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Formulation and Evaluation of Matrix-based Sustained Release Tablets of Quetiapine fumarate and the Influence of Excipients on Drug Release

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ABSTRACT

The aim of the present study was to develop and characterize an oral sustain release drug delivery system for commonly prescribed antipsychotic Quetiapine fumarate. Hydrophilic matrix based tablets using different concentrations of different grades of hydroxypropyl methylcellulose (HPMC) viz. K100 LV and K4M CR was developed using wet granulation technique. The prepared tablets were of 50mg dose and were designed for once-daily administration. The formulations prepared were evaluated for the release of Quetiapine fumarate over a period of 24 hrs. using USP type II dissolution test apparatus. The prepared tablets were evaluated for physical properties. The in- vitro drug release studies revealed that the tablets containing 15% of HPMC K4M CR of the total tablet weight showed satisfactory results and was able to control the release over 22 hrs. Further the influence of commonly used excipients viz. Lactose, MCC and Starch 1500 was studied on the selected formulation. The in-vitro release data of prepared formulations followed Korsmeyer- Peppas and Higuchi kinetics strongly. The selected formulation was compared with the marketed product for the drug release pattern and was matched using similarity factor (f_2) above 50. In conclusion, the dissolution profiles and the mathematical model fittings indicate that release of Quetiapine fumarate can be effectively controlled by use of hydrophilic matrix systems.

Keywords: Quetiapine fumarate, matrix systems, sustain release, hydroxypropyl methylcellulose (HPMC).

INTRODUCTION

Quetiapine fumarate (QF) (bis [2-(2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl)]ethoxy)ethanol] fumarate, a dibenzothiazepine derivative, is a recent antipsychotic drug with an atypical neuropharmacological profile. Quetiapine is the antipsychotic that has the highest serotonin/dopamine binding ratio, being the serotonin type 2 (5-HT_2)-receptor blocking effect about twice as strong as the dopamine D2-receptor blocking effect [1]. Due to this binding pattern, quetiapine causes minimal extrapyramidal side effects. It is readily absorbed from the gastrointestinal track with oral bioavailability of about 83% and a plasma elimination half life ranging from 6-7hours. Administration of QF in the sustain release dosage form as once daily would be more desirable as this formulation is intended to be given to schizophrenic patients. The sustain release form would also control the mood for longer period of time by maintaining the plasma concentration of drug well above the therapeutic concentration. It appears as effective as the older antipsychotics producing side effects no worse than those encountered with standard antipsychotics. This characteristic makes quetiapine well tolerated and effective in patients who are particularly susceptible to these severe side effects, including the elderly and adolescents and those with preexisting dopaminergic pathologies, such as Alzheimer's disease and Parkinson's disease.

Literature survey revealed that no work has been published till date on the sustain release dosage form of Qurtiapine fumarate. An effort was therefore made to develop simple and effective sustain release tablets of Quetiapine fumarate using a polymer matrix system. Hydroxypropyl methyl cellulose (HPMC) is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral sustain release drug delivery system [2]. The transport phenomena involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with the gastrointestinal fluid, HPMC swells, gels and finally dissolves slowly [3]. The gel becomes viscous acting as a protective barrier to both, the influx of water and the efflux of drug in solution [4, 5]. As reported by Ford et al, [6] the proportion of polymer in the formulation increases the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix. Narasimhan and Peppas [7]. showed that the dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer swelling and dissolution as well as the corresponding rate of the drug release are found to increase with use of lower viscosity grades of polymers.

The rate of drug release form HPMC matrix is dependent on various factors such as type of polymers, drug, drug-polymer ratio, particle size of drug and polymer, and the type and amount of fillers used in the formulation.

Starch is one of the most widely used excipient in the manufacturing of solid dosage forms. Most native starches consist of two polymers of glucose, that is, branched amylopectin and essentially linear amylose [8]. Physically or chemically modified starches have been used in sustain release tablets because of their cold water swelling capacityand gel barrier formation. Rak et al, [9] and van Aerde and Remon [10] studies the possibility of using thermally modified starches for controlled drug release. Herman and Remon [11] found that only fully pregelatinized starches containing low amount of amylose (25% and lower) could produce a strong enough gel layer to ensure a sustained drug release. The polymeric Excipients like starches are able to control the release over 20 hrs. from tablets loaded with 20-60% drug. Other advantages of cross linked high amylose starches may be the absence of erosion , limiting swelling and the fact that increasing degree of crosslinking results in increased water uptake rate and drug release rate. The use of partially pregelatinized starches in combination with other polymers, such as hypromellose, in SR tablets have not been fully examined. Therefore, the influence of Starch 1500 with lactose and MCC, on drug release for m HPMC 2208 has been investigated as a part in this study.

