



In Vitro Drug Release Kinetics of Tramadol HCl-Ethocel Matrix Tablets and Studying the Effect of Co-Excipients on the Release Pattern

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SUMMARY. Preparation of matrix tablets with rate controlling polymers is the simplest and most widely used method for achieving desired controlled release rate of drugs. The objective of the present study was to evaluate the effect of concentration and particle size of Ethocel Premium 100P and 100FP and also the co-excipients like HPMC, starch and CMC on the release kinetics of Tramadol HCl from matrix tablets. For this purpose, different formulations of Tramadol HCl matrix tablets were prepared at various drug to polymer ratios by dry granulation method. Different physical and quality control tests were performed on the prepared tablets followed by *in vitro* drug release studies through USP method I dissolution test (rotating basket method). Different kinetic models were applied on the release profiles to determine drug release kinetics and release mechanism. Similarity factor f_2 and difference factor f_1 were applied for checking the similarities and dissimilarities between the release profiles. The results showed that Ethocel 100FP that have fine particle size than Ethocel 100P has a more retardant effect on the release profile, especially when the drug to polymer ratio was 10:4 which leads towards the achievement of anomalous non-Fickian release kinetics. The Co-excipients used in some formulations enhanced the release rate of TH from the matrix tablets.

INTRODUCTION

Tramadol hydrochloride (TH) is an opioid analgesic widely used in clinical field for relief of physical pain due to surgical operation and chronic pain like low back pain, cancer pain, diabetic neuropathy, polyneuropathy and osteoarthritis¹⁻⁵. Because of the fast metabolism in human body, the effective duration of TH is only 4 h so to maintain effective plasma concentration; TH should be administered 4-5 times a day to achieve the expected therapeutic effect. This frequent dosing results in decreased patient compliance and increased side effects like increase in dependence or habit forming. Therefore it is necessary to develop a controlled release system for TH which results in extension of the therapeutic time.

Preparation of matrix tablets with rate controlling polymers is the simplest and most widely used method for achieving desired controlled release rate of drugs. Hydrophobic polymers have many advantages like good stability at varying pH values and moisture levels and a well-established safe application⁶. Ethocel an ethyl cellulose ether derivative is an extensively used hydrophobic polymer in controlled release matrix tablets. Many authors have reported a successful use of Ethocel as rate limiting agent⁷⁻⁹ but no one has so far used different viscosity grades of Ethocel as rate limiting agents for controlling the release of TH. Ethocel Premium is among the very few water insoluble excipients that are approved and accepted globally for pharmaceutical applications.

KEY WORDS: Controlled release drug delivery, Ethocel 100 fine particle premium (100FP), Ethocel 100 premium, Kinetic models, Similarity and difference factors, Tramadol HCl.

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The conventional Ethocel 100 Premium (100P) was studied for its effect on the release of TH from tablets at different drug to polymer ratios in this study. The effect of particle size of the polymer was studied by investigating the release of the drug from finely milled form of this polymer *i.e.* Ethocel 100 Fine Particle (100FP) premium. Also the effect of different co-excipients like starch, HPMC and CMC on the release profile of TH was investigated.

MATERIALS AND METