed for maintaining a therapeutically effective concentration of drug in systemic circulation for longer period of time as well as to reduce side effects. A number of dosage forms have been designed and fabricated to disintegrate or dissolve or release the drug in the stomach, after which it gets absorbed through the small intestine (Talukdar & Fassihi et al., 2004). However, gastrointestinal motility, a vigorous and variable phenomenon, presents a major impediment to the effectiveness of controlled delivery system. The real issue in the development of oral controlled release dosage form is not just to prolong the delivery of drugs for more than 12 hours but to prolong the residence time of dosage forms in the stomach or somewhere in the upper small intestine until all the drug is retained for the desired period of time. Floating drug delivery systems (FDDS) or hydrodynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time (Whiteland et al., 1996). After the release of the drug, the residual system is emptied from the stomach.

Materials and Method

Eprosartanmesylate was obtained as gift sample from hetero drugs from Hyderabad, hydroxyl propyl methyl cellulose K100m, hydroxyl propyl methyl cellulose K15m, polyox WSR coagulant, polyox WSR301, polyox WSR N80, from colorcon, goa, lactose Monohydrate from DMV-Fonterra excipients, Microcrystalline cellulose from signet Madhya Pradesh, magnesium stearate, ethylcellulose, sodiumbicarbonate, tromethamine from Merck, Polyvinylpyrrolidone (PVPK-30), citric acid, sodium lauryl sulphate from Sd fine chemicals, Mumbai, and gelucire.

Method of preparation

Wet granulation technique was selected as a process of preparation of tablets of Eprosartan mesylate (EPM) as the drug exhibits poor flow property and compressibility Index. EPM, lactose and micro-crystalline cellulose were blended in a rapid mixer granulator for 5 minutes (Garg R, Gupta 2008). PVP k30 was dissolved in water under stirring to obtain a binder solution. Material was granulated using binder solution in rapid mixer granulator. The granules were dried in rapid dryer till a Loss on drying (LOD) of less than 3.0%w/w was achieved. Dried granules were passed through 20 mesh and blended with extra granular materials for 10 minutes. The blend was lubricated by adding lubricant (Magnesium Stearate) for 5 minutes (Gupta & Robinson 1992, Park & Robinson 1984). The lubricated blend as shown in table 1 & 2 was compressed using 19.2 X 8.75mm biconvex and capsule shape punches.

8	Tromethamine	--	--	--	--	--	--	--	--	--	--
9	Micro Crystalline cellulose (Avicel 101)	100	100	100	130	115	115	--	50	200	150
10	Magnesium stearate	10	10	10	10	10	10	10	10	10	10
	Total weight(mg)	800	800	800	800	800	800	800	800	800	800

Preformulation studies

Bulk density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml

Tapped density (DT): It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume (Chawla et al., 2003).

Hausner's ratio: Hausner's ratio is the ratio of tapped density to bulk density

Compressibility index (I): It indicates the ease with which a material can be induced to flow.

The compressibility index (< 10) indicates excellent flow properties and above (>30) exhibits very poor flow as per I.P limits (Tao S & Desai 2005).

Characterization of drug substances:

Weight variation: Twenty tablets were selected randomly in every batch and average weight was calculated (as per I.P, limit $\pm 5\%$ for more than 350mg tablets). Then the deviation of individual weight values from average weight and standard deviation were calibrated and checked according to the range (Jeganath et al., 2018).

Friability: Twenty tablets are weighed and placed in a plastic chamber and closed, which was revolved at 25rpm for 4 min. The tablets are then reweighed to % loss in weight. The friability of the tablets was determined. The value should be (<1%) as per I.P limits.

Hardness: The crushing strength was determined using Pfizer hardness tester. Ten tablets were randomly selected from each batch (Surana & Kotecha 2010). In the tablets the crushing strength was additionally transformed to tensile strength. It was measured in terms of kg/cm².

Thickness: Thicknesses of five randomly selected tablets from each batch were measured with a digital Vernier caliper. Then average thickness and standard deviation was calculated. Tablet thickness should be controlled with in 5% variation from standard values (Sheu et al., 2010).

Estimation of drug content:

Five tablets were powdered. The powdered sample equivalent to 368 mg of drug was transferred to a 100ml volumetric flask (Vinod et al., 2010). 10ml methanol was added to dissolve the drug and remaining volume was made up to 100ml with 0.1N HCl, sonicate for 60 minutes and the solution was filtered. From the filtrate, 1ml of solution was transferred to 100ml volumetric flask and the volume was made up to 0.1N HCl (Tao & Desai 2005) . The sample was analyzed by using UV spectrophotometer against blank at 234nm.

