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Original Research Article

FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLETS OF DARIFENACIN HYDROBROMIDE

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ABSTRACT

The objective of this research work was to develop extended release tablets of Darifenacin Hydrobromide using different hydrophilic polymers like HPMC K15M, HPMC K100M, Metalose60SH 50, Xanthan gum by direct compression method. Various amounts of polymers was used in the twenty one proposed formulations (F1to F21) for the study of release rate retardant effect at 15%, 20%, and 30% of total weight of tablet matrix respectively. Then the tablets were evaluated in terms of their physical parameters (weight variation, hardness, friability and thickness), drug content and in-vitro release studies. All the formulations showed compliance with pharmacopoeial standards, their in-vitro dissolution study were conducted using USP dissolution apparatus type-II (paddle method) in 900 ml 0.1 N HCl for first 2 hrs and remaining period performed in 7.4 pH phosphate buffer at 100rpm for a total period of 24hrs. The release mechanisms were explored and explained by Zero order, Higuchi, First order and Krosmeyer-Peppas equations. Based on the dissolution data comparison with innovator product, formulation F17 was found as the best formulation. The drug release profile of this formulation was well controlled and uniform throughout the dissolution studies. The drug release of formulation F17 followed First Order kinetic model and the mechanism was found to be non-Fickian/anomalous according to Korsmeyer-Peppas equation.

Key words: Darifenacin Hydrobromide, Direct Compression, Hydroxy propyl methyl cellulose, Metalose 60SH 50, Extended Release.

INTRODUCTION

Extended release drug delivery system achieves a slow release of the drug over an extended period of time or the drug is absorbed over a longer period of time. Extended release dosage form initially releases an adequate amount of drug to bring about the necessary blood concentration (loading dose, D_L) for the desired therapeutic response and therefore, further amount of drug is released at a controlled rate (maintenance dose, D_M) to maintain the said blood levels for some desirable period of time. The sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and respiratory dosage forms are terms used to identify drug delivery system that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose[1,2]. Extended release formulation is an important program for new drug research and development to meet several unmet clinical needs. There are several reasons for attractiveness of these dosage forms viz. provides increase bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, Reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug[3,4].

MATERIALS AND METHODS

Materials[5]

Darifenacin Hydrobromide, HPMC K15M, HPMC K100M, Metalose 60SH 50, Xanthan gum and Magnesium stearate, Di calcium Phosphate obtained from Active Pharma Labs.

Methods

Drug Excipient Compatibility Studies

Compatibility study was carried for pure Darifenacin Hydrobromide and combination of Darifenacin Hydrobromide with excipients. Fourier transfer infra red (FTIR) spectroscopic (shimadzu, Japan) studies were carried out by approximately diluting the sample with dried potassium bromide and acquiring infrared (IR) spectrum in the range of 400 to 4000cm^{-1} .

Formulation of Extended release matrix tablets of Darifenacin Hydrobromide by direct compression method

Various formulations of Darifenacin Hydrobromide Extended release tablets were prepared using different polymers at 15%, 20%, 30% Concentration of total weight of tablet matrix respectively. Sifted the drug, Dibasic Calcium Phosphate (A-Tab), Hypromellose through #30 mesh and mixed the blend in a polybag for uniform distribution of API. Required amount of Magnesium stearate was weighed, passed

through #80 mesh and blended with above blend. The Blend was compressed using 8.0mm Round shaped standard concave punches.

EVALUATION OF PARAMETERS[6, 7, 8]

1. Angle of repose

It was measured by fixed funnel method. The fixed funnel method employ a funnel that was secured with its tip at a given height 'h', above graph paper that was placed on a flat horizontal surface. Granules were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel, 'r' being the radius of base of the conical pile. The angle of repose is then calculated as

$$\tan \theta = h / r \quad (or) \quad \theta = \tan^{-1} h / r$$

Where θ = angle of repose

2. Determination of bulk density and tapped density

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus .The density apparatus was set for 100 taps and after that, the \volume (V_f) was measured and continued operation till the difference between two consecutive readings was found to be less than 2.0 %. The bulk density, and tapped density were calculated using the following formulas.

$$\text{Bulk density} = W / V_o$$

$$\text{Tapped Density} = W / V_f$$

W = weight of the powder, V_o = initial volume V_f = final volume.