The aim of the present study was to design and develop the sustain release matrix tablets of Quetiapine fumarate, and to study the effect of different filler excipients on the drug release profiles.

EXPERIMENTAL SECTION

2.1 Materials

Quetiapine fumarate was provided as a gift sample by Lupin Research Park (Pune, India). HPMC 2208 with various viscosity grades (Methocel K4M premium CR and Methocel K100 LV) was received as a gift sample from Colorcon Asia, Pvt. Ltd. (Mumbai, India). Microcrystalline cellulose (Avicel pH 102) was received as a gift sample from Signet chemical Co-operation, Mumbai. Lactose, Magnesium stearate and talc were purchased from Loba Chemie Pvt. Ltd., Mumbai. All other chemicals and reagents were of analytical grades.

2.2 Preparation of tablets

Matrix tablets were prepared by wet granulation method the composition of various formulations is given in Table 1. Quetiapine fumarate and the polymer grades used of HPMC *viz.* K100 LV and K4M CR were initially passed through 40# sieve. The drug and the polymer used were then proportionately mixed in a mortar for 10-15 mins. Filler excipient were than added and the resulting mixture was again mixed for further 10 mins. Granulation was done using Isopropyl Alcohol. The wet mass was passed through 16 # sieve and it was dried in an oven at 40^0C for 20-30 mins. The dried granules were again passed through 16 # sieve and blended with talc and magnesium stearate. The resulting granules were evaluated for the flow properties. Tablets were compressed on 10mm flat punch on a 12 station mini press tableting machine (Rimek, India). Seven different formulas having different concentrations of HPMC K4M CR and HPMC K100LV were prepared. These tablets were evaluated for drug release and to study the effect of polymer concentration on drug release.

Table 1: Different Tablet Compositions*

Name of ingredient	Quantity (mg) per Tablet #						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Quetiapine fumarate	110	110	110	110	110	110	110
HPMC K4M CR	-	-	-	52.5	70	105	140
HPMC K100 LV	70	105	140	-	-	-	-
Lactose	159.5	124.5	89.5	177	159.5	124.5	89.5
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	7	7	7	7	7	7	7
Total	350	350	350	350	350	350	350

** HPMC indicates hydroxypropyl methylcellulose.*
 # formulations F1-F3, contains 20,30 and 40% of HPMC K100LV and F4-F7, contains 15, 20, 30 and 40% of HPMC K4M CR respectively.

2.3 Evaluation of tablets

As mentioned in the preparation of tablet section, to study the effect of polymer concentration of drug release, 7 different formulas, having different concentrations of polymer HPMC were developed. Figure 1 shows the drug release profiles of the 7 formulations studied.

The prepared tablets were tested as per standard procedure [17] for weight variation (n=20), hardness (n=6), thickness (n=6), drug content and friability. Hardness of the tablets was determined by using Monsanto tablet hardness tester, Friability test (n=10) was conducted using Roche friabilator (F. Hoffman-La Roche Ltd, Basel, Switzerland). Thickness of the tablets was measured by digital Vernier calipers (Aerospace). Drug content of QF was analyzed by measuring the absorbance of standard and samples at λ=246nm using the UV/Visible spectrophotometer (Jasco model-V-550, Tokyo, Japan) and comparing the content from a standard calibration curve. Further the similarity factor f_2 for the release of QF between the test product and that of the marketed formulation, Quel SR (IPCA Pharmaceuticals), was performed.

2.4 Study of filler Excipients

From the dissolution profile of the prepared tablets it was found that the tablets were showing the initial burst effect. So, to overcome this problem different excipients were tried. For the study of filler excipient one selected formulation was used. Various different fillers like, lactose, MCC and partially pregelatinized starch (Starch 1500) were selected for the study. 3 formulations with 3 different Excipients were prepared, and the resulting tablets were evaluated for various parameters. The in-vitro dissolution was carried out and the effect of change in filler was observed over the % drug release.