In-vitro buoyancy studies: The *in-vitro* buoyancy was determined by Floating Lag Time (FLT) as per the method. The tablets were placed in a 100ml glass beaker

containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as FLT. The total floating duration was also determined (Vibin Bose et al., 2018 & Johnson 1971).

In-vitro drug release: The dissolution test was carried out using USP XXIII dissolution testing apparatus II (paddle method). The test was performed at 50 rpm paddle speed and 900 ml of dissolution medium (0.1 N HCl), at $37 \pm 0.5^\circ\text{C}$. An aliquot of 5 ml of the sample solution was withdrawn at different time intervals and the absorbance was measured by using UV-visible spectrophotometer at 234nm for EPM respectively after appropriate dilution (Mamjek & Moyer 1980).

Drug Release Kinetics: To determine the values of coefficient of determination (R²) and the mechanism of drug release from the formulations, the data were treated according to zero-order (cumulative percentage drug released *vs.* time,), first order (Log cumulative percentage drug retained *vs.* Time, the Higuchi equation (Cumulative percentage drug released *vs.* square root of time) models (Urquhart & Theeuwes 1984).

Result and Discussion

Characterization of blend and tablets of EPM

The formulations F-I to F-XX found to have varying bulk density, tapped density, compressibility index and Hausner's ratio which ranged from 0.48 ± 0.34 gm/cc to 0.55 ± 0.21 gm/cc, 0.63 ± 0.09 gm/cc to 0.68 ± 0.19 gm/cc, $14.0 \pm 0.16\%$ to $25.7 \pm 0.09\%$ and 1.16 ± 0.13 to 1.34 ± 0.018 respectively. The observed values were within I.P limits and also demonstrate good flow property for the developed formulation (Table 3).

Table 3: Characterization of blend of EPM

Parameter	Bulk density(gm/cc)	Tapped density(gm/cc)	Hausner ratio	Compressibility index
F-I	0.53 ± 0.08	0.67 ± 0.08	1.26 ± 0.05	20.8 ± 0.09
F-II	0.53 ± 0.12	0.67 ± 0.9	1.26 ± 0.02	20.8 ± 0.10
F-III	0.48 ± 0.34	0.63 ± 0.10	1.31 ± 0.06	23.8 ± 0.12
F-IV	0.51 ± 0.54	0.65 ± 0.11	1.27 ± 0.10	21.5 ± 0.14
F-V	0.51 ± 0.21	0.65 ± 0.18	1.27 ± 0.10	21.5 ± 0.15
F-VI	0.49 ± 0.31	0.64 ± 0.12	1.30 ± 0.02	23.4 ± 0.09
F-VII	0.53 ± 0.054	0.65 ± 0.09	1.22 ± 0.02	18.4 ± 0.14
F-VIII	0.54 ± 0.65	0.67 ± 0.08	1.24 ± 0.15	19.4 ± 0.21
F-IX	0.51 ± 0.31	0.66 ± 0.09	1.29 ± 0.14	22.4 ± 0.09
F-X	0.55 ± 0.05	0.68 ± 0.07	1.23 ± 0.09	19.11 ± 0.31
F-XI	0.51 ± 0.36	0.66 ± 0.08	$1.29 \pm$	22.7 ± 0.09

			0.05	
F-XII	0.53 ± 0.09	0.68 ± 0.19	1.28 ± 0.10	19.11 ± 0.31
F-XIII	0.49 ± 0.05	0.66 ± 0.18	1.34 ± 0.018	25.7 ± 0.09
F-XIV	0.52±0.21	0.67 ± 0.23	1.28 ± 0.21	22.3± 0.12
F-XV	0.53 ± 0.18	0.68 ± 0.09	1.28 ± 0.12	22.0 ± 0.15
F-XVI	0.52 ± 0.19	0.67 ± 0.07	1.28 ± 0.14	22.3 ± 0.17
F-XVII	0.55 ± 0.21	0.64 ± 0.09	1.16 ± 0.37	14.0 ± 0.16
F-XVIII	0.54 ± 0.14	0.65 ± 0.07	1.20 ± 0.45	16.9 ± 0.17
F-XIX	0.53 ± 0.39	0.66 ± 0.20	1.24 ± 0.21	19.6 ± 0.21
F-XX	0.54 ± 0.34	0.63±0.09	1.16 ± 0.13	14.2 ± 0.21

The formulations F-I to F-XX have varying weight variation between 800± 0.7mg to 800±4.4mg, hardness between 10 kg/cm² to 12 kg/cm², thickness between 5.89±0.02mm to 6.05±0.06mm, percentage of friability between 0.038±0.01% to 0.061±0.05% and percentage of drug content between 98.58±0.09% to 103.41±0.02%. The results were within I.P specifications as shown in Table 4.

