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Formulation and Evaluation of Once Daily Sustained Release Tablet of Eprosartan Mesylate Involving Dissolution Enhancement Approach.

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ABSTRACT

The objective of the study was to develop and evaluate once daily sustained release tablet of Eprosartan mesylate involving dissolution enhancement approach for treating hypertentsion. For dissolution enhancement approach solid dispersion of Eprosartan mesylate in carrier PVP K30 at Drug: carrier ratio of 1: 0.25 was done by solvent evaporation method using methanol as solvent. Sustained release tablets were prepared by direct compression method using different polymers Ethocel 10FP, Eudragit RSPO and Eudragit RLPO. SR tablets containing Eprosartan mesylate were developed using different drug: polymer concentration.Evaluation of solid dispersion blend was done by FT-IR study, DSC and saturated solubility. FT-IR study revealed no chemical interaction between drug and polymers used. Pre compression parameters like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio were within the limits. Post compression parameters like hardness, thickness, friability, weight variation test and drug content complied with pharmacopoeial limit for the tablets. The result of *in vitro* dissolution studies indicated tablets containing blend of Eudragit RSPO and Ethocel 10FP (B11) has better sustained release action. To evaluate the effect of Eudragit RSPO and Ethocel 10FP, 3^2 factorial design was employed. The mechanism of drug release was found to follow First order kinetic model, because derived correlation coefficient 'r' (0.8555) and Korsmeyer-Peppas kinetic model suggesting that erosion is the predominant mechanism controlling the drug release. Stability study at $40^0C\pm2^0C$ / 75 ± 5 % RH revealed that there was no significant change in disintegration time, drug content and % CDR after 30 days.

Keywords: 3^2 full factorial design, Eprosartan mesylate, Solid Dispersion, sustained release tablet

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INTRODUCTION

The Angiotensin II type 1 receptor blocker (ARB) eprosartan is a nonbiphenyl nontetrazole angiotensin II type 1 receptor (AT1) antagonist, which acts to decrease total peripheral resistance. Eprosartan acts at vascular AT1 receptors (postsynaptically) and at presynaptic AT1 receptors, where it inhibits noradrenaline release. Eprosartan, therefore, represents a useful therapeutic option in the management of patients with hypertension, including those with a history of stroke or with co-morbid type 2 diabetes mellitus.

The main aim of the present study is to formulate and evaluate once daily sustained release tablet containing Eprosartan mesylate involving dissolution enhancement approach.

Eprosartan has Elimination half-life 5-9 hours and has low bioavailability 13%. Sustained release dosage form maintains the plasma concentration for longer period of time and avoids initial higher plasma concentrations, so that dose related side effects can be avoided. The rationale for development of a once daily sustain release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effects while improving the management of the diseased condition.

Oral route has been the commonly adapted and most convenient route for drug delivery because of more flexibility in the formulation, patient compliance and   convenient for a physician during dose adjustment. An ideal oral controlled drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period.

Dissolution enhancement is achieved through solid dispersion technique. Solid dispersion can be defined as ''A dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting– solvent method''. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The solvent evaporation method aims to dissolve the drug and carrier simultaneously in a common solvent, followed by the removal of solvent by evaporation [1-15].

MATERIALS AND METHODS

Materials

The drugs used for the study was purchased from local pharmaceuticals. All reagents used were of analytical grade and used without further purification. analytical grade

Instruments

Formuation and evaluation of tablet was carried out by use of the equipments available in the institution.

Each instrument was properly calibrated before use. The names of the instruments used along with company name and model number are mentioned in the table.

