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"DESIGN AND EVALUATION OF EXTENDED RELEASE FORMULATIONS OF METOPROLOL SUCCINATE USING COMBINATION OF FENUGREEK GUM WITH OTHER POLYMERS"

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ABSTRCT

The present work was an effort to develop matrix type extended release tablets of Metoprolol succinate. Matrix tablets of Metoprolol succinate were prepared by using primary natural polymer fenugreek gum and secondary polymer Guar gum and HPMC K4M. Compatibility between drug and polymer was evaluated by FTIR. Matrix tablets were evaluated for pre and post formulation studies. The prepared formulations showed satisfactory pre and post compression parameters. The in-vitro drug release from formulation F1 to F11 ranged from 92.31% to 108.41%. The drug release for the formulations F3 and F11 followed first order with non fickian anomalous diffusion mechanism. The model independent parameters for formulation F3 and F11 were found to be 67.11 and 55.02 % in 9hrs. It was concluded that matrix tablets of Metaprolol succinate were successful in extending the drug release for 12 hrs and the formulations were stable for the duration of the study.

KEYWORDS: Extended release, Metaprolol succinate, Fenugreek gum, HPMC K4M, wet granulation, compression coating.

INTRODUCTION

The oral route is the most popular route for administration of a drug, which is due to the ease of the administration and also offers more flexibility in gastrointestinal targeting of drug.[1] Extended release formulations are useful for increasing the bioavailability of drug, prolong duration of effective blood levels by reduction frequency of administration, possible increased distribution of drug and reduce the side effects.[2]

Metaprolol succinate, selective adrenergic receptor-blocking agent used in the management hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism. Metaprolol succinate was selected as a model drug in this study because it is freely water soluble, and the half-life of drug is relatively short approximately 4-6 hrs thus warrant the use of extended release formulation for prolong action and to improve patient compliance.[3]

The fenugreek gum is being used both in controlling drug release as well as targeting it to specific sites and as natural polymer.[4]

MATERIALS AND METHODS

Metaprolol succinate was obtained as a gift sample from Zydus cadila, Ahmedabad, India. Fenugreek was obtained by S.K Industries Jodhpur. HPMC K4M was obtained by Colorcon Asia Pvt Ltd, Goa, India. PVP K 30 was obtained by Himedia laboratories pvt. Ltd. Mumbai, India. Crosspovidone was obtained by Ozone Int, Mumbai, India. Lactose, Magnesium stearate, and Talc were obtained from S.D. Fine Chem. Ltd, Mumbai, India. All other chemicals were of analytical grade.

METHODS

Fourier Transform Infrared Spectroscopy study

The FTIR spectra of pure drug and prepared formulations were taken for studying compatibility. The samples were scanned. The peaks of drugs and samples were obtained in the scanning range of 400-4000 cm^{-1} by using FTIR spectrometer (Shimadzu 84000S).

Preparation of matrix tablets

Matrix tablets containing Metaprolol succinate were prepared by direct compression, wet granulation, and compression coating method using various drug and polymer ratio. The ingredients were mixed and punched into a tablets by using 9 mm punch to obtain tablets desired specification.

Table 1: Composition of Metoprolol matrix tablets from F1-F11

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Metaprolol Succinate	40	40	40	40	40	40	40	40	40	40	40
Fenugreek gum	40	60	60	30	30	30	30	30	30	60	60
HPMC K4M	60	80	80	80	80	80	80	80	80	80	80
Guar gum	50	-	-	-	-	-	-	-	-	-	-
PVP K30	-	5%	5%	-	5%	-		-	-	5%	7%

Ethyl cellulose	-	-	-	2%	-	10%	4%	6%	-	-	-
Crospovidone	-	-	-	-	-	-	-	-	-	-	5%
MCC	25	25	-	-	-	-	-	-	-	25	-
Lactose	-	-	25	25	25	25	25	25	25	-	25
Magnesium stearate	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Talc	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%

PRE COMPRESSION STUDIES[5]

Bulk Density

Weighed quantity of granules was transferred into a 50ml measuring cylinder without tapping and the volume occupied by granules was measured. Bulk density was measured using the following formula.

Pb = M/Vo

Where, Pb = Bulk density

M = Mass of blend

Vo = Untapped volume (n=3)

Tapped Density

Weighed quantity of granules was taken into graduated measuring cylinder volume occupied by granules was noted down. The measuring cylinder was subjected to 500 taps in tapped density tester (Electro Lab USP II), the change in volume is noted down. Tapped density was measured using the following formula.

Pt = M/Vt

Where, Pt = Tapped density

M = Mass of blend

Vt = Tapped volume (n=3)

Compressibility Index

Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density. Table 8 shows the percentage compressibility index and its flow characteristics. The percentage compressibility of granules were determined using the following formula.

CI = Pt – Pb / Pt × 100.

Where, CI = Compressibility Index.

Pb = Bulk density, Pt = Tapped density, Pt = Tapped density (n=3).

Hausner's ratio

It is measurement of frictional resistance of the drug. Table 8 shows the Hausner's ratio and its flow characteristics. It was determined by ratio of tapped density and bulk density.

H = Pt / Pb

Where, Pb = Bulk density (n=3).

Angle of Repose

Weighed quantity of granules was passed through a funnel kept at a height of 2cm from the base. The powder is passed till it forms heap and touches the tip of funnel. Table 8 shows the Angle of repose and its flow characteristics. The radius was measured and angle of repose was calculated using the following formula. (n=3).

tanθ =h/r

Where, h and r the height and radius of the powder cone respectively.

POST COMPRESSION STUDIES

Hardness of tablets[6]

Hardness of tablets was tested using Monsanto hardness tester. Scale was adjusted to zero and the tablet held between the moving jaw and pressure was applied by these jaws until the tablet braked. Hardness of tablets is measured in terms of Kg/cm^2. Study was performed in triplicate.

Thickness and diameter

By using dial meter (Mitutoyo, Japan) thickness and diameter of all prepared formulations was measured by taking the average of three readings in mm. It was reported as mean ± SD (n=3).

Weight variation test

Weight variation test was carried out by using an electronic weighing balance. 20 tablets were weighed individually and the average weight was noted and % deviation of each tablet weight was determined by the following equation.

$$Percent\ deviation\ (PD) = \frac{W_{avg} - W_{initial}}{W_{initial}} x\ 100$$

Where,

W_{avg} = Average weight of tablet, $W_{initial}$ = individual weight of tablet.

Friability of tablets[7]

10 pre-weighed tablets were allowed to fall down for 100 revolutions by using Roche friabilator. The weight loss was calculated and % friability was then calculated by.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

Where, W = weight of tablet.

Drug content

The drug content was determined by crushing (10) tablets in glass mortar and pestle and shaking the powder equivalent to weight of one tablet with 100ml of phosphate buffer pH 6.8 for 48 hours and this was filtered using Whatman filter paper and suitably diluted and finally analysed using UV spectrophotometer (1601, Shimadzu, Kyoto, Japan) using suitable blank at 222nm.

In-vitro release study

The drug release study was performed using dissolution test apparatus (Electro lab, Mumbai, India) with a paddle speed of 50 rpm. Dissolution medium consisted of 900ml 0.1N HCL maintained at 37±0.5^{0}c. Then the tablet was dropped into the dissolution medium. After this the samples were withdrawn at 0.15, 0.30, 1,1.30, 2, hours and after 2hours 0.1N HCL medium was replaced by phosphate buffer pH 6.8.The samples were withdrawn at 3,4,5,6,7,8,24hrs and each time it was replaced with fresh dissolution media. Amount of drug in each aliquot was assayed on a UV-spectrophotometer (Shimadzu 1601, Japan) at 222nm using a suitable blank.

Swelling index[8]

The matrix tablets were weighed (W_1) and kept separately in petridish with 5ml of phosphate buffer with pH 6.8. The tablets were removed at the time intervals of 1,2,3,4,5,6,7 and 20 hours from the petridish and excess water was removed carefully using the filter paper. The swollen tablets were then weighed again (W_2) and the percentage of hydration was calculated using the formula.

$$\text{Swelling Index} = \frac{W2 - W1}{W1} \times 100$$

Drug Release kinetics and mechanism[9]

Zero order kinetics: Zero order was calculated by the following equation.

$$Q_t = Q_0 - K_0 t$$

Where,

Q_t = Drug release at time't', Q_0 = Initial drug concentration, K_0 = Zero – order rate constant (hr^{-1}).

First Order Kinetics: First–order was calculated by the following equation.

$$\log C = \log C_0 - K_t / 2.303$$

Where,

C = Amount of drug remained at time't', C_0 = Initial amount of drug, K_t = First order rate constant (hr^{-1}).

Higuchi's model: Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = Kt^{1/2}$$

The graph was plotted between SQRT and cumulative % drug release.

Korsmeyer-Peppa's model: Korsmeyer Peppa's Model indicates the study mechanism of drug release from the matrix tablets which also describes the drug behavior from polymeric systems.

$$M_t / M_\infty = Kt^n$$

Where, K = constant incorporating structural and geometric characteristics of the drug dosage form.

n = Release exponent

Model independent kinetics[10]

A. Dissolution efficiency

Dissolution efficiency is used to translate the profile difference into a single value. Dissolution efficiency was calculated by using following equation.

$$DE\ \% = \frac{\int_0^t y\ dt}{y_{100}} t \times 100$$

Where, y is the drug percent dissolved at time t.

B. Mean dissolution time

Mean dissolution time represents the mean time for drug molecules to completely dissolve. It is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of the polymer. MDT was calculated by using the following equation.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Where *'i'* is the dissolution sample number, *'n'* is the number of dissolution sample time, *'tmid'* is the time at the midpoint between *'i'* and *'i-1'*, and *'ΔM'* is the amount of drug dissolved between *'i'* and *'i-1'*.

Stability studies: The selected formulations were stored at room temperature in desiccators and at 40 ± 2°C / 75 ± 5 % RH for 2 months to analyze the stability of the formulations

RESULT AND DISCUSSION

Excipient compatibility studies

Fourier Transform Infrared spectroscopy studies

FTIR analysis of pure Metoprolol succinate showed characteristics peaks O-H stretching (hydrogen bonding) at 3122.01 $cm^{-}1$, C-H stretching (aromatic) at 2994.02 $cm^{-}1$, C-H stretching of CH_2 at 2929.24 $cm^{-}1$, C-H stretching – 2823.71 cm^{-1}. The same peaks were also reported in drug loaded matrix tablet. There were no change (or) shifting of the characteristic peaks in matrix tablets suggested that there were no significant drug polymer interaction. This indicated the that drug was stable in the formulation.

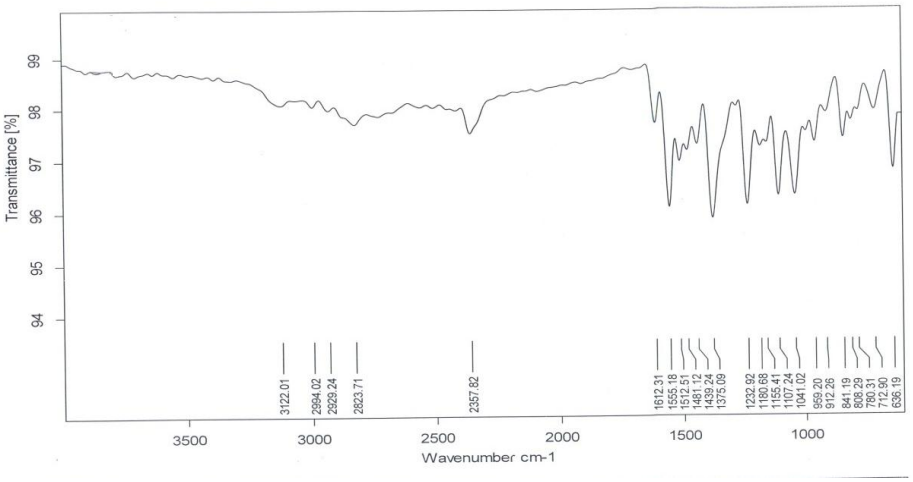

Figure 1: FTIR spectra of Metaprolol succinate.