3. Compressibility index or Carr's index

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. It can be calculated as

$$\text{Carr's Index} = \text{Tapped Density} - \text{Bulk Density} / \text{Tapped Density} \times 100$$

4. Hausner's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

EVALUATION OF TABLETS[9]

The Prepared extended release tablets were evaluated for the following parameters

Hardness: Monsanto hardness tester was used to evaluate the hardness of tablet. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero reading was taken. The upper plunger was then forced against a spring by turning a threaded bold until the tablet fractures. As the spring is compressed, a pointer rises along a gauge in the barrel to indicate the force. The force of fracture was recorded, and the zero force

reading was deducted from it. Ten tablets of each formulation were evaluated.

Thickness and diameter: Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier calipers. It was determined by checking ten tablets from each formulation.

Friability: Weigh accurately 20 tablets and place them in the friability test apparatus. Adjust the timer to 4 minutes. Operate the apparatus at 25 ±1 RPM and observe the tablets while rotating, such that no tablet sticks to the walls of the apparatus. Take the tablets out and observe for possible capping / breaking as none of these should be observed for the test to be valid.

Weigh the tablets, after dusting excess powder from their surface.

Friability in %, is calculated using the formula: -

Friability = (W1-W2)×100/W1

Where **W1** = Initial weight of the tablets taken,

W2 = Final weight of the tablets after testing.

Weight Variation: Twenty tablets were sampled randomly. Tablets were weighed individually and average weight was calculated. Deviation of each tablet from average weight was calculated and percent deviation was computed. The deviation is compared with the Pharmacopoeial limits.

INVITRO DISSOLUTION STUDIES

The release of Darifenacin Hydrobromide from the ER tablet was studied for period of 24 hours i.e, 2hours in 900ml of 0.1N HCL and remaining period in 900ml of hoshate buffer as dissolution medium using USP dissolution apparatus paddle type at 100 rpm and 37±0.5°C. An aliquot (5ml) was withdrawn at 1,4,8,12,16,20,24hr time intervals and were placed with same volume of fresh dissolution media after each withdrawal. The samples were analyzed spectro-photometrically for drug content at 215nm wavelength.

Comparison of dissolution profiles : The similarity factor (f_2) was employed to evaluate the release profiles of various formulations compared with the ideal release profile.

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} X\, 100 \right\}$$

Where 'n' is the number of dissolution time points, and R and T are the references and test dissolution values at time t. The similarity factor (f_2) is a logarithmic transformation of the sum-squared error of differences between the experimental drug release T_t and the ideal drug release R_t for over all time points 'n'. The similarity factor fit the result between 0 and 100. It is approached 0 as the dissimilarity of the test and the reference profile increased, whereas, it attained 100 when the test and the reference profile were identical.

Table.1.Similarity Factor Range

S.No	Similarity factor	Significance
1	<50	Test and reference profiles are dissimilar
2	50-100	Test and reference profiles are similar
3	100	Test and reference profiles are identical
4	>100	The equation yields a negative values

DRUG RELEASE KINETICS[10, 11]:

Zero order release rate kinetics:

To study the zero order release kinetics the release rate data are fitted to the following equation

$F=K_0t$ Here, F is the fraction of drug release

K_0 is the rate constant

T is the release time

First order model:

This model has also been used to describe absorption and/elimination of drug, the release of the drug which followed first order kinetic can be expressed by the equation

$$\text{Log } C=\log c_0-kt/2.303$$

Where, C_o is the initial concentration of drug

K is the first order rate constant

t = is the time

Higuchi release model:

To study the higuchi release kinetics, the release rate data was fitted to the following eqution

$$F=K_H.t^{1/2}$$

Where, F is the amount of the drug release

K_H is the release time, t is the release time.

Korsmeyer and peppas model:

The release rate data were fitted to the following eqution,

$$Mt / M\infty = Kt^n$$

Where, Mt / M∞ is the fraction of drug release

K_M is the release constant, t is the release time

RESULTS

Table.2.Batch Composition for Formulations F1- F21

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Darifenacin hydrobromide	15	15	15	15	15	15	15	15	15	15	15	15
Dibasic calcium phosphate	152	142	122	152	142	122	152	142	122	152	142	122
Methocel K15M	30	40	60	0	0	0	0	0	0	0	0	0
Methocel K100M	0	0	0	30	40	60	0	0	0	0	0	0
Metalose 60SH 50	0	0	0	0	0	0	30	40	60	0	0	0
Xanthan gum	0	0	0	0	0	0	0	0	0	30	40	60
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
TOTAL WEIGHT(mg)	200	200	200	200	200	200	200	200	200	200	200	200