Table 4: Characterization of EPM tablets

Parameter	Weight variation (mg)	Hardnes (kg/cm²)	Thickness (mm)	% Friability	% Drug content
F-I	800± 3.6	10-12	5.92 ± 0.02	0.042± 0.11	100.54± 0.8
F-II	800 ± 0.7	10-12	5.90 ± 0.03	0.042± 0.11	98.62 ± 0.90
F-III	800 ± 2.5	10-12	5.89 ± 0.02	0.041 ± 0.14	102.03± 0.40
F-IV	800 ± 3.7	10-12	5.96 ± 0.03	0.056 ± 0.10	99.09 ±1.01
F-V	800 ± 2.6	10-12	5.97 ± 0.02	0.051 ± 0.54	100.04± 0.98
F-VI	800 ± 3.0	10-12	5.92± 0.03	0.052 ± 0.10	101.04 ± 0.50
F-VII	800 ± 1.5	10-12	5.98± 0.02	0.038 ± 0.01	101.01± 0.75
F-VIII	800 ± 2.8	10-12	5.99± 0.03	0.054 ± 0.51	101.36± 0.65
F-IX	800 ± 2.2	10-12	5.87± 0.05	0.048 ± 0.15	101.52± 0.70
F-X	800± 2.2	10-12	5.98± 0.02	0.059 ± 0.21	100.38± 0.40
F-XI	800 ± 3.6	10-12	6.02± 0.03	0.044± 0.31	101.25 ±0.90
F-XII	800 ±4.4	10-12	6.05± 0.06	0.061± 0.01	103.41 ± 0.02
F-XIII	800 ± 4.0	10-12	5.99± 0.05	0.062 ± 0.05	101.08 ± 0.70
F-XIV	800 ± 2.4	10-12	5.92± 0.02	0.058± 0.09	102.02± 0.10
F-XV	800 ± 2.5	10-12	5.93 ± 0.03	0.041 ± 0.23	100.12± 0.20
F-XVI	800 ± 2.7	10-12	5.96 ± 0.04	0.055 ± 0.21	98.58 ± 0.09
F-XVII	800± 1.8	10-12	5.98 ± 0.05	0.05 ± 0.01	102.5 ± 0.50
F-XVIII	800± 2.2	10-12	5.96 ± 0.05	0.05 ± 0.02	102.8 ± 0.60

F-XIX	800± 1.1	10-12	5.92 ± 0.04	0.061± 0.05	98.69± 0.70
F-XX	0.54 ± 0.34	10-12	5.94 ± 0.05	0.052 ± 0.04	99.84 ± 0.80

FTIR Studies:

The EPM and excipients interaction was studied by comparing the FTIR spectrum of the optimized blend (FX) with that of EPM drug as shown in Fig 1-2. The comparison study demonstrates that there was no interaction between the drug and other ingredients of the formulation.