2.5 Dissolution testing

Dissolution studies were performed using the USP XXVIII, paddle-rotating method (Electrolab dissolution tester, TDT-08, India) at 37 °C ± 0.5 °C and 50 rpm using 0.1 N HCl in the initial 2 hours and phosphate buffered solution, pH 6.8 (PBS) till the end of the study [12] , as the dissolution media. Dissolution studies were carried out in triplicate. A 2 ml aliquot of sample was withdrawn at regular time intervals, filtered and then these samples were diluted 10 folds with distilled water and then assayed spectrophotometrically at 246 nm. The cumulative % drug release was calculated for the formulations and the drug release data were curve fitted using PCP Disso v3.00 software to study the possible mechanism of drug release from hydrophilic swollen matrices.

2.6 Mechanisms of drug release.

To analyze the mechanism of drug release from the matrix tablets, the release data were fitted to the following equations [13-14]:

Zero- order equation: $Q = k_0 t$

Where, Q is the amount of drug released at time t, and k_0 is the release rate;

First- order equation: $\log (100-Q) = \log 100 - k_1 t$

Where, Q is the percentage of drug release at time t, and k_1 is the release rate constant;

Higuchi's equation: $Q = k_2 t^{1/2}$

Where, Q is the percent of drug released at time t, and k_2 is the diffusion rate constant

.

Korsmeyer Peppas equation: $Mt/ M\infty = k\ t^n$
Where, $Mt/ M\infty$ is the fractional solute release, t is the release time, k is the kinetic constant and n is an exponential value.

2.7 Control of Burst

After the evaluation of the prepared tablets for the drug release it was observed that there existed an initial burst release in the first 1-2 hrs, in which about 35-40% of the drug was released. The changing of filler excipient in the formulation also did not helped much to control the burst. So to control the initial burst effect two more formulations were tried which contained a combination of the two polymer grades HPMC K100LV (10%, 15%) and HPMC K4M CR (12.5%, 15%). These formulations were then evaluated for physical parameters and also for dissolution profile.

2.8 Wettability

The ability of tablet to absorb water or the process of water penetration into the tablet was examined by calculating the contact angle between the tablet surface and a water droplet. A drop of colored solution was deposited on the surface of the dry tablet with the help of a syringe and needle. In the initial 15 seconds 5-10 snaps were taken and the contact angle was measured by drawing a tangent to the curvature of the drop [8].

2.9 Similarity factor (f_2) Analysis

In- vitro release profile of the marketed QF sustain release tablets (SR) tablets, (Quel SR, IPCA) was performed under similarity conditions as used for in- vitro release testing of the test product for the release of QF. The similarity factor between the two formulations was determined using the data obtained from the drug release pattern. The data was analyzed by the following formula shown in equation 1. [15].

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

Where, **n** = number of pull points, W_t = Optional weight factor, R_t = Reference profile at time point t and T_t = Test profile at same time point.

RESULTS AND DISCUSSION

The SR tablets of QF were prepared as there was no literature available on the prepared dosage form and QF was a drug of choice in case of many psychotic patients. Wet granulation was the prepared technique for making SR formulations, as the other techniques did not give satisfactory flow properties due to the fluffiness of the drug.

3.1 Physical Properties

The results obtained for the weight variation, hardness, thickness, friability, and drug content are given in Table 2, all the prepared formulations were seen to be complying with the official requirements of uniformity of weight. The drug content was found to be close to 100% of the label claim for QF in all the formulations. The hardness and friability, the measures of strength of the tablets were found to be 6-7 kg/cm^2 and <1% respectively, these values were within limit. Thus all the physical parameters of the compressed matrices were found to be practically within controls.

Table 2: Physical properties of Formulations Prepared *
*** SD indicates Standard deviation.**

Test	Results						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Weight variation (mg)±SD	349±0.018	351±0.03	351±0.022	347±0.052	349.8±0.067	350.3±0.023	351±0.0094
Hardness (kg/cm^2)	6-8	6-8	6-8	6-8	6-8	6-8	6-8
Thickness (mm)±SD	3.48±0.07	3.51±0.04	3.52±0.02	3.58±0.05	3.50±0.034	3.49±0.047	3.56±0.035
Friability (%)	0.243	0.376	0.276	0.476	0.392	0.287	0.429
Drug content (%)	98.65	97.54	99.65	98.22	98.43	99.56	97.89

