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DESIGN AND CHARECTERIZATION OF QUETIAPINE FUMARATE CONTROLLED RELEASE TABLETS

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Abstract:
In the present work, an attempt has been made to develop controlled release tablets of Quetiapine fumarate by selecting different grades of HPMC and Ethyl cellulose as retarding polymers. All the formulations were prepared by direct compression method using 12mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F3 formulation showed maximum % drug release i.e., 97.3 % in 8 hours hence it is considered as optimized formulation. Whereas the formulations containing HPMCK100M showed more retarding with increasing concentration of polymer. The formulations with Guar gum were unable to produce the desired rug release pattern.

Key Words: *Quetiapine fumarate, HPMC K15M, HPMC K100 M, Guar gum, Controlled Release tablets.*

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INTRODUCTION:

This is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process.

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities, pharmaceutical formulations, mainly because of patient acceptance and convenience in administration.

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are tablets and capsules. But the important drawback of these dosage forms is the difficulty to swallow [1-5].

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized".

Extended-release drug products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products [6-10].

Delayed-Release Drug Products: A dosage form that releases a discrete portion or portions of drug at a time or at times other than promptly after administration, although one portion may be released promptly after administration.

Targeted-Release Drug Products: A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics [7-9].

The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery [10-12].

MATERIALS AND METHODS:

Quetiapine fumarate obtained from Hetero laboratories, Mahabubnagar, HPMC K15M obtained from SD Fine Chemicals, Hyderabad, HPMC K100M from SD Fine Chemicals, Hyderabad, Guar gum from SD Fine Chemicals, Hyderabad, Magnesium stearate obtained from SD Fine Chemicals, Talc obtained from SD Fine Chemicals, Hyderabad, MCC pH 102 obtained from SD Fine Chemicals Hyderabad.

Formulation of Quetiapine fumarate Controlled release Tablet by Direct- Compression:

Composition of preliminary trials for Quetiapine fumarate Controlled release Tablet by direct compression is shown in table 1. All the ingredients were weighed.

Table 1: Composition of preliminary trials for Quetiapine fumarate Controlled Release Tablet

INGREDIENT	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Quetiapine fumarate(mg)	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K15M	50	100	150	200	-	-	-	-	-	-	-	-
HPMC K100M	-	-	-	-	50	100	150	200	-	-	-	-
GUAR GUM	-	-	-	-	-	-	-	-	50	100	150	200
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Mg. Stearate	5	5	5	5	5	5	5	5	5	5	5	5
MCC pH102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
TOTAL	500	500	500	500	500	500	500	500	500	500	500	500

Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 12mm flat punch, B tooling. Each tablet contains 100mg of Quetiapine fumarate and other pharmaceutical ingredients.

Formulation of Quetiapine Fumarate Controlled Release Tablets

Evaluation Parameters:

Precompression parameters:

1. Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$$D_b = M / V_b$$

Where, M is the mass of powder

V_b is the bulk volume of the powder.

2. Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$$D_t = M / V_t$$

Where,

M is the mass of powder

V_t is the tapped volume of the powder

3. Angle of Repose (Θ):

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\tan(\Theta) = h / r$$

$$\Theta = \tan^{-1}(h / r)$$

Where,

Θ is the angle of repose.

h is the height in cm

r is the radius in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel.

Relationship between angle of repose and powder flow property.

Table 2: Angle of Repose as an Indication of Powder Flow Properties

Sr. No.	Angle of Repose(^{0})	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very Poor

4. Carr's index (or) % Compressibility:

It indicates powder flow properties. It is expressed in percentage and is give by,

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where,

Dt is the tapped density of the powder and

Db is the bulk density of the powder.

Table 3: Relationship between % Compressibility and Flow Ability

Sr no.	% Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very Poor
6	<40	Very Very Poor

5. Hausner Ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, D_t is the tapped density, D_b is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression Parameters:

1. Weight Variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in table No. 4.

Table 4: Weight Variation Specification as per IP

Average Weight of Tablets	%Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

Hardness:
Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Thickness:
Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

Friability (F):
Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

In-Vitro drug Release:
Invitro dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 6 hours. The samples were withdrawn at regular time intervals of 30 min, 1, 2, 3, 5, 6, 7 & 8 hours respectively.