Ingredients(mg)	F13	F14	F15	F16	F17	F18	F19	F20	F21
Darifenacin hydrobromide	15	15	15	15	15	15	15	15	15
Dibasic calcium phosphate	152	152	142	142	122	122	152	142	122
Methocel K15M	15	0	20	0	30	0	0	0	0
Methocel K100M	15	0	20	0	30	0	15	20	30
Metalose 60SH 50	0	15	0	20	0	30	15	20	30
Xanthan gum	0	15	0	20	0	30	0	0	0
Magnesium stearate	3	3	3	3	3	3	3	3	3
TOTAL WEIGHT(mg)	200	200	200	200	200	200	200	200	200

Table.3.Pre compression parameters

Formulation	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.416±0.57	0.480±0.18	27.25±0.93	11.2±0.51	1.12±0.39
F2	0.414±0.41	0.475±0.24	26.25±0.22	11.5±0.91	1.14±0.26
F3	0.412±0.25	0.467±0.22	26.45±1.22	11.7±0.83	1.13±0.41
F4	0.436±0.34	0.502±0.46	23.56±1.24	13.1±0.46	1.15±0.28
F5	0.476± 0.28	0.472±0.82	27.54±0.38	12.7±0.43	1.14±0.62
F6	0.443±0.48	0.509±0.56	28.97±0.52	12.9±0.2	1.15±0.13
F7	0.452 ± 0.38	0.518±0.27	25.56±0.28	11.2±0.34	1.13±0.25
F8	0.426 ± 0.21	0.485±0.38	27.23±0.98	12.1±0.54	1.14±0.19
F9	0.472±0.26	0.539±0.63	26.74±0.9	12.4±0.35	1.14±0.24
F10	0.423±0.57	0.478±0.18	25.43±0.69	11.5±0.59	1.13±0.36
F11	0.423±0.21	0.478±0.21	23.26±0.60	11.5±0.63	1.12±019
F12	0.418±0.52	0.473±0.76	24.12±0.54	12.0±0.22	1.13±0.41
F13	0.420 ±0.33	0.490±0.22	22.52±1.12	12.5±0.46	1.15±0.62
F14	0.414 ±0.18	0.485±0.63	28.54±0.75	12.8±0.32	1.12±0.42
F15	0.455± 0.20	0.462±0..31	27.59±0.63	13.0±0.18	1.12±0.17
F16	0.462± 0.24	0.484±0.34	28.20±0.29	11.8±0.42	1.14±0.22
F17	0.424±0.38	0.475±0.42	27.61±0.98	10.9±0.29	1.12±0.21
F18	0.482±0.46	0.553±0.18	26.86±0.52	12.8±0.39	1.14±0.29
F19	0.452±0.20	0.520±0.15	25.52±0.52	11.2±0.25	1.10±0.25
F20	0.425±0.38	0.492±0.25	27.23±0.69	12.5±0.40	1.14±0.17
F21	0.422±0.46	0.525±0.32	24.15±0.70	12.9±0.2	1.15±0.62

All values are expressed as mean ± SD, n=3

Table.4.Post compression parameters

Formulation	Hardness (kg/cm²)	Thickness (mm)	Weight variation(mg)	Friability	Drug Content %
F1	8.1	3.45±0.2	200±0.24	0.20±0.02	99.25±0.49
F2	9.1	3.56±0.8	201±0.20	0.18±0.02	99.17±0.62
F3	8.2	3.49±0.6	200±0.42	0.22±0.03	100.4±0.58
F4	8.5	3.53±0.4	198±1.24	0.43±0.05	98.64±1.24
F5	9.2	3.42±0.4	200±0.26	0.18±0.03	99.52±0.72
F6	9.1	3.61±0.2	200±0.21	0.20±0.03	100.2±0.78
F7	8.3	3.67±0.8	200±0.26	0.40±0.08	99.75±1.22
F8	9.4	3.60±0.5	200±0.28	0.32±0.04	99.52±1.07
F9	9.2	3.57±0.2	199±0.40	0.38±0.01	99.89±1.22
F10	9.5	3.63±0.4	200±0.25	0.12±0.015	99.97±0.46
F11	9.6	3.62±0.3	201±0.18	0.24±0.02	99.24±0.54
F12	8.3	3.57±0.7	200±0.22	0.16±0.04	99.62±0.56
F13	8.5	3.63±0.7	200±0.21	0.53±0.06	99.19±1.23
F14	9.5	3.55±0.3	198±1.43	0.29±0.06	99.73±0.76
F15	8.7	3.65±0.6	200±0.42	0.35±0.08	99.25±0.48
F16	9.7	3.52±0.7	200±0.26	0.24±0.03	99.75±0.98
F17	9.8	3.59±0.4	200±0.20	0.19±0.01	98.82±1.25
F18	9.4	3.71±0.3	200±0.29	0.17±0.005	99.59±0.26
F19	8.7	3.52±0.5	198±0.25	0.22±0.02	97.59±0.52
F20	9.5	3.55±0.7	201±0.12	0.20±0.05	99.52±0.42
F21	9.7	3.65±0.4	200±0.25	0.50±0.04	99.70±0.35