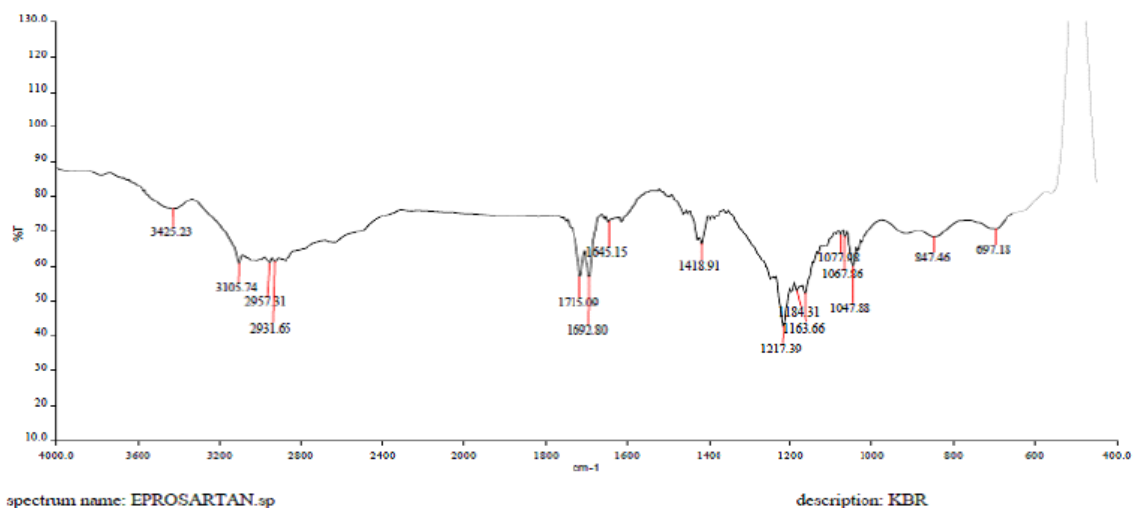


Fig. 1: FTIR of EPM

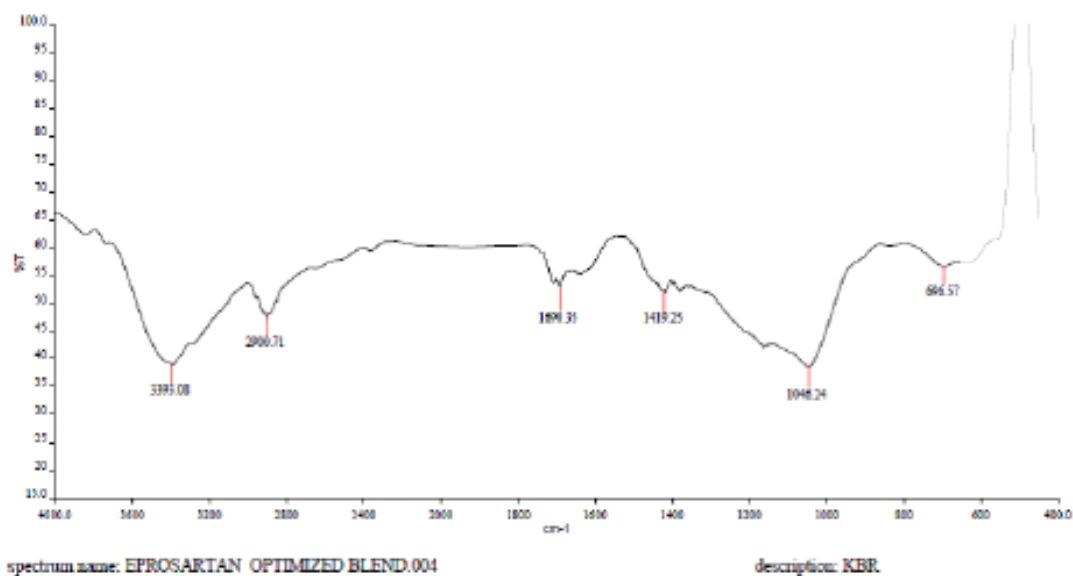


Fig. 2: FTIR of optimized formulation blend

***In-vitro* drug release studies of EPM:**

Dissolution studies

The Cumulative percentage drug release data of all formulations were shown in table 5 , 6 & 7 .The formulations of drug release at 12hrs time were found in the range between 19±1.30 to 100±1.4%.

Swelling Studies:

The average swelling index for all formulations was determined. For formulations F-II to F-XX the swelling index values for 12hrs time was ranged between 103.0±1.39% to 135.4± 0.73 % and 111.2± 0.24% to 90.3± 0.23%.

From the dissolution and swelling index results, it was identified that formula F-X had drug release of 95±0.83% and swelling index was maintained constantly in range of 105.6±0.16% to 95.24±0.34 in 12hrs.

Table 5: Cumulative Percentage Of Drug Release of Various formulations(F1-F7)

S.No	Time (hr)	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII
1	0	0	0	0	0	0	0	0
2	1	71 ± 1.20	2 ± 0.60	2 ± 1.0	4 ± 0.5	33 ± 0.6	59 ± 1.8	2 ± 0.60
3	2	94 ± 1.80	4 ± 0.80	4 ± 0.8	5 ± 0.6	51 ± 0.8	68 ± 1.4	4 ± 0.61
4	4	-	5 ± 0.80	4 ± 0.9	7 ± 0.6	63 ± 0.6	82 ± 0.6	6 ± 1.00
5	6	-	7 ± 1.00	6 ± 0.8	12 ± 0.6	68 ± 0.4	88 ± 0.61	8 ± 0.80
6	8	-	13 ± 1.0	12 ± 0.6	14 ± 0.8	77 ± 1.0	101 ± 1.5	11 ± 1.20
7	10	-	17 ± 0.8	19 ± 0.8	21 ± 0.8	80 ± 1.3	-	15 ± 0.61
8	12	-	20 ± 1.3	29 ± 0.8	29 ± 0.8	100 ± 1.4	-	19 ± 1.30

Table 6: Cumulative Percentage Of Drug Release of Various formulations(F8-F14)

S.No	Time (hr)	F-VIII	F-IX	F-X	F-XI	F-XII	F-XIII	F-XIV
1	0	0	0	0	0	0	0	0
2	1	9 ± 1.00	12 ± 0.83	29 ± 0.63	7 ± 0.98	18 ± 0.63	29 ± 0.75	30 ± 0.81
3	2	14 ± 1.30	17 ± 1.03	41 ± 0.83	12 ± 0.63	24 ± 0.84	44 ± 1.16	48 ± 0.75
4	4	19 ± 1.32	24 ± 0.81	47 ± 0.83	17 ± 0.062	31 ± 0.81	72 ± 0.75	51 ± 0.89
5	6	24 ± 1.02	30 ± 1.26	56 ± 0.98	23 ± 0.93	40 ± 0.63	80 ± 1.17	68 ± 1.37
6	8	39 ± 0.81	37 ± 0.63	65 ± 1.75	30 ± 0.81	48 ± 0.63	84 ± 0.83	75 ± 0.632
7	10	46 ± 1.03	50 ± 0.83	81 ± 0.75	34 ± 1.03	57 ± 0.98	94 ± 0.81	80 ± 1.16
8	12	55 ± 0.63	57 ± 0.54	95 ± 0.83	39 ± 0.84	66 ± 1.37	98 ± 1.03	96 ± 0.98

Table 7: Cumulative Percentage Of Drug Release of Various formulations (F15-F20)

S.No	Time (hr)	F-XV	F-XVI	F-XVII	F-XVIII	F-XIX	F-XX
1	0	0	0	0	0	0	0
2	1	20 ± 1.16	24 ± 0.63	10 ± 1.16	11 ± 0.82	22 ± 0.73	18 ± 1.03

3	2	28±0.63	28±1.04	12±0.82	14 ±0.84	26 ±0.81	23±0.75
4	4	38±1.03	35±1.26	16±1.03	19±0.75	30 ±0.98	31±1.86
5	6	42±0.63	40 ±0.81	21±0.83	22±0.89	36 ±0.82	34±1.26
6	8	47±0.98	52±1.26	32±0.81	31±0.75	42±1.36	39±0.83
7	10	52 ±1.37	58±1.03	39±0.81	38±1.37	45±1.50	45 ±1.21
8	12	55±1.36	66±1.03	49±0.83	51 ±1.26	51±0.79	49±84