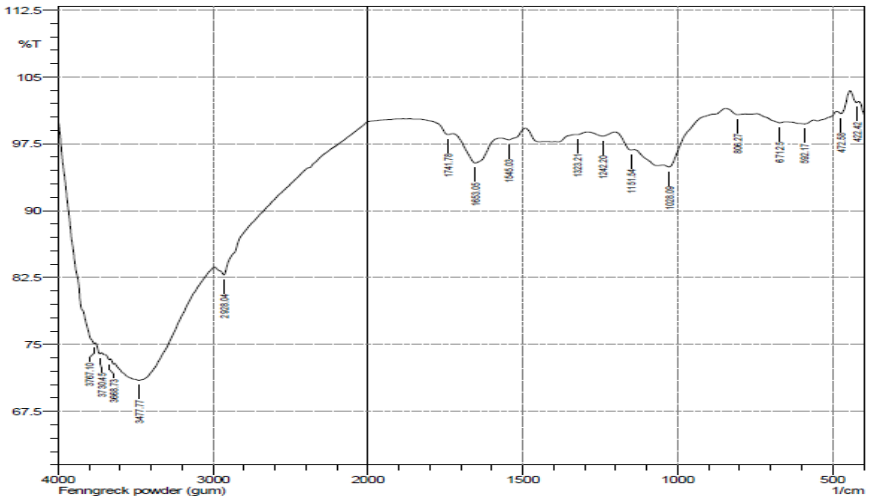

Figure 2: FTIR spectra of Fenugreek gum.

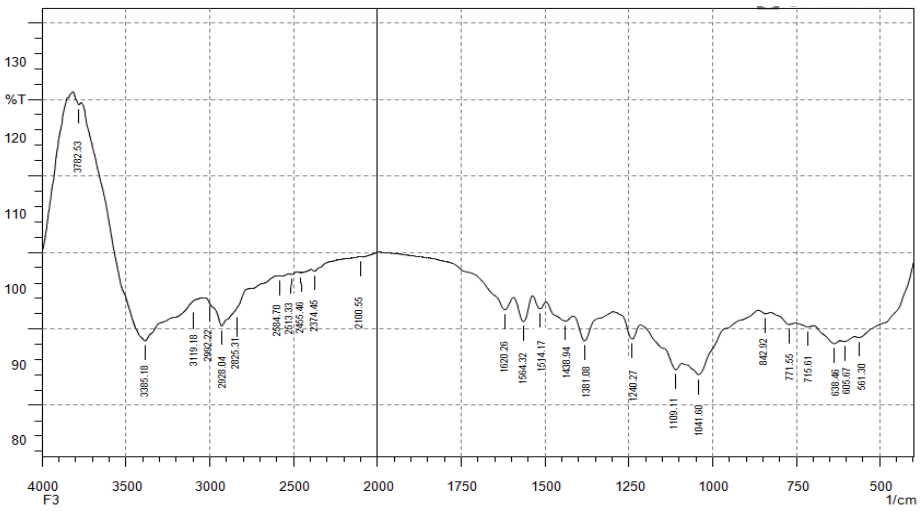

Figure 3: FTIR spectra of formulation F3.

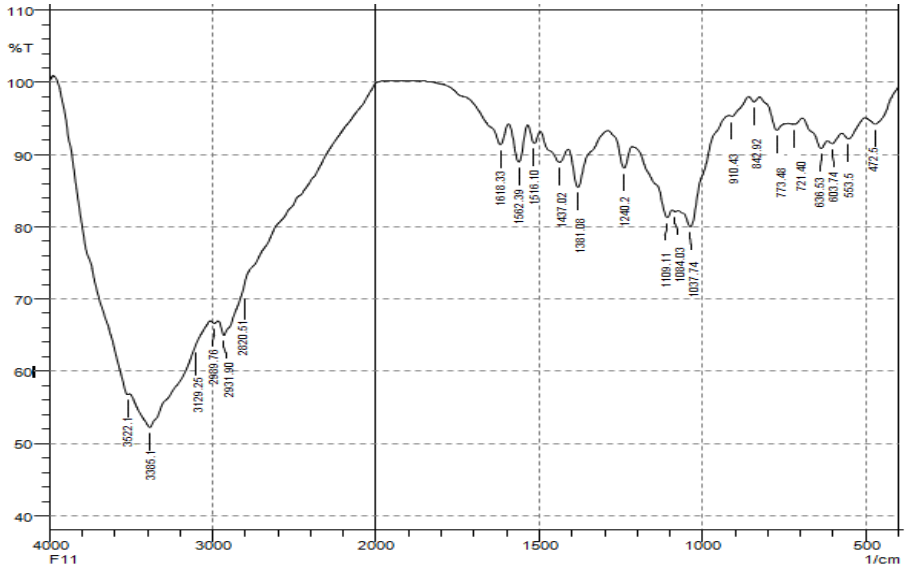

Figure 4: FTIR spectra of formulation F11

The Precompression parameters of all the formulation were found to be satisfactory.