All values are expressed as mean ± SD, n=3

Table.5. % Cumulative drug release of formulations F1-F21

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	18.5	15.3	14.2	12.0	14.8	13.3	35.6	33.4	29.1	27.2	22.5	21.3	19.2
4	30.2	26.5	22.4	33.7	29.2	31.5	57.2	55.3	50.7	43.3	39.5	33.5	32.3
8	55.4	51.3	48.4	57.6	52.5	40.2	84.8	73.5	67.2	52.9	53.5	47.5	56.8
12	81.3	76.8	70.2	67.8	62.3	52.4	99.3	85.6	75.4	67.8	61.7	65.6	79.2
16	99.5	88.2	86.6	74.0	72.5	59.8	-	98.4	89.5	84.4	71.2	69.5	97.7
20	-	98.3	93.5	78.9	76.4	64.2	-	-	101.5	98.2	77.5	72.5	-
24	-	101.7	100.4	87.5	80.5	72.3	-	-	-	102	79.7	74.1	-

Time(hrs)	F14	F15	F16	F17	F18	F19	F20	F21
0	0	0	0	0	0	0	0	0
1	30.3	16.7	28.3	13.8	9.8	22.5	18.5	11.6
4	46.8	27.3	39.2	36.2	35.3	35.6	25.3	34.6
8	60.3	43.4	52.4	58.6	61.7	60.8	44.6	56.2
12	85.2	69.7	76.7	76.3	78.9	81.5	74.2	65.3
16	99.3	82.9	88.5	86.7	89.7	102.5	85.7	71.2
20	-	98.2	99.8	91.5	97.5	-	101.5	77.5
24	-	-	-	97.8	101.2	-		85.2

Table.6.Similarity factor analysis of *In vitro* drug release of F3, F5, F6, F16, F17, F18

Formulation	Similarity factor (F_2)
F3	56.46
F5	59.11
F6	51.26
F16	41.10
F17	79.11
F18	48.90

Table.7.Release Kinetics Comparision

Release Kinetics	Correlation coefficient(R^2) (Reference)	Correlation coefficient(R^2) (F17)
Zero order	0.953	0.933
First order	0.981	0.997
Higuchi	0.990	0.989
Korsmeyer-Peppas	0.9986	0.9983

The 'n' value is 0.69 for the optimised formulation (F17) i.e., n value was between 0.45 and 0.89 this indicates anomalous transport (non fickian diffusion).