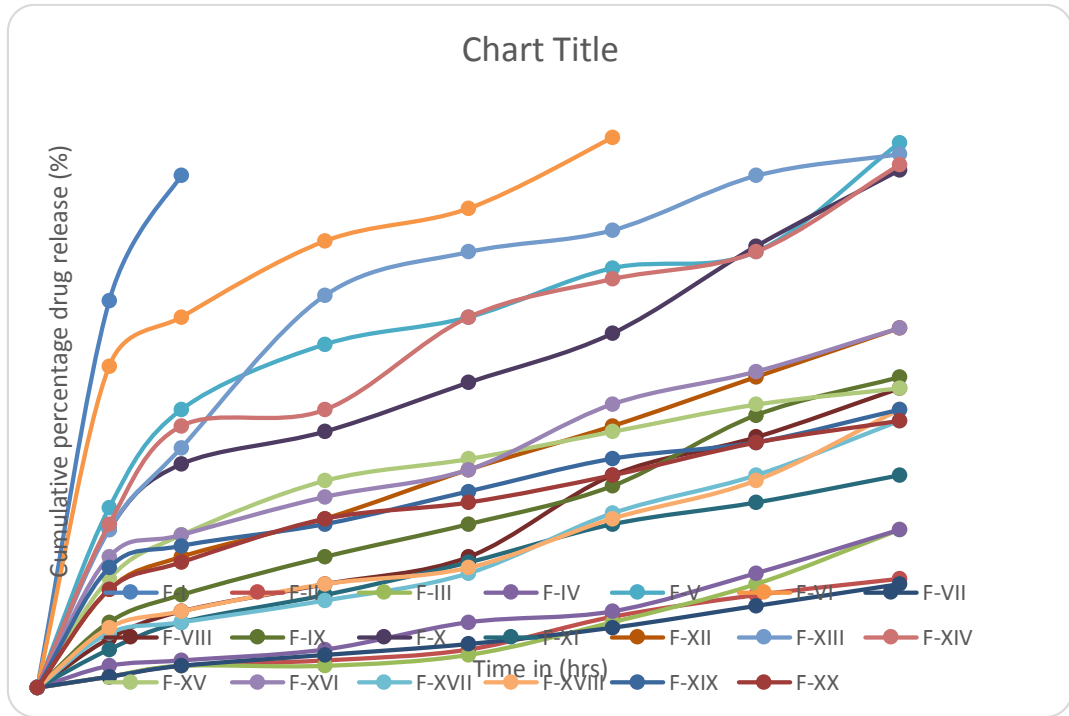


Fig. 3: Cumulative Percentage Of Drug Release of Various formulations(F1-F20)

Table 8: *Invitro* drug release Kinetics data of optimized formulation (F-X)

Time (hrs)	Log time	SQRT of time (\sqrt{t})	Cumulative %drug release	Log cumulative % drug release	Cumulative % drug remaining	Log cumulative % drug remaining
0		0	0	0	100	2
1	0	1	29	1.462398	71	1.851258
2	0.30103	1.41421	41	1.612784	59	1.770852
4	0.60206	2	47	1.672098	53	1.724276
6	0.77815	2.44949	56	1.748188	44	1.643453
8	0.90309	2.82842	65	1.812913	35	1.544068
10	1	3.16227	81	1.9084855	19	1.278754
12	1.07918	3.46410	95	1.977724	5	0.699

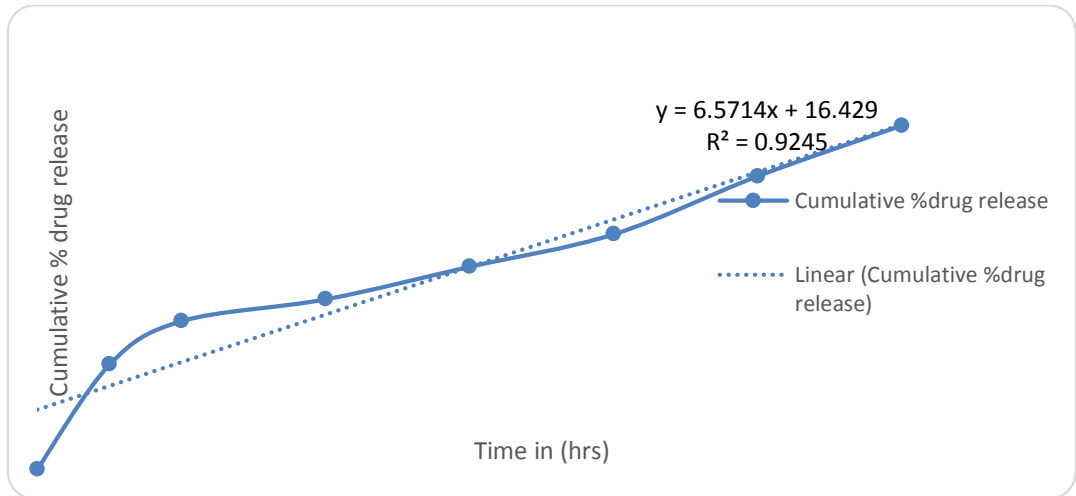


Fig. 4: Optimized formulation zero order plot of EPM (F-X)