Table 1: List of instruments

Name of equipment	Name of company and model
Digital Balance	Wensar, INDIA
Multi station rotary Tablet punching machine	Pharma Tech
Hardness Tester	Monsanto
Friability Tester	Roche
Dissolution Apparatus	Veego, INDIA
UV-Visible Spectrophotometer	Shimadzu analytical pvt. Ltd., JAPAN- UV 1800
Fourier Transform Infrared Spectrophotometer	Shimadzu analytical pvt. Ltd., JAPAN
Humidity Chamber	Singhla scientific Industries, INDIA

Methodology

Identification of pure drug with melting point test and solubility test along with analytical method for the estimation by UV spectrum was carried out. Compatibility study of drug with excipients was done by FT-IR study

Solid dispersion of drug with carrier PVP K30 and solvent methanol was carried out using solvent evaporation technique. In order to maintain patient compliance of the tablet dose, the solid dispersion of drug with carrier was preselected at ratio of 1:0.25 respectively. Evaluation of the prepared solid dispersed powder was carried out by saturated solubility test, DSC study and FT-IR study.

Fomulation of tablet: Tablet was prepared by direct compression method. All ingredients were weighed accurately. Except Magnesium stearate and talc, all other ingredients were sifted through 40# sieve. Purified talc and magnesium state were sifted through 60# sieve and then mixed with other ingredients.The powders were blended thoroughly using mortar and pestle after which it was taken for compression. Tablets were compressed by using concave punches on multi-station rotary tablet punching machine.

Post compression studies of each prepared batch were done followed by *In vitro* dissolution study. Optimized formulation was reproduced and checked for reproducibility and stability studies.

RESULT AND DISSCUSSION

Melting point of drug

Capillary tube method

Melting point of Naproxen Sodium was determined by capillary tube method and it was found to be 245 ºC -249ºC. This value is in accordance to that reported in literature (Std 248 ºC -250ºC)

Analytical Method for the Estimation of Eprosartan Mesylate by UV Spectrum

Determination of λmax of Eprosartan Mesylate in 0.1N HCl:-

λmax : 228 nm in 0.1N HCL (Std at 227 nm as per IP)