3.2 In- Vitro release studies

As the drug in study had a slight solubility in water moderate molecular weight HPMC is used as a rate controlling

polymer (K4M CR and K100LV) to retard the release of drug from a matrix at levels of 15 to 40% w/w in tablets prepared. The effect of polymer level on the release of the drug from matrix tablets was studied for tablets containing 15%, 20%, 30% and 40% of the polymer. (Formulations F1 to F7). Figure 1 shows that the amount of HPMC and as well as the grade used affects the release rate of the drug. Tablets containing 15% and 20% of K4M CR showed >90% release in 20 hrs. and the tablets containing 30% to 40% of K4M CR showed a more retardation giving only 64-77% of the drug release at the end of 20 hrs. In comparison to this the tablets containing K100 LV 20% showed complete drug release at the end of 10hrs. this may be due to the erosion of the polymer as it is of a very low viscosity. High percentages of K100LV i.e. 30% and 40% showed complete drug release in 14 and 16hrs. respectively. Thus, indicating that higher the percentage of the polymer more is the drug release retardation.

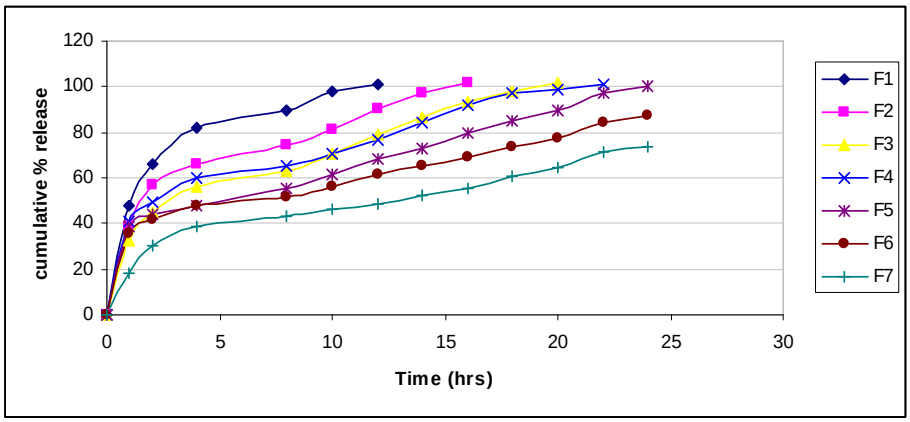


Figure 1: In-Vitro drug release pattern of formulations F1-F7

3.3 Drug release mechanism

The obtained release data from the in-vitro dissolution study from various formulations was fitted to the mathematical models. The kinetic models included First order, Higuchi equation (matrix system) and Korsmeyer-Peppas model. Table 3 shows the data obtained from the model fitting, for all the 7 formulations studied (F1-F7) along with their R^2 values, K constant, and n exponential value. The overall curve fitting showed that the drug release from the sustained release matrix tablets followed either Higuchi equation or the Korsmeyer- Peppas model. The values of the exponential factor 'n' were found to be in between 0.2871- 0.3747 indicating the Fickian diffusion- controlled drug release. The correlation co-efficient R^2 was same time best fitting to the Matrix system and some time to the Korsmeyer-Peppas equation which was adequate from the sustain release systems. However, looking at the negligible variation in the R^2 values for the release of the drug QF, the release data analysis applying these mathematical models can be purely empirical.

Table 3: Release kinetics of the prepared formulations

	R^2				n	K
	Zero- order	**1st order**	**Higuchi**	**Korsmeyer-Peppas**		
F1	0.5166	0.8526	0.9293	0.9812	0.2871	39.65
F2	0.6634	0.9202	0.9564	0.9839	0.3152	32.16
F3	0.7880	0.9621	0.9821	0.9899	0.3637	25.64
F4	0.6498	0.9305	0.9529	0.9808	0.2903	30.88
F5	0.7470	0.9485	0.9841	0.9573	0.3007	15.93

3.4 Influence of different filler Excipients on drug release

The fillers used were lactose which is very common filler in most of the formulations, and is a simple sugar. The second filler was MCC which is cellulosic in nature and is mainly used as binder in dry state and as disintegrate when in solvent, but is not as soluble in water as lactose. Starch 1500 is a pregelatinised starch containing low amount of amylase and that's why could produce a strong enough gel layer. Figure 2 shows the drug release profile from the formulations containing different filler Excipients. From the figure it was seen that the drug release was slower for MCC and slowest for starch 1500 than the formulation with lactose. The drug release differences between tablets containing lactose and MCC can be attributed mainly to the excipient solubility. Lactose being more soluble, it releases the drug faster by the formation of pores in to the tablet, while MCC shows a slower release which may

be due to its low solubility in water as compared to that of lactose. Use of starch 1500 as a filler excipient, in HPMC matrices may bring about retardation effect resulting from interactions between HPMC and starch 1500 that can affect the properties of the gel layer around the tablet, hence showing the slowest drug release in comparison. This slow release may be due to slower penetration of water front towards the center core of the matrix as well as the property of starch to hydrate and form a gel layer barrier due to intramolecular hydrogen bonds in the highly branched amylopectin [16]. The use of different fillers was tried to control the burst but, the burst was not seen to be controlled to the required extend.