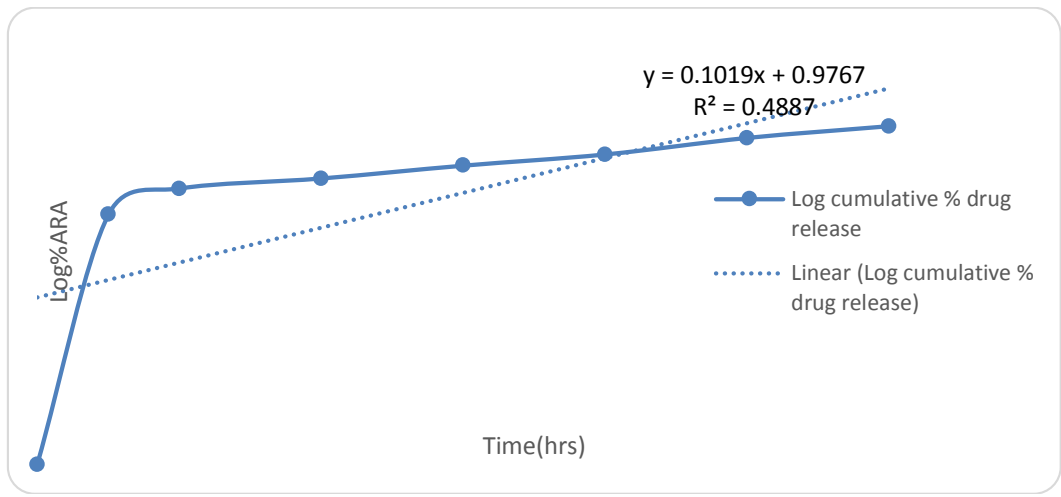


Fig. 5: Optimized formulation first order plot of EPM (F-X)

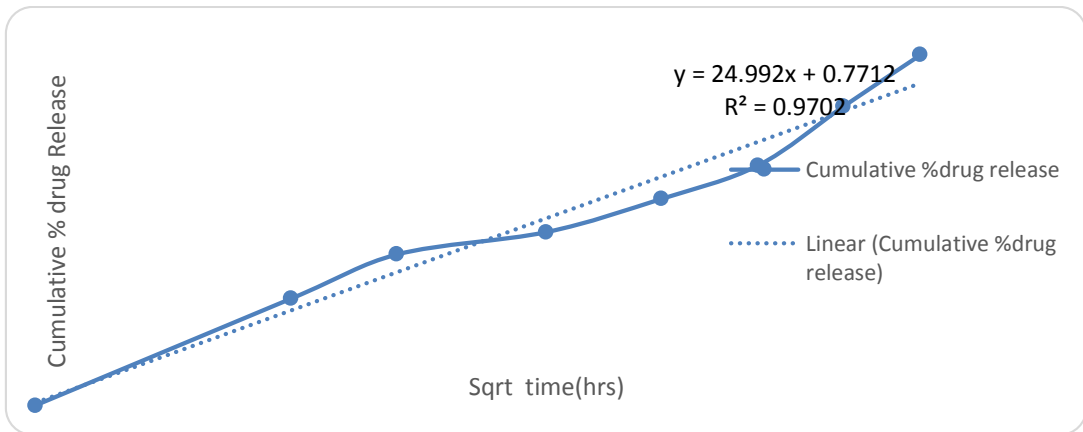


Fig. 6 : Optimized formulation Higuchi plot of EPM (F-X)