Assay:
10 tablets were weighed and triturated. The tablet triturate equivalent to 10 mg of the drug was weighed accurately, dissolved in pH 1.2 buffers and diluted to 100 ml with the same. Further dilutions were done suitably to get a concentration of 10 µg/ ml with simulated gastric fluid pH 1.2. Absorbance was read at 210 nm against the reagent blank, and the concentrations of Quetiapine fumarate in µg/ ml was determined by using the regression equation.

Y = 0.007x + 0.001
Drug content in mg / tablet = conc. µg/ml * dilution factor
% Drug content = drug content in mg * 100 / label claim.

RESULTS AND DISCUSSION:

From the dissolution profile of formulations prepared with guar gum as polymer it was evident that the formulations prepared with HPMC K15M as retarding polymer in low concentrations the polymer was unable to produce the required retarding action to the tablets. As the concentration of polymer increases the retarding nature was also increased. HPMC K15 M in the concentration of 150 mg showed good % drug release i.e., 97.3 in 8 hours. Where as in the concentration of 200 mg it showed less drug release due to increased retarding nature of polymer.

Where as in case of formulations prepared with HPMC K100 M as retarding polymer, the formulations with 50 mg concentration of polymer showed complete drug release in 6 hours only, whereas the concentration of polymer increases the retarding nature also increased. The Formulation Containing HPMC K100M in 100 Mg Concentration Showed good retarding nature with required drug release in 8 hours i.e., 82.3%.

Where as in case formulations prepared with Guar gum as retarding polymer, as the concentration of polymer increases the retarding nature was also increased. When compared with HPMC polymers it was failed to produce desired drug release pattern.

From the above results it was evident that the formulation F3 is best formulation with desired drug release pattern extended up to 8 hours.

Standard Calibration Curve of Quetiapine fumarate:

Table 5: Concentration and absorbance obtained for calibration curve of Quetiapine fumarate In 0.1 N hydrochloric acid buffer (pH 1.2)

S. No.	Concentration (µg/ml)	Absorbance* (at 298 nm)
1	2	0.193
2	4	0.34
3	6	0.461
4	8	0.579
5	10	0.709
Correlation Coefficient = 0.9985 y = 0.0636x + 0.0751		

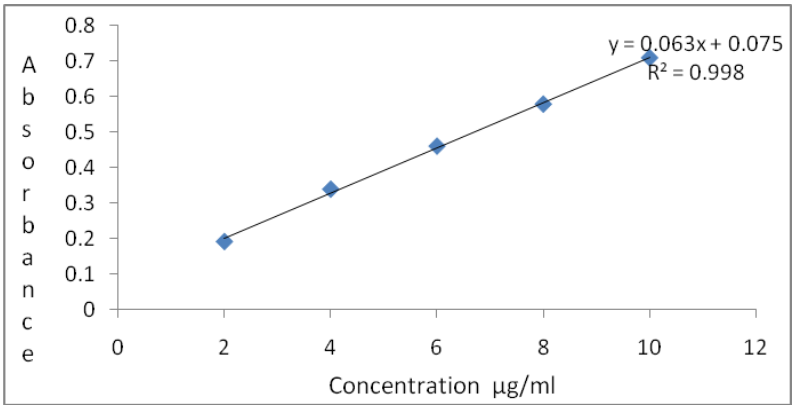

Fig 1: Standard graph of Quetiapine fumarate in 0.1 N HCl

Table 6: Concentration and Absorbance Obtained for Calibration Curve of Quetiapine fumarate In pH 6.8 Phosphate Buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 299nm)
1	2	0.193
2	4	0.331
3	6	0.446
4	8	0.553
5	10	*0.677*
Correlation Coefficient = 0.9982 y = 0.0595x + 0.083		