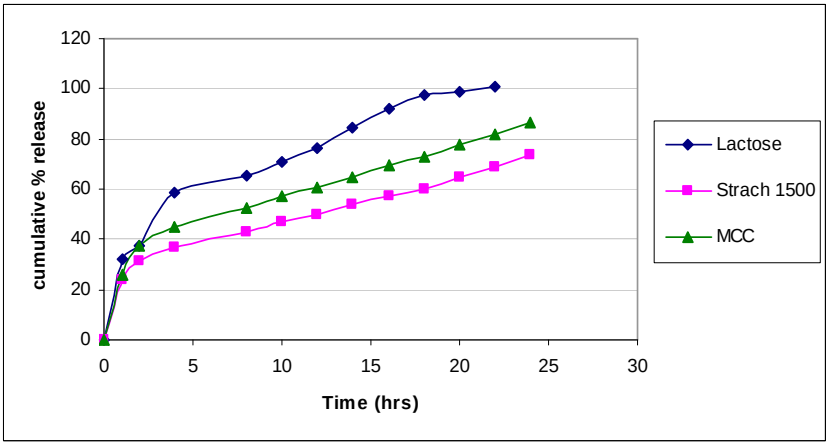


Figure: 2 Drug release from formulations containing various different fillers

Control of Burst

The selected formulation (F4) shows expected release pattern with more than 90% drug release over 20hrs, but it showed 40% release in the initial hour which was not appropriate. This burst release may be due to more time required for wetting of tablet containing high viscosity grade polymer (K4M CR). As a result more time was required for the formation of diffusion layer leading to higher percentage of drug release initially. This problem was overcome by combining the two polymer grades K4M CR with low viscosity grade K100LV which take less time for wetting and gives rapid formation of the diffusion layer.

The results of the dissolution study and the drug release profile of these two formulations containing different ratios of K100LV and K4M CR (B1 and B2) is shown in table 4 and figure 3 respectively.

Table 4: % drug release from B1 and B2

Time (hrs)	% Release	
	B1	B2
1	23.75±0.23	26.7±0.52
2	27.52±0.54	38.51±0.48
4	32.18±0.65	49.64±0.38
8	45.18±0.14	57.67±0.26
10	51.42±0.32	65.68±0.27
12	57.58±0.36	73.38±0.22
14	66.13±0.76	78.86±0.19
16	75.41±0.54	84.58±0.51
18	84.31±0.43	88.83±0.43
20	93.24±0.42	94.7±0.33
22	97.95±0.17	97.52±0.87

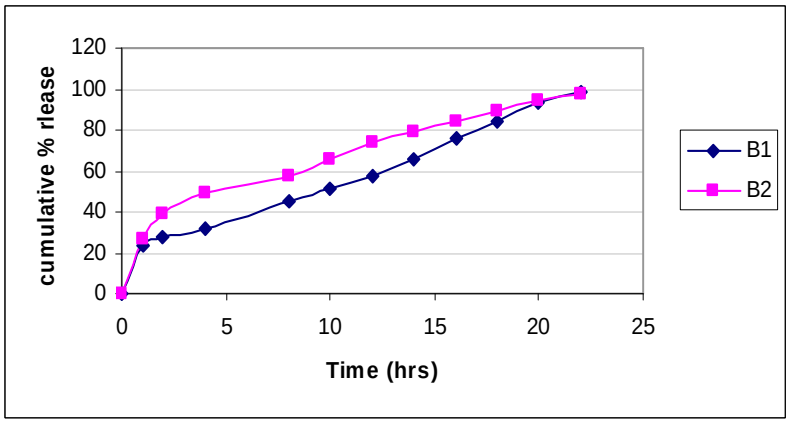


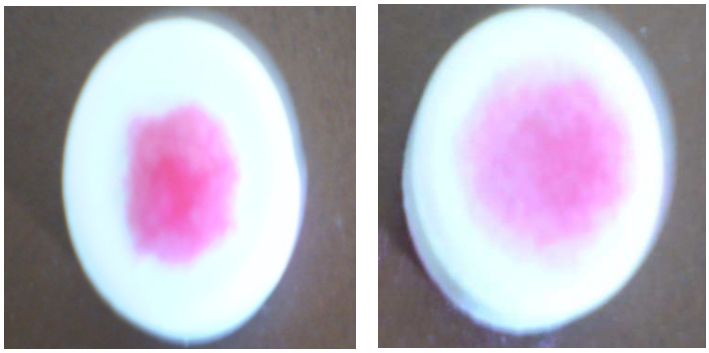
Figure 3: Drug release profile of formulations B1 and B2