Solubility

Solubility of drug was determined in 5 different media. It was found that Eprosartan Mesylate was insoluble in water and soluble in ethanol, methanol, and buffer.
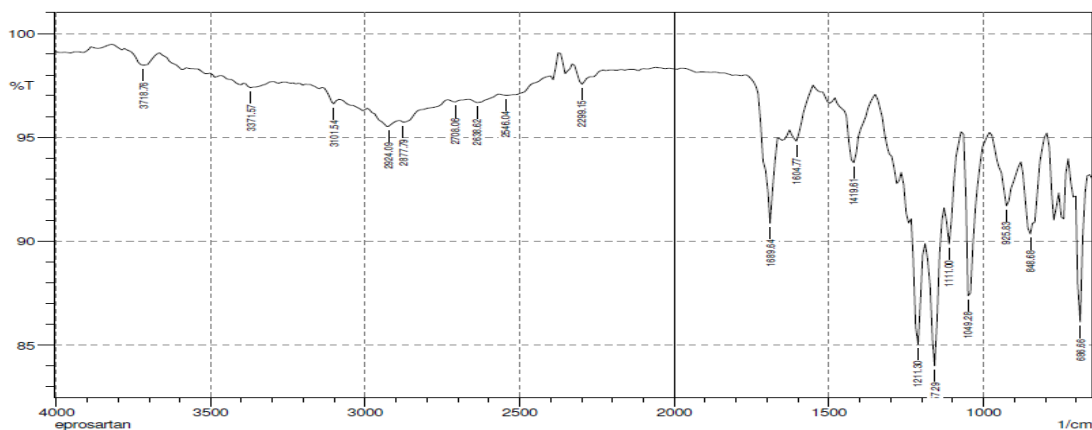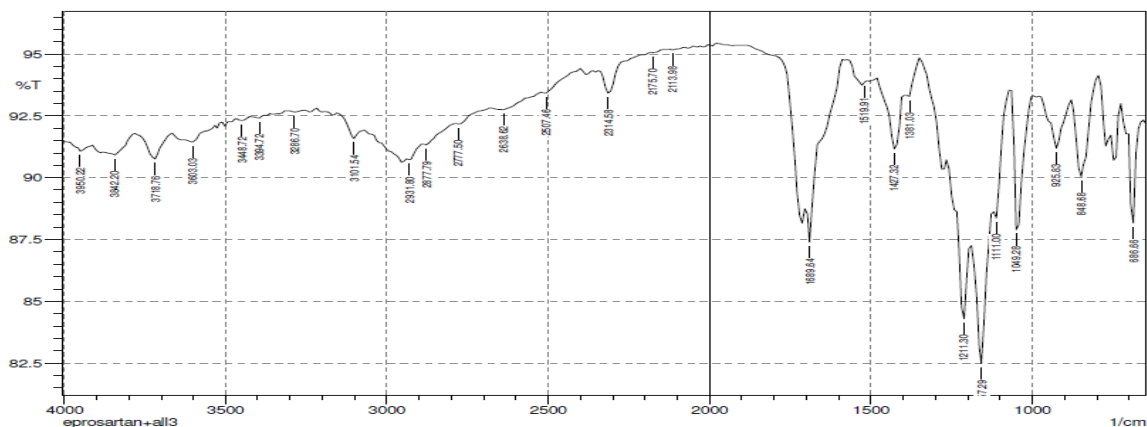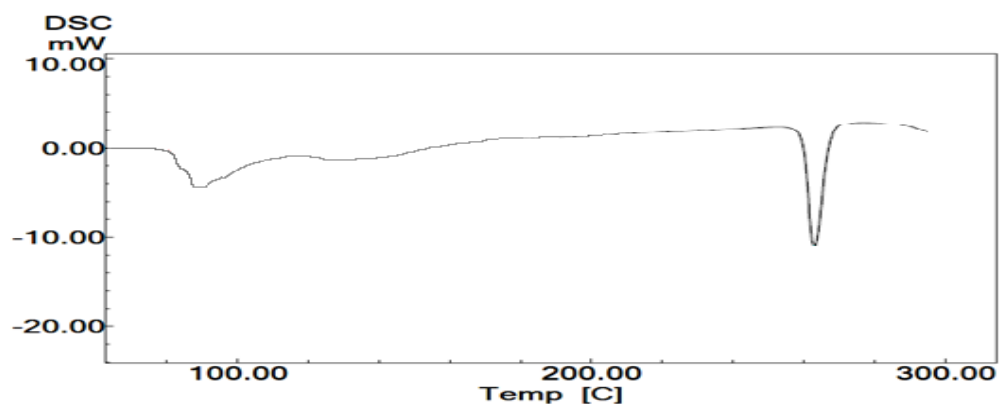
Drug - Polymer compatibility study

Figure 1: FTIR spectra of drug Eprosartan mesylate

Figure 2: FTIR spectra of Drug + Ethocel 10FP + Eudragit RL PO + Eudragit RS PO+ PVP K30
Characterization of solid dispersion

Figure 3: DSC of Solid Dispersion of Eprosartanmesylate: PVP-K30 (1:0.25)

Conclusion

Enhanced dissolution of Eprosartan was achieved in a relatively easy, simple, quick, inexpensive, and reproducible manner. The solid dispersion of Eprosaratan Mesylate with PVP-K30 in the weight ratio 1:0.25 was selected because of dissolution efficiency and lesser increase in the bulk of raw materials. Physical characterization of solid dispersion was carried out by FTIR and DSC. FTIR study suggested absence of any kind of chemical interaction between Eprosartan mesylate and PVP-K30 when formulated in solid dispersion. DSC study suggested that the Eprosartan mesylate was dispersed in PVP-K30 and was still present in crystalline form.