The physical property of tablet like hardness, friability, thickness, diameter, drug content and weight variation were found to be within limits (table 2).

Table 2: Pre compression parameter

Formulation	Bulk Density gm/cc	Tapped Density gm/cc	Hausner's Ratio	Carr's Index%	Angle Of Repose
F1	0.541±0.33	0.612±0.22	1.13±0.21	11.45±0.15	23.65˚±0.85
F2	0.491±0.47	0.567±0.63	1.14±0.63	12.55±0.21	20.85˚±0.95
F3	0.502±0.32	0.582±0.23	1.15±0.41	13.81±0.65	22.38˚±0.21
F4	0.493±0.63	0.562±0.77	1.14±0.74	12.52±0.14	23.47˚±0.29
F5	0.523±0.36	0.601±0.85	1.14±0.69	13.34±0.64	24.68˚±0.34
F6	0.474±0.32	0.557±0.46	1.16±0.85	14.69±0.74	21.74˚±0.68
F7	0.411±0.22	0.467±0.57	1.13±0.56	14.87±0.41	25.89˚±0.41
F8	0.494±0.54	0.464±0.41	1.14±0.47	12.41±0.14	22.11˚±0.77
F9	0.554±0.68	0.645±0.86	1.15±0.33	14.00±0.33	25.35˚±0.94
F10	0.521±0.21	0.541±0.56	1.13±0.23	11.89±0.28	23.69˚±0.47
F11	0.503±0.89	0.569±0.41	1.14±0.89	12.47±0.66	24.78˚±0.98

Table 3: Post compression parameters.

Formulation	Hardness (Kg/cm^2)	Thickness (mm)	Weight Variation (mg)	Friability (%)	Drug Content (%)
F1	6.8±0.35	3.145±0.001	213±0.95	0.365±0.32	95.65±0.32
F2	6.7±0.45	3.224±0.002	206±0.98	0.256±0.47	96.42±0.75
F3	6.9±0.21	3.176±0.003	205±0.93	0.195±0.26	99.21±0.63
F4	5.1±0.35	2.535±0.001	176±0.88	0.205±0.74	97.36±0.85
F5	5.5±0.33	2.565±0.000	175±1.07	0.267±0.69	98.67±0.33

F6	5.4±0.65	2.595±0.005	174±0.12	0.321±0.85	95.82±0.14
F7	5.0±0.11	2.540±0.002	178±0.89	0.395±0.69	96.12±0.32
F8	5.8±0.65	2.521±0.004	175±0.65	0.275±0.68	97.32±0.45
F9	5.6±0.85	2.511±0.002	174±0.47	0.185±0.63	95.47±0.19
F10	6.4±0.45	3.197±0.001	206±0.86	0.245±0.23	99.12±0.65
F11	6.7±0.69	3.195±0.002	207±0.95	0.278±0.11	99.47±0.45

Swelling study

The swelling studies were conducted for all formulations i.e. F1 to F11. All the formulations were hydrated generally by keeping the tablets in contact with phosphate buffer pH 6.8 for 20h. The highest swelling i.e. 398.41% was observed with the formulation F11 (fig 5, 6).