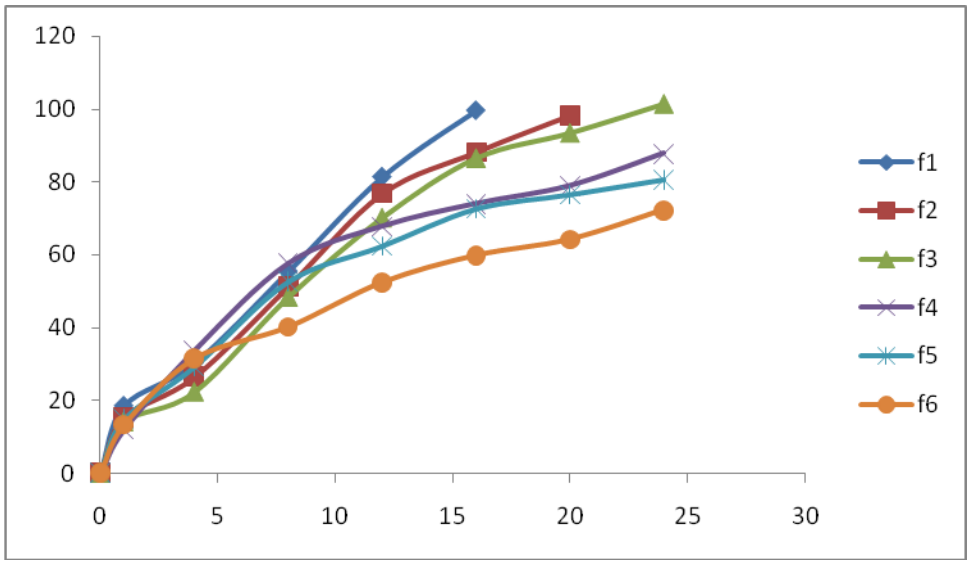
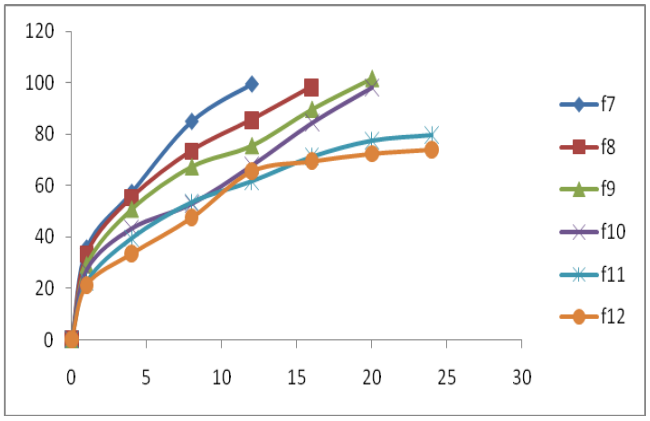
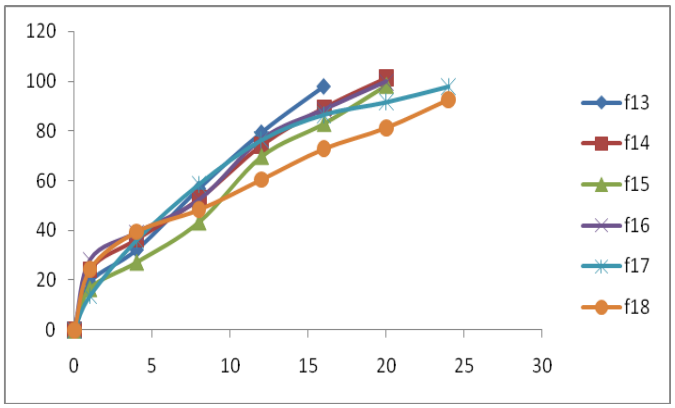