Pre-Compression Study

Table 2:Pre-compression parameter of tablet batch (B1-B9) prepare by individual polymers (Ethocel 10FP, Eudragit RL PO and Eudragit RS PO)

Parameters (n=3)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk Density (g/ml)	0.363± 0.006	0.376± 0.006	0.381± 0.013	0.368± 0.004	0.369± 0.009	0.372± 0.004	0.381± 0.009	0.394± 0.006	0.383± 0.011
Tapped Density (g/ml)	0.431± 0.003	0.439± 0.006	0.442± 0.001	0.425± 0.009	0.429± 0.005	0.431± 0.000	0.439± 0.013	0.461± 0.011	0.437± 0.001
Angle of Repose (θ)	36.12°	34.69°	34.21°	34.11°	33.95°	33.81°	34.21°	34.96°	32.21°
Carr's Index (%)	15.77± 1.23	14.35± 1.21	13.80± 0.69	13.41± 1.69	13.98± 1.69	13.68± 2.13	13.21± 1.66	14.53± 1.34	12.35± 1.11
Haunser's Ratio	1.18± 0.001	1.16± 0.006	1.16± 0.001	1.15± 0.009	1.16± 0.004	1.16± 0.006	1.13± 0.009	1.16± 0.004	1.14± 0.006

Table 3: Pre-compression parameter of tablet batch (B10-B13) prepare by combination of polymers (Ethocel 10FP, Eudragit RL PO and Eudragit RS PO)

Parameters (n=3)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Surface Appearance	White and smooth	White and smooth	White and smooth	White and smooth	White and smooth	White and smooth	White and smooth	White and smooth	White and smooth
Weight Variation	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Hardness (kg/cm^2)	8.0± 0.21	8.1± 0.23	8.2± 0.25	8.2± 0.25	8.2± 0.26	8.3± 0.24	8.3± 0.24	8.4± 0.22	8.4± 0.27
Friability (%)	0.231	0.312	0.251	0.268	0.339	0.113	0.291	0.213	0.112
Drug Assay (%)	98.1	98.2	101.2	99.7	99.1	97.1	98.5	99.2	102.3

Discussion: From above table flow property of tablet prepare by polymer (B1-B9) have good flow property and tablet prepare by combination of polymer(B10-B13) have fair flow property and tablet prepare by combination of both polymer in factorial design (F1-F9) have good flow property.

Post-Compression Study

In vitro Drug release study

Table 4: %drug reease study of tablet prepare by factorial design for combination of polymer Eudragit RS PO and Ethocel 10FP

| TIME (hr)	%DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	38.22	35.87	30.55	32.57	29.52	26.87	29.35	27.24	22.55
2	43.27	38.97	34.55	35.87	32.57	29.17	32.46	29.62	24.74
3	47.87	42.13	39.18	39.82	35.63	31.51	35.37	32.53	26.85
4	51.21	45.82	42.32	43.71	39.37	35.52	38.24	35.17	28.38
5	56.81	49.87	45.83	47.87	43.87	38.51	41.53	37.78	31.04
6	59.27	52.82	49.32	51.96	46.81	41.87	43.63	39.59	33.53
7	64.97	55.80	51.32	54.87	49.87	45.42	46.81	42.95	35.75
8	68.87	58.85	55.52	57.73	53.87	48.52	49.94	44.47	38.35
9	71.15	61.84	57.62	60.76	56.97	51.81	52.06	47.37	41.24
10	74.96	63.89	59.12	63.66	59.52	53.36	55.85	50.84	44.96
11	77.35	66.79	62.71	66.11	63.89	56.11	58.53	52.08	48.53
12	80.17	69.27	65.12	69.26	65.26	59.84	62.92	55.30	53.74
20	99.32	98.24	96.35	96.13	94.56	92.46	96.35	93.76	87.46
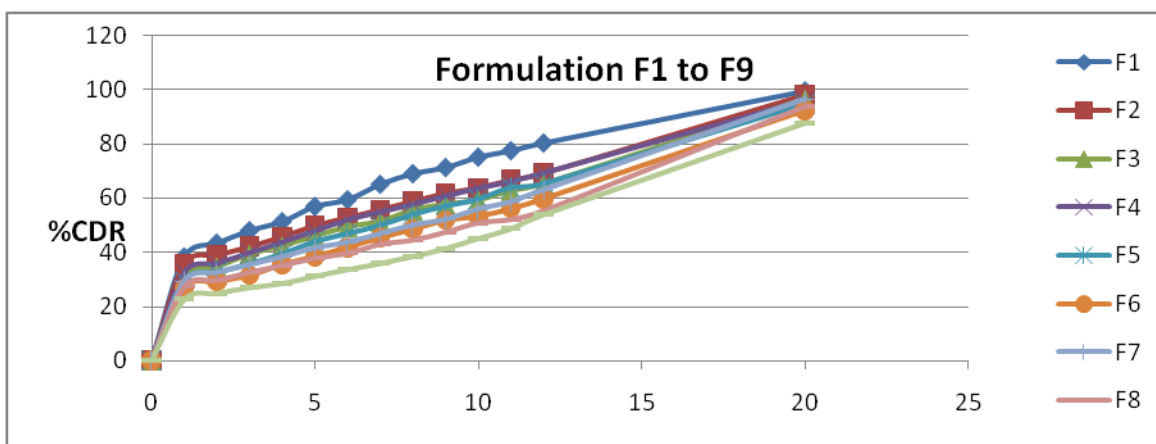
Figure 4: Dissolution profile of Factorial design batches F1-F9