Swelling study

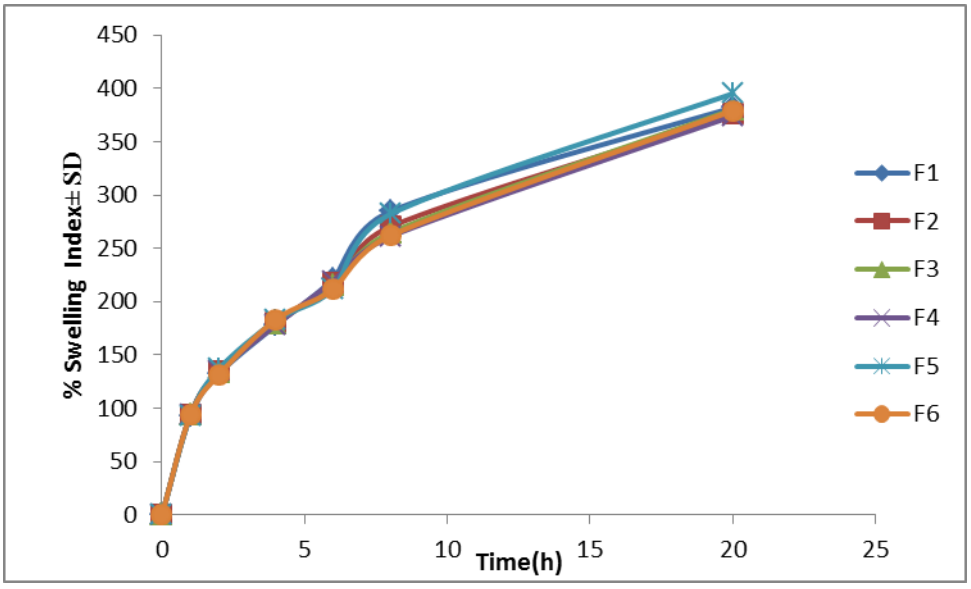

Figure 5: Swelling index of F1 to F6

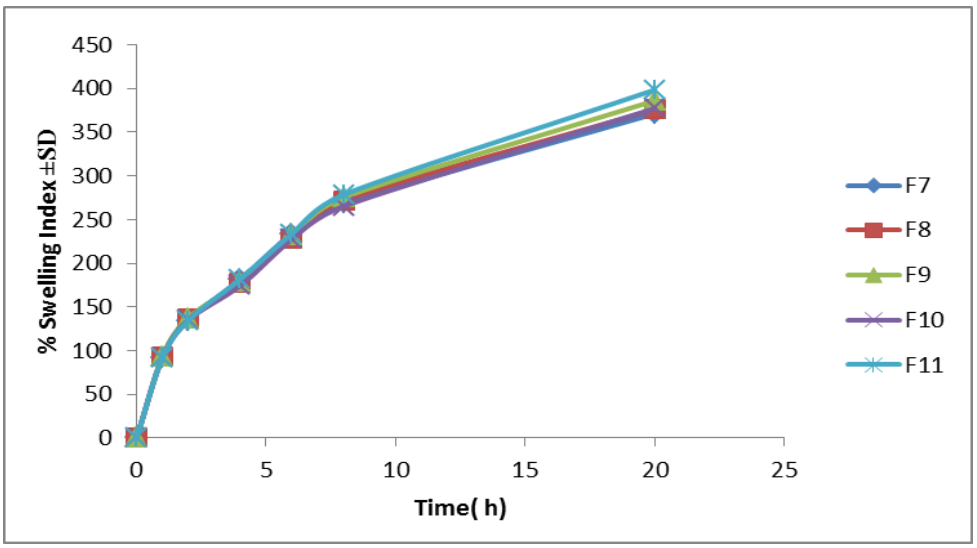

Figure 6: Swelling Index F7 to F11

In-vitro release studies

The in-vitro cumulative drug release profile of formulation F1 (containing fenugreek gum, Guar and HPMC K4M by direct compression) showed 108.41%, in 9 hrs. Similarly in-vitro drug release profile of formulation F2, F3, F4 and F5 (contains fenugreek gum, EC and HPM C K4M by wet granulation) was 107.63%, 95.64%, 94.86%, 96.6%, respectively in 9 hrs (fig 7). Similarly in-vitro drug release profile of formulations F6, F7, F8 and F9 (containing Fenu greek gum, EC and HPMC K4M & prepared by wet granulation) was 92.41%, 93.62%, 94.31%, 95.10% respectively in 9 hrs. The in-vitro drug release profile of formulation F10 & F11 (containing Fenugreek gum, PVP K30 and HPMC K4M prepared by compression coating) was 92.31 & 95.02 respectively in 9 hrs (fig 8). However, formulation F3 & F11 showed highest drug release among the prepared formulations. Hence formulation F3 & F11 were selected formulations.