Fig.1. Invitro release profile of tablet formulationsF1-F6

X-axis: Time in hours, Y-axis: %drug release





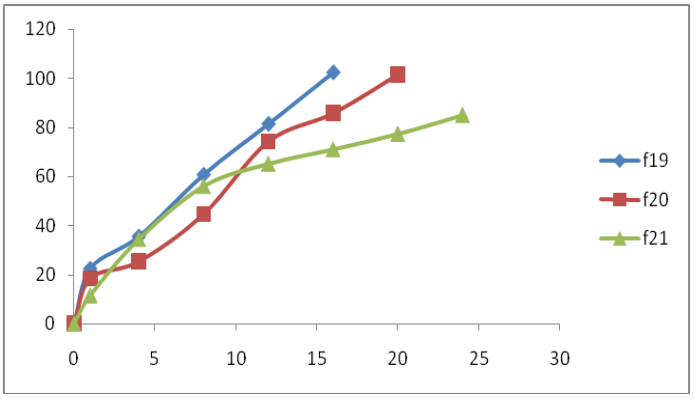


Fig.2.Invitro release profile of tablet formulations F7 – F21

X-axis Time in hours, Y-axis: % drug release

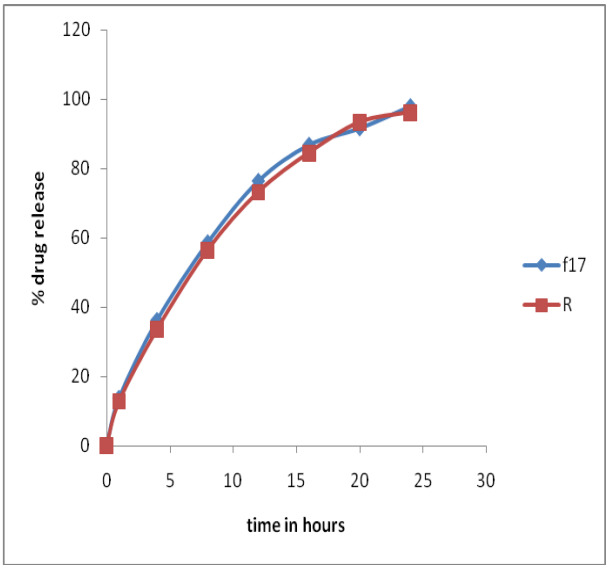


Fig.3.Comparison of Invitro drug release of Reference product and optimized formulation (F17)

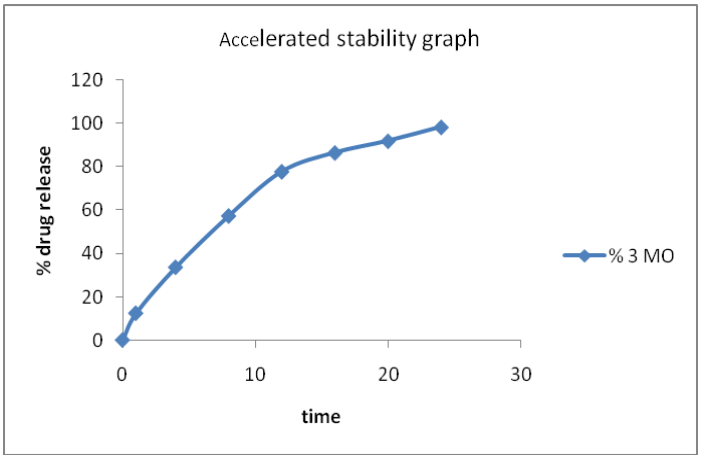


Fig.4. Accelerated stability graph of F17

Kinetic studies for F17 formulation:

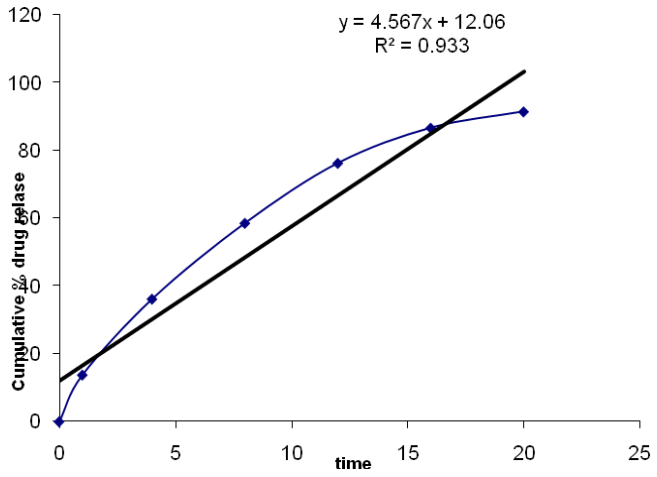


Fig.5. Zero order plot for optimized formulation (F17)