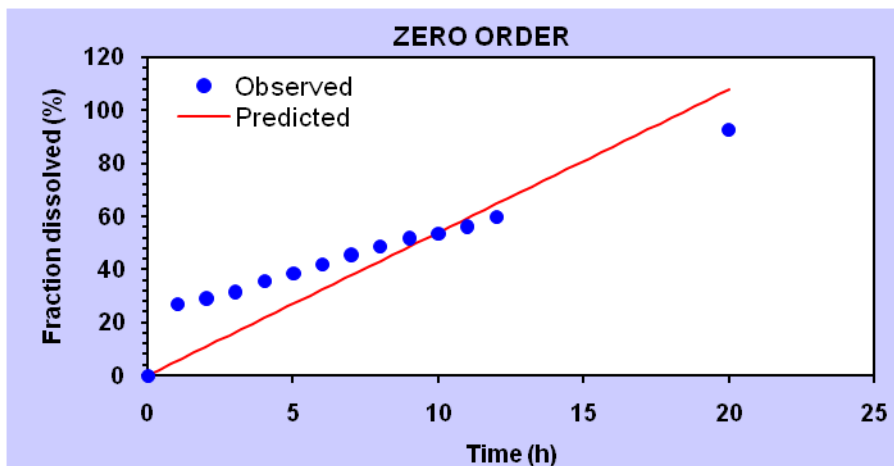**Applications of *in vitro* Drug release characterizations models or release kinetic model.**
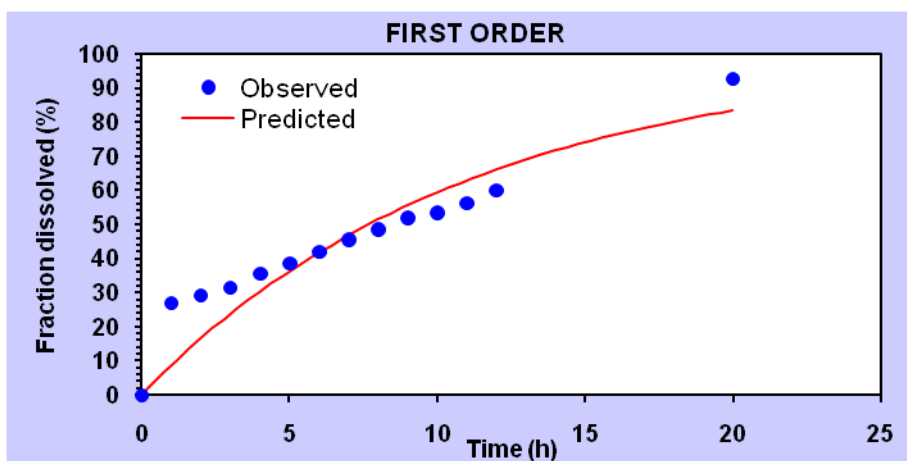