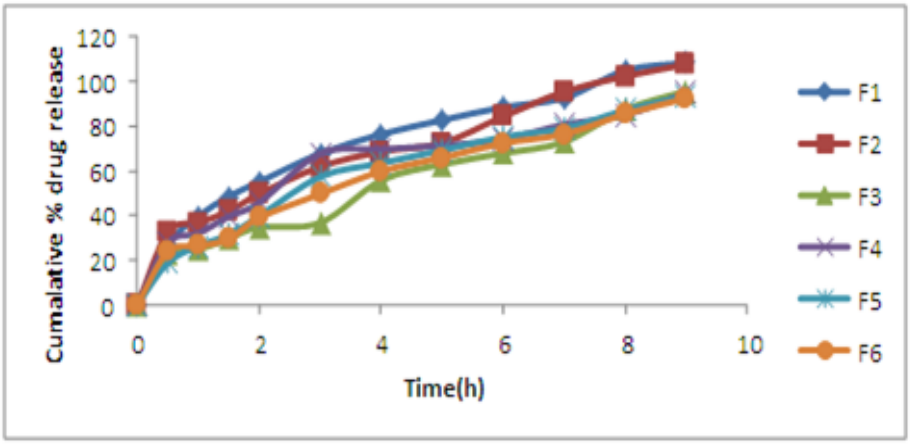

Figure 7: Cumulative drug release F1, F2, F3, F4, F5 and F6

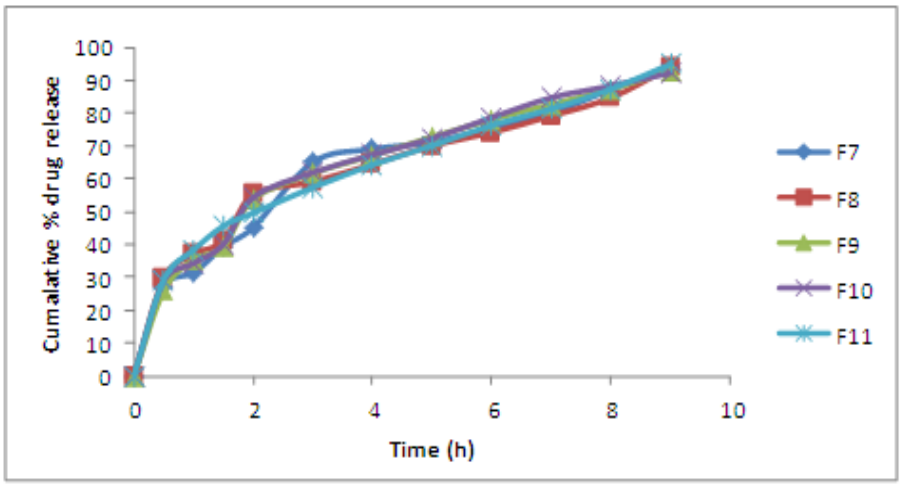

Figure 8: Cumulative drug release F7, F8, F9, F10, and F11

Release Kinetics

All prepared formulation of F1 to F11 was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas equations to ascertain the pattern of drug release. It was found that formulation F1, F3, F4, F5, F7, F8 and F9 followed first order kinetics and formulation F2, F6, F10, F11 followed zero order kinetics. The formulations followed a diffusion type of drug release since the regression co-efficient values were near to linearity for Higuchi's model. The release exponent value for the formulation F3 and F11 is $0.45 < n < 0.89$, which indicated the mechanism of drug release was non-Fickian anomalous diffusion (table 4).

Table 4: Drug release kinetics from F1 to F11 formulations.

Formulation	Correlation coefficient(r^2)			Korsmeyer-peppa's Model(n)
	Zero order	First order	Higuchi	
F1	0.871	0.967	0.946	0.484
F2	0.970	0.873	0.923	0.460
F3	0.904	0.926	0.942	0.488
F4	0.895	0.969	0.956	0.439
F5	0.940	0.982	0.986	0.569
F6	0.913	0.868	0.958	0.670
F7	0.902	0.986	0.968	0.478
F8	0.899	0.986	0.964	0.492
F9	0.942	0.992	0.984	0.480
F10	0.977	0.930	0.935	0.757
F11	0.983	0.885	0.938	0.692

Model independent parameters like MDT and % DE were evaluated for the all the formulations. The MDT values of metoprolol succinate in 9 hrs varied between 2.386 to 4.048hrs and the % DE values of varied between 55.02 to 73.48%. Formulation F3 and F11 which were prepared by wet granulation and showed higher % CDR, MDT and % DE values. The formulations F3 and F11 were selected as best formulations (Table 5).

Table 5: Model Independent Kinetics of metoprolol succinate.

Formulation	MDT(hrs)	$\%DE_{9hr}$
F1	2.500	72.21
F2	3.273	59.07
F3	2.959	67.11
F4	2.503	72.77
F5	2.902	67.74
F6	2.475	72.49
F7	2.386	73.48
F8	2.509	72.11
F9	2.665	70.38
F10	2.471	58.81
F11	4.048	55.02

Stability study

Stability study of selected formulations was carried out at room temperature and at 40 ± 2°C / 75 ± 5% RH for 2 months. There was no variation in physical appearance, drug content & in-vitro dissolution profile of the formulation at different storage conditions.