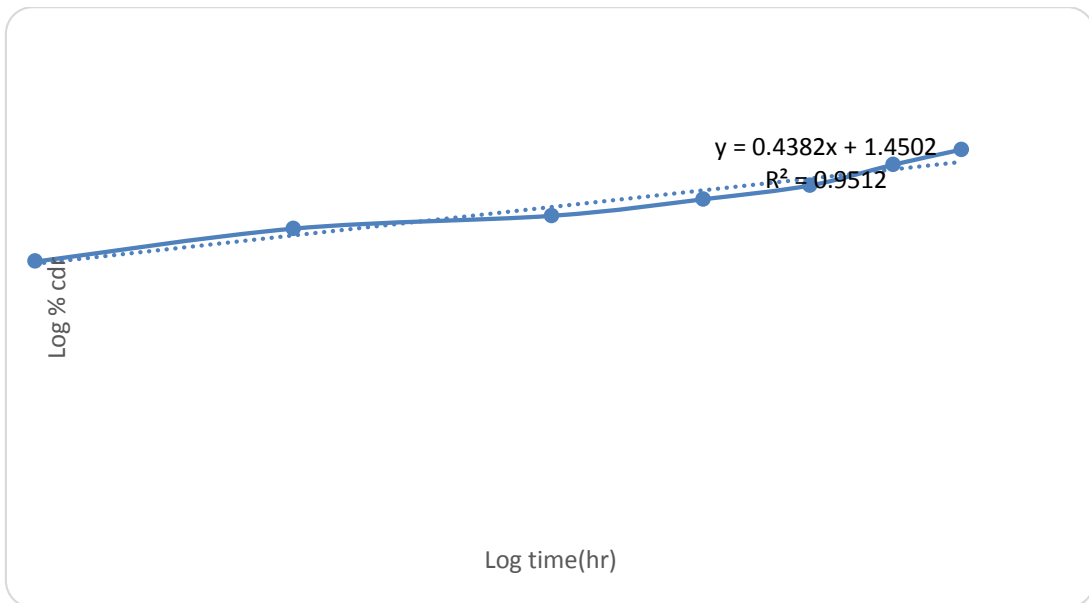


Fig. 7 : Optimized formulation Peppas plot of EPM (F-X)

Table 9: Co-efficient of determination and 'n' values of optimized formulation of EPM (F-X)

Formulation	R ² values				n values
	Zero order	first order	Higuchi	Korsmeyer peppas	Korsmeyer peppas
F-X	0.9240	0.8470	0.9700	0.9290	0.380

The optimized formulation F-X has coefficient of determination (R^2) values of 0.9240, 0.8470, 0.9700 and 0.9290 for Zero order, First order, Higuchi and KorsmeyerPeppas respectively. A good linearity was observed with the zero order, the slope of the regression line from the Higuchi plot indicates the rate of drug release through the mode of diffusion and to further confirm the diffusion mechanism, data was fitted into the KorsmeyerPeppas equation which showed linearity with n value of 0.380 for optimized formulation (Table 9). Thus n value indicates the Fickian diffusion mechanism. The presence of swelling and crosslinked polymers within the matrix structure might be responsible for the drug release controlled by more than one process. Thus, the release kinetics of the optimized formulation was best fitted into Higuchi model and showed zero order drug release with Fickian diffusion mechanism.

Summary

Hypertension was one of the most common cardiovascular diseases in the world, affecting a greater proportion of the adult population. Eprosartanmesylate, were angiotensin II receptor antagonist used for treatment of high blood pressure. The drug has poor bioavailability due to limited oral absorption and maximum absorption at proximal intestine. This warrants the use of GRDDS for sustained release formulation in order to get prolonged action and to improve patient compliance. Eprosartan mesylate gastroretentive tablets were prepared by hydrophilic swellable polymer like Polyethylene oxide (Polyox), Hydroxy Propyl Methyl Cellulose (HPMC) polymers, diluents and lubricants. Total of twenty (F-I to F-XX) formulations were prepared and F-X was found to be the best formulation (Polyox WSR Coagulant 30mg and HPMC K100M 30mg). Drug and polymers was subjected for compatibility study using DSC and FTIR studies, which revealed that there was no interaction between drug and polymers. Wet granulation method was used for preparation of different formulations and the granules were evaluated for precompression parameters before compression of tablets. The results obtained from these studies indicated that the powder blend had good flow properties. The prepared tablets were evaluated for physical characterisation like thickness, hardness, friability, weight variation and drug content. The physical parameters of prepared gastroretentive tablets of Eprosartan Mesylate comply with IP specifications. The optimized formula F-X (Polyox WSR Coagulant 30mg and HPMC K100M 30mg) has $95.0 \pm 0.83\%$ drug release and maintains constant swelling index $95.24 \pm 0.34\%$ - $105 \pm 0.16\%$ up to 12hr period of time. The release kinetics of the optimized formulation was best fitted into Higuchi model ($R^2 = 0.9700$) and showed zero order ($R^2 = 0.9240$) drug release with Fickian diffusion mechanism.

Conclusion

The research work fabricated with the technique of wet granulation method and 20 formulations were made with all the suitable excipients with different composition and studied the evaluation ranging from preformulation studies to all the formulated ingredients. The tablets prepared were also evaluated for their suitable tests such as General appearance, Thickness, Hardness or Crushing strength Test, Friability Test, Estimation of drug content, *In-vitro* buoyancy studies and *In-vitro* drug release and the results obtained for the performed tests

were found with in the range of their each test specified limits. Among all the formulations prepared, F-X (Polyox WSR Coagulant 30mg and HPMC K100M 30mg) holds the promise for the present study and the drug release was maximum in the range at 12hr of time and the other evaluation tests results also shown as a best formulation.

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