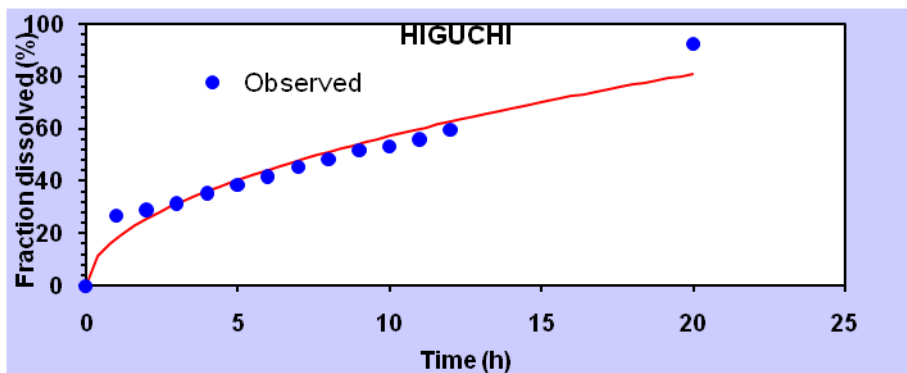**Figure 5: Zero order kinetic model**

Figure 6: First order kinetic model

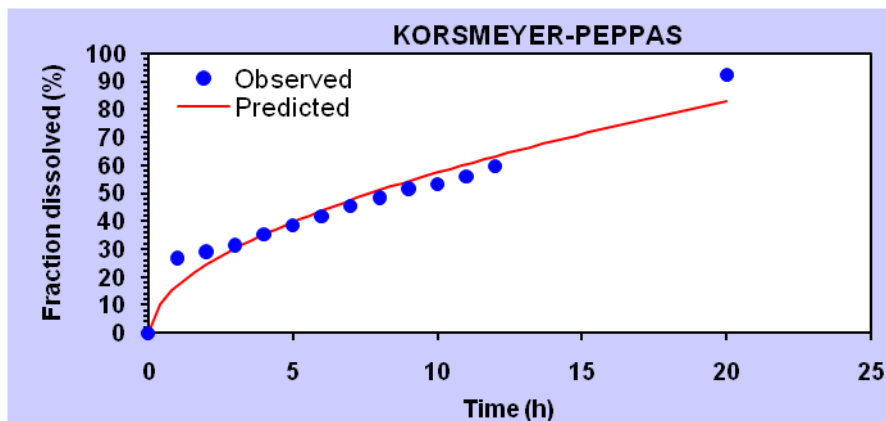

Figure 7: Higuchi kinetic model

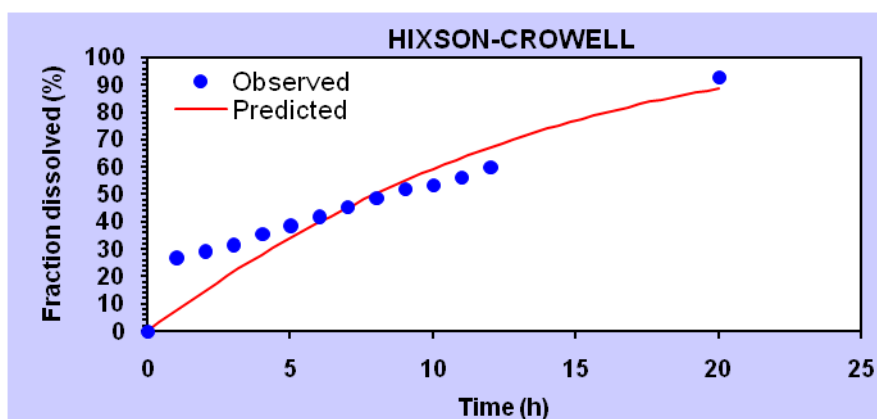**Figure 8: Korsmeyer-Peppas kinetic model**