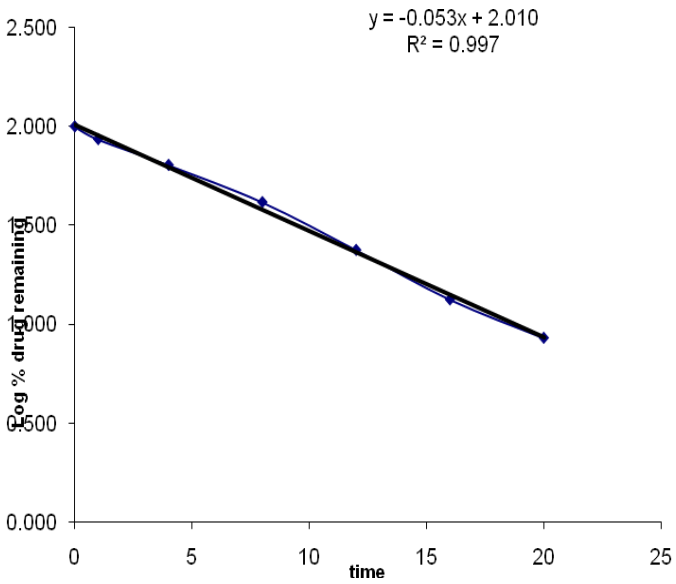


Fig.6. First order plot of F17

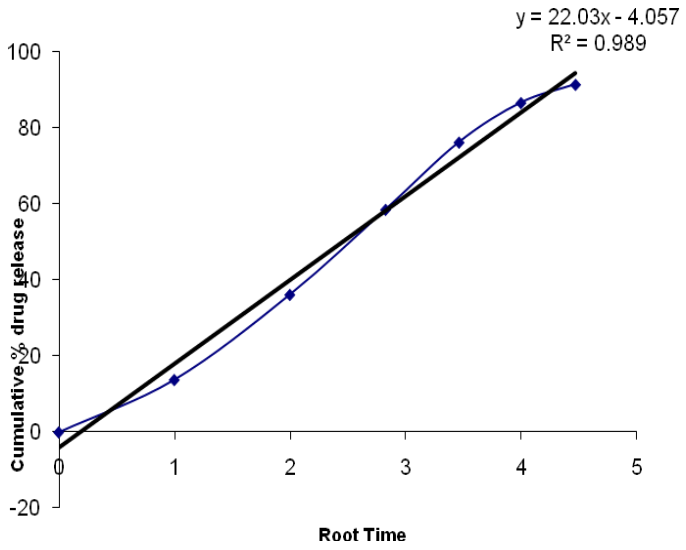


Fig.7.Higuchi plot of F17 formulation

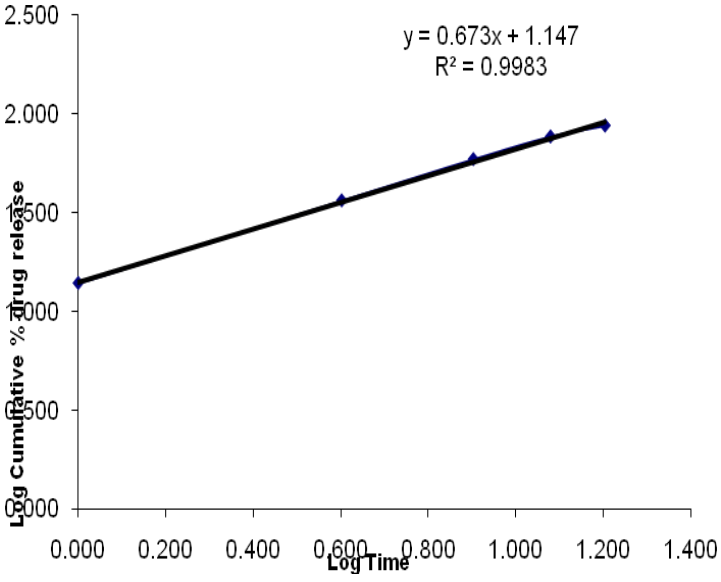


Fig.8. Korsmeyer-Peppas plot of F17 formulation

DISCUSSION

Drug Excipient Compatibility Studies

According to guidelines on impurity of drug product the drug product containing 15 mg dose /day acceptance criteria is 0.5%. Drug – excipient compatibility indicates that the all used excipients in the formulation are compatible with the drug by HPLC, impurities was less than 0.5%.

Pre compression parameters: Table No.3 shows that the angle of repose of different formulations was found between 22.5 to 28.9 which indicates that material had excellent flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.412g/cm^3 to 0.482 g/cm^3.Tapped density was found between 0.467g/cm^3 to 0.553 g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 10.9-13.1 and Hausner's ratio from 1.12-1.15 which reveals that the blends have fair flow character.

Post compression parameters: Table no.4 shows that the Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be in between 8 - 10 kg/cm^2.All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 – F21 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The % drug content for all the formulations were close to 100 and varied between 98.64 to 100.4%.

CONCLUSION

- An optimized formulation was obtained for F17. Formulations F1 to F16 and F18 to F21were failed due to less in vitro drug release compared to innovator. Even though all the formulations are releasing the drug but those are not comparable to innovator product.
- Among all formulations HPMC K15M and HPMC K100M 30% concentration (1:1 ratio) showed better release as a polymer to extend the drug release. The f17 formulation was compared with marketed product for drug release pattern and was matched using similarity factor (f2) which showed that formulation F17 performed similar to marketed product therapeutically.
- The stability data reveals that the F17 formulation showed a negligible change in drug content after storage in various conditions for three months according to ICH guidelines

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