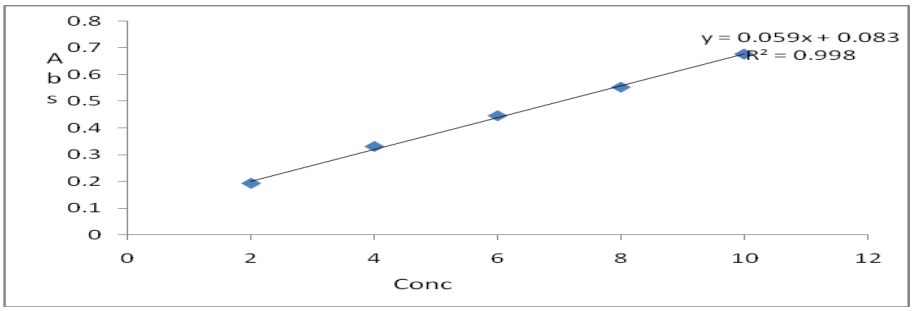

Fig 2: Standard graph of Quetiapine fumarate in pH 6.8 Phosphate buffer

Table 7: Pre-compression parameters of Quetiapine fumarate Tablets					
Formulations	**Bulk Density (gm/cm^2)**	**Tap Density (gm/cm^2)**	**Carr's Index (%)**	**Hausner ratio**	**Angle Of Repose(Ɵ)**
F_1	**0.45**	**0.55**	**18.18**	**1.22**	**27.91**
F_2	**0.47**	**0.55**	**14.54**	**1.17**	**28.23**
F_3	**0.50**	**0.58**	**13.79**	**1.16**	**29.34**
F_4	**0.46**	**0.55**	**16.36**	**1.19**	**26.71**
F_5	**0.50**	**0.58**	**13.79**	**1.16**	**29.34**
F_6	**0.47**	**0.55**	**14.54**	**1.17**	**28.23**
F_7	**0.50**	**0.58**	**13.79**	**1.16**	**29.34**
F_8	**0.41**	**0.50**	**18**	**1.21**	**26.78**
F_9	**0.41**	**0.50**	**18**	**1.21**	**26.78**
F10	**0.42**	**0.51**	**18.24**	**1.20**	**26.68**
F11	**0.48**	**0.56**	**18.12**	**1.21**	**26.70**
F12	**0.41**	**0.54**	**18.11**	**1.22**	**26.71**

Table 8: Post-Compression Parameters of Quetiapine fumarate Tablets

FD	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F_1	494	4.5	5.5	0.43	97.23
F_2	504	4.3	5.5	0.34	98.55
F_3	510	4.2	5.5	0.49	98.16
F_4	495	4.2	5.4	0.47	99.34
F_5	502	4.3	5.5	0.49	98.16
F_6	508	4.3	5.5	0.34	98.55
F_7	510	4.4	5.4	0.49	98.16
F_8	494	4.5	5.5	0.34	99.25
F_9	506	4.4	5.5	0.34	99.25
F10	501	4.4	5.5	0.43	98.6
F11	502	4.3	5.5	0.54	98.7
F12	504	4.5	5.5	0.43	98.5