Figure 9: Hixson-Crowell kinetic model

Table 5: Release kinetic model of optimized batch F6

FINAL OPTIMIZED BATCH	VARIABLE	ZERO ORDER	FIRST ORDER	HIGUCHI	KORSMEYER-PEPPAS	HIXSON CROWELL
(F6)	REGRESSION (R^2)	0.6761	0.8555	0.9484	0.9500 n-0.532	0.8345

Discussion: From above table kinetic model apply to batch F6 and marketed product have R^2 value of ZERO ORDER highest one respectively (0.9878 and 0.9844) and Hixson crowell R^2 value (0.9863 and0.9841) had not vast different between batch F6 and theoretical dissolution profile.

Conclusion: The drug release follows first order kinetic.

Results of Analysis of Variance (ANOVA):

EFFECT OF X1 AND X2 ON % DRUG RELEASE AT 20 hrs.

Table 6: Regression Statistics

REGRESSION STATISTICS					
MULTIPLE R			0.9861		
R SQUARE			0.972393		
ADJUSTED R SQUARE			0.926381		
STANDARD ERROR			0.954971		
OBSERVATIONS			9		
	DF	SS	MS	F	SIGNIFICANCE F
REGRESSION	5	96.36518	19.27304	21.1334	0.015189
RESIDUAL	3	2.735911	0.91197		
TOTAL	8	99.10109			

Table 7: Coefficients

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
B0	94.94444	0.711794	133.3876	9.29E-07	92.6792	97.20969	92.6792	97.20969
B1	-2.58833	0.389865	-6.63904	0.006963	-3.82906	-1.34761	-3.82906	-1.34761
B2	-2.72333	0.389865	-6.98532	0.006022	-3.96406	-1.48261	-3.96406	-1.48261
B12	-1.48	0.477486	-3.09957	0.053313	-2.99957	0.039573	-2.99957	0.039573
B11	-0.84167	0.675267	-1.24642	0.301069	-2.99067	1.307334	-2.99067	1.307334
B22	0.863333	0.675267	1.278507	0.29101	-1.28567	3.012334	-1.28567	3.012334

Table 7: Equation (Full Model and Reduced Model)

Equation
Full Model
$Y1 = 94.44 - 2.58X1 - 2.72 X2 - 1.48X12 - 0.841X1^2 + 0.8633X2^2$
Reduced Model
$Y1 = 94.44 - 2.55X1 - 2.72 X2$

The full model was evolved and refined by excluding the terms for which the level of significance was greater than 0.05. The significant levels of the coefficients b11, b12 and b22 were found to be P = 0.30106, 0.0533, and 0.29101 respectively, so they were omitted from the full model to generate a reduced model equation. The resultant refined polynomial equation is

given below. The coefficients b0, b1 and b2 were found to be significant at P<0.05; hence, they were retained in the reduced model. The following refined equations were generated to check the effect of in-dependent variables on Y1, Dependant variable is shown below.

Y1 =94.44–2.55X1 -2.72 X2

Reproducible Batch

Table 8: Evaluation of Reproducible batch

In vitro Dissolution		Drug Assay (%) = 96.9
Time (hr)	% Drug Release (n=3)	
0	0	Similarity Factor (f_2) = 87.65
1	25.34	
2	28.58	Difference Factor (f_1) = 2.26
3	32.36	
4	36.69	
5	39.47	
6	40.79	
7	46.36	
8	48.89	
9	51.37	
10	53.56	
11	56.47	
12	60.16	

Conclusion: Batch produced reproducible results and it is confirmed that whenever tested again, it give similar results

Stability Studies

Tablet was placed in the modified stability chamber for accelerated stability study at 40 ± 2 0C and 75 ± 5 % RH for 1 month.

After a period of one month, the sample were observed for any change in physical parameters. It was observed that surface was devoid of any change in color or appearance of any kind of odour in it. No changes in the smoothness of the tablets were noted. At the end tablets were analysed for physical appearance, percentage drug content, hardness, and in vitro drug release studies

Table 9: Evaluation of F6 batch after one month Stability studies.

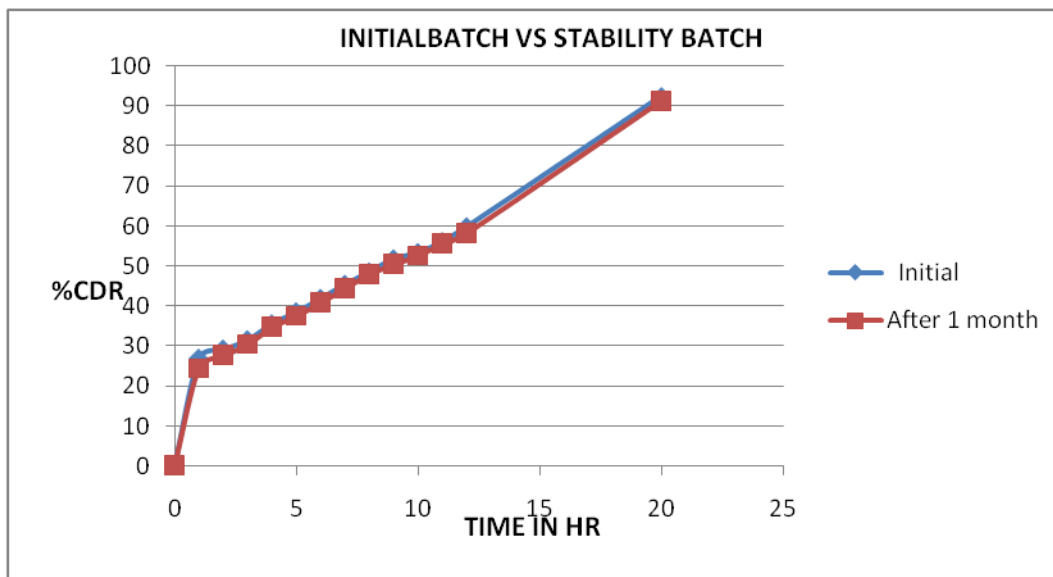| PARAMETER			
In vitro dissolution study	Time (hr)	%drug release	
		Initial	After 1 month
	1	26.87	24.34
	2	29.17	27.58
	3	31.51	30.36
	4	35.52	34.69
	5	38.51	37.47
	6	41.87	40.79
	7	45.42	44.36
	8	48.52	47.89
	9	51.81	50.37
	10	53.36	52.56
	11	56.11	55.47
	12	59.84	58.16
	20	92.46	91.23
Drug assay		97.1	96.8
Colour		Colourless	ColourlesS
Hardness		8.3± 0.24	8.2± 0.22

Figure 10:Comparison of Initial batch B6 vs. Stability batch

Discussions: From above table and graph stability data of optimize batch have similar result after accelerated stability testing. There was no considerable change in drug content and % drug release.

Conclusion: From the above stability data after 1 month reveals that optimized batch F6 have sufficient stability at 40º and 75 % RH.

CONCLUSION

In the present study the formulation of once daily sustained release tablet of Eprosartan mesylate was found to be good without chipping, capping and sticking. The drug content was uniform and well within the accepted limits with low values of standard deviation indicating uniform distribution of drug within the formulation. IR spectroscopic studies indicated that the drug is compatible with polymers and coexcipients. Combination of Eudragit RSPO with Ethyl Cellulose give more desirable sustain release than the individual polymers Eudragit RLPO, Eudragit RSPO and Ethocel 10FP. Based on this formulation batch F6 showed the better release (cumulative % drug release: 62.92% for 12 hrs and 96.35 for 20 hrs). indicated that the drug release was follows erosion type of dissolution. The sustained release tablet of Eprosartan mesylate with improved dissolution provides a better option for increasing the therapeutic activity and patient compliance in treating hypertension.

ACKNOWLEDGEMENT

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