3.5 Wettability

Drug release from HPMC matrix tablets is based on the glassy transition of the polymer into a rubbery glass that occurs as a result of water absorption of the polymer in the matrix. The drug release mechanism is determined by the structural characteristics of the gel layer (swelling, uniformity of polymer hydration, and gel strength) and by gel layer erosion. Therefore, rapid gel formation to prevent rapid ingress of water into the matrix as well as high gel strength is critical factors in drug release from HPMC matrices.

It was found that water penetration into the tablet containing HPMC K100LV was much faster as compared to the tablets containing HPMC K4M CR. This observation was confirmed by contact angle measurement. This study indicated that the water penetration capacity of the tablets containing HPMC K100LV was higher than K4M CR. The contact angle for the samples was similar ($30\text{-}57^0$) and less than 90^0, indicating good surface wettability behavior of these matrices [8]., but tablets containing K100LV showed much faster penetration and the rate of contact angle change was also significantly faster.

Figure 4 gives you the pictures of tablet wettability, of tablets with K4M and with K100LV. Thus, it was indicated from this study that due to more wetting of the tablets containing low viscosity grade polymer, the drug release from the formulations F1-F3 was much faster as compared to the other formulations containing high viscosity polymer grade.



(a) (b)

Figure 4: Water droplet and it's absorption into (a) tablet containing K4M CR and (b) tablet containing K100 LV

3.6 Similarity Factor

The principles purposes of dissolution testing are 3-fold: (1) for quality control, to ensure the uniformity of product from batch to batch; (2) to help to predict bioavailability for formulation development; and (3) as a measure of change when formulation changes are made to an existing formulation. So, to compare the release pattern from two different formulations of the same drug f_2 factor can be used. Similarity factor analysis between the prepared tablets

and Quel SR tablets (marketed) for the release of QF showed an f_2 factor (f_2 = 61.45) greater than 50. As shown in figure 5, the f_2 factor confirms that the release of QF from the prepared tablets was similar to that of the marketed tablet.

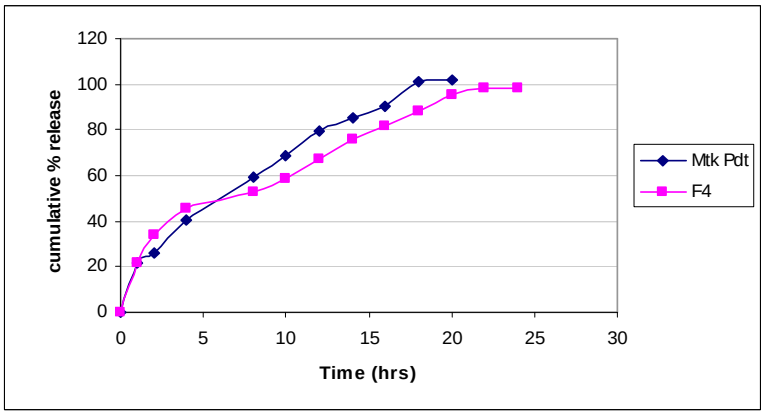


Figure 5: Comparative in vitro drug release of selected formulation (F4) with marketed product for similarity factor f_2

CONCLUSION

All the prepared formulations with HPMC polymer grades had good flow properties before compression and the tablets showed weight uniformity and mechanical strength. All the formulations resulted in slow drug release depending upon the type and concentration of the polymer grade. Drug release was found to be affected by the concentration of the polymer; increasing concentration resulted in decreased drug release. The formulation containing 15% of K4M CR grade of HPMC showed satisfactory results sustaining the effect of the drug over 20 hrs. to give once daily dose. The formulation containing Starch 1500 as a filler excipient showed the slowest drug release. The water absorption into the tablet containing K100LV was much faster as compared to the tablets containing K4M CR; this observation was confirmed by the contact angle measurement. The similarity factor (f_2) value above 50 indicated the similarity between the marketed and prepared tablets.

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