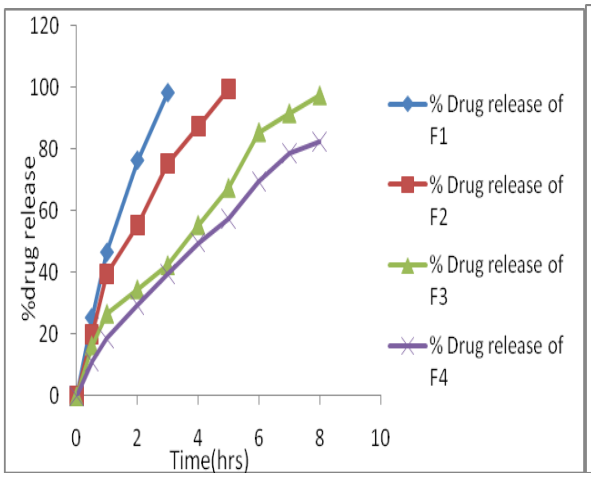

Fig 3: Dissolution profile of formulations Prepared with HPMC K15M polymer

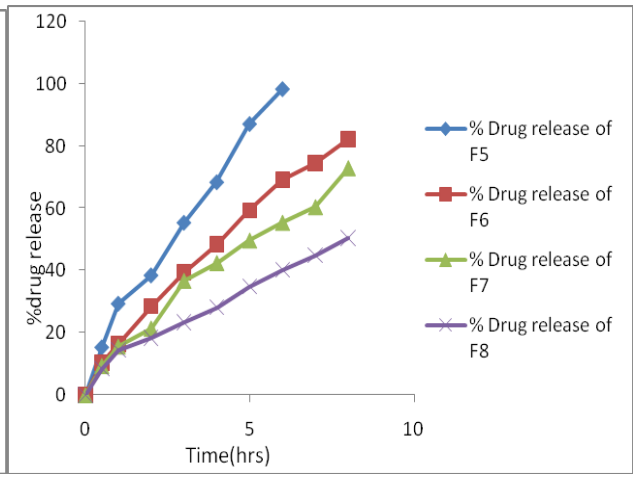

Fig 4: Dissolution profile of formulations prepared with HPMC K100M polymer

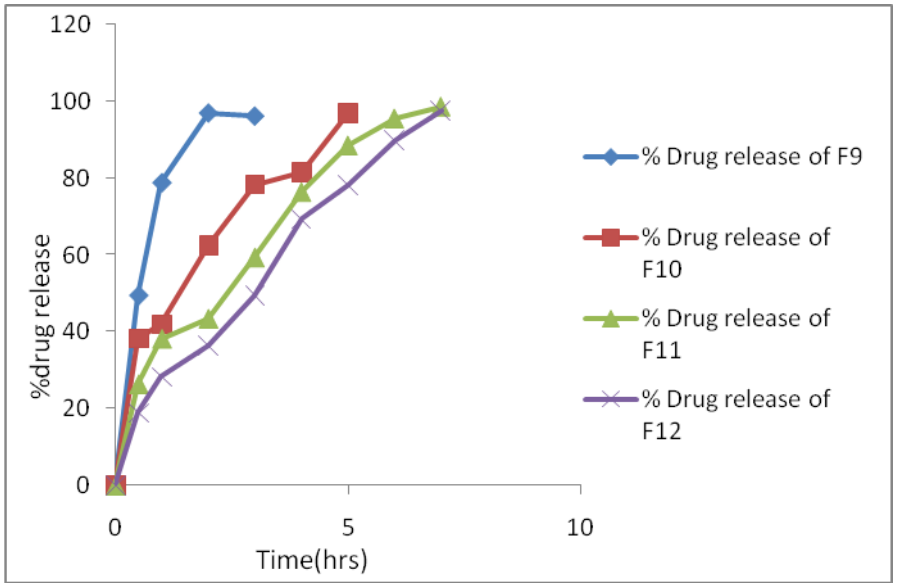

Fig 5: Dissolution profile of formulations prepared with Guar gum as polymer

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

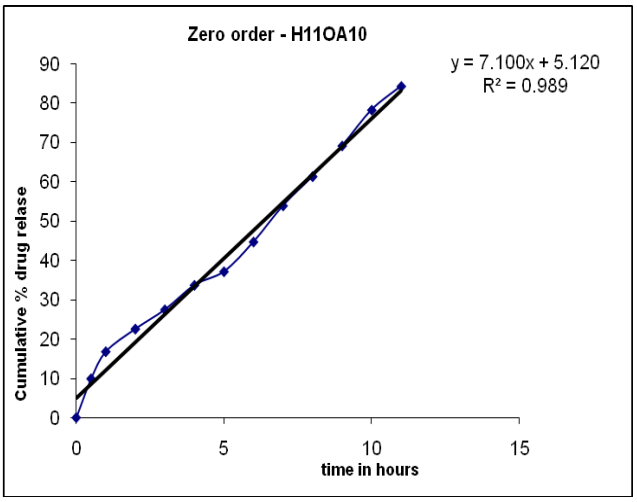