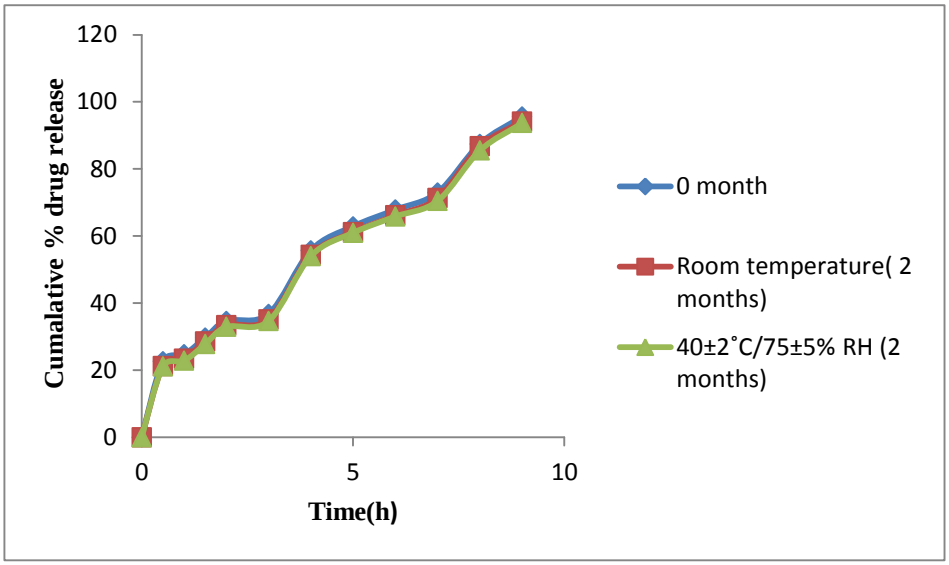

Figure 9: Comparison of in-vitro drug release profile of F3 at 0 months, room temperature (2 months), and 40±2˚C/75±5% RH (2 months).

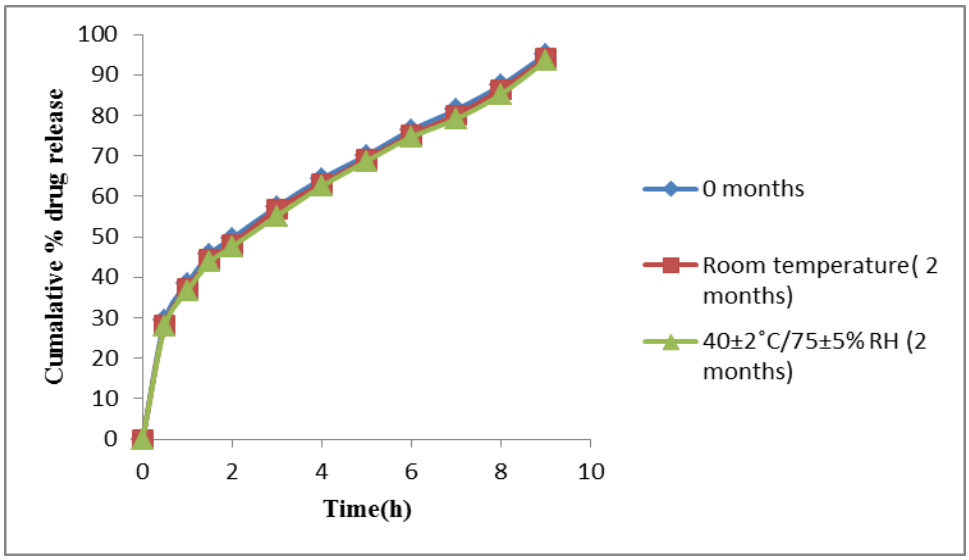

Figure 10: Comparison of in-vitro drug release profile of F11 at 0 months, room temperature (2 months) and 40±2˚C/75±5% RH (2 months).

CONCLUSION

During this study, it was found that drug and polymer ratio influences the drug release behaviour. The formulation prepared by combination of Fenugreek gum with HPMC K4M retarded the drug release effectively for 12 hrs. Formulation F3 and F11 were found to be suitable for Extended release drug delivery system.

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