Fig 6: Zero Order Release Kinetics Graph

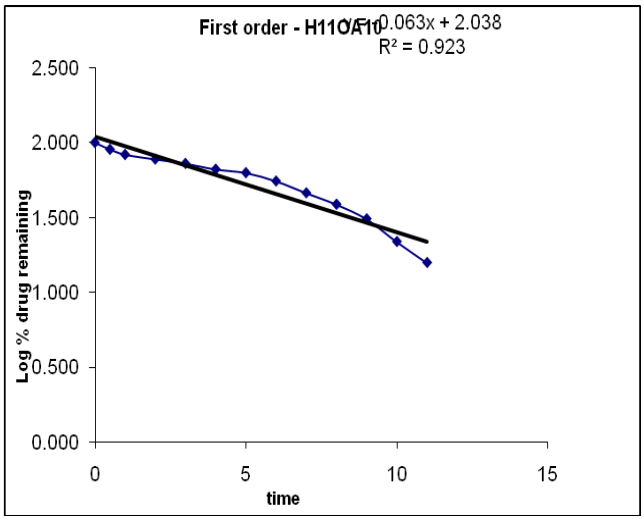

Fig 7: First Order Release Kinetics Graph

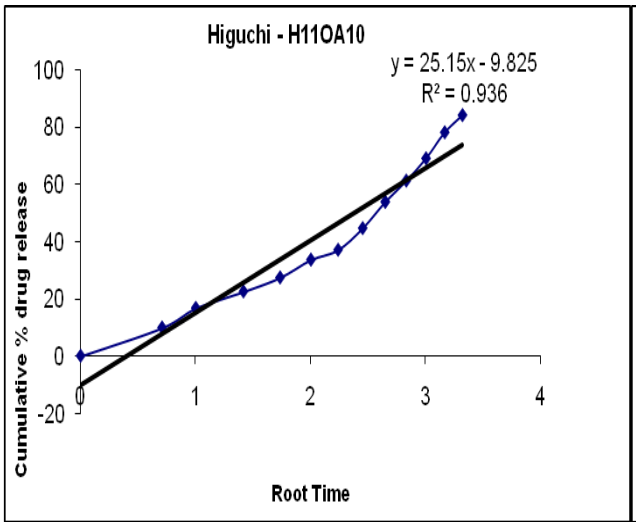

Fig 8: Higuchi Release Kinetics

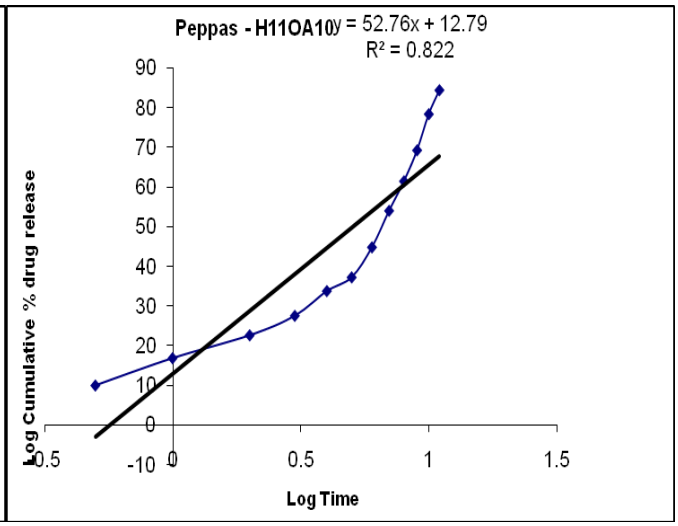

Fig 9: Kars Mayer Peppas Graph

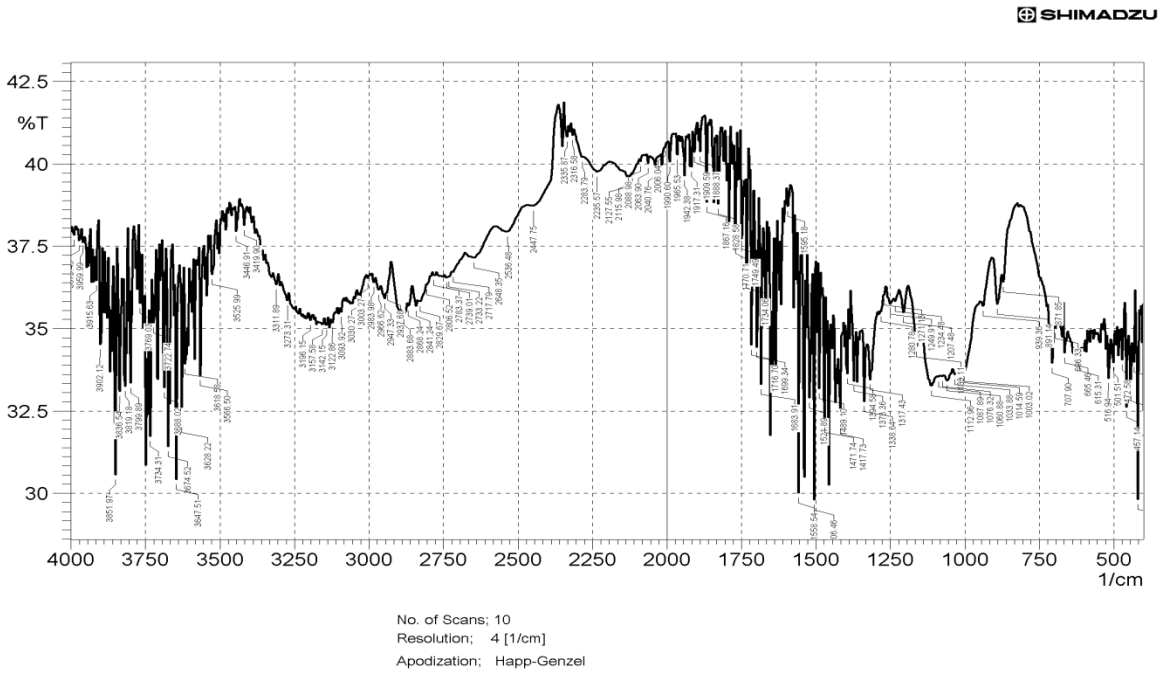

Fig 10: FT-IR Spectrum of Pure Drug

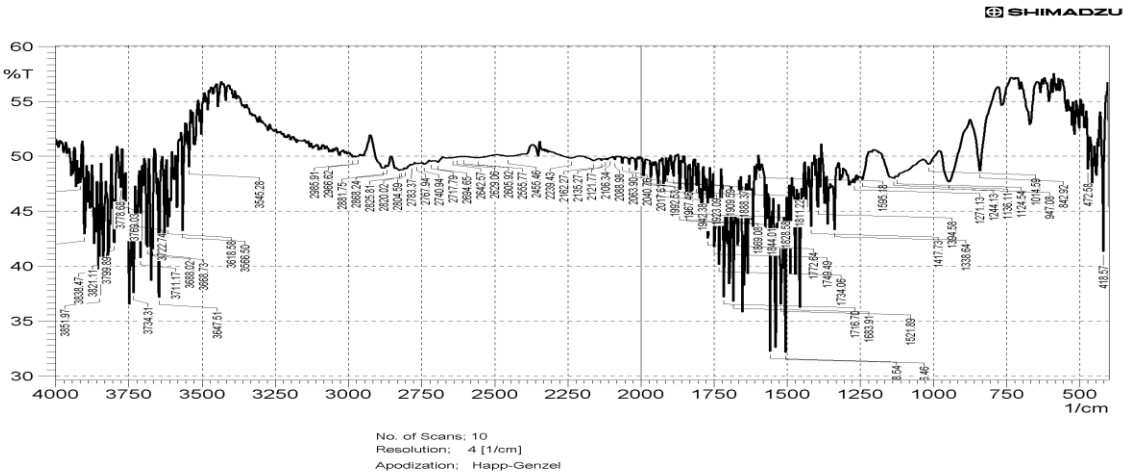

Fig 11: FT-IR Spectrum of Optimized Formulation

CONCLUSION:

Where as in case formulations prepared with Guar gum as retarding polymer, as the concentration of polymer increases the retarding nature was also increased. When compared with HPMC polymers it was failed to produce desired drug release pattern.

From the above results it was evident that the formulation F3 is best formulation with desired drug release pattern extended up to 8 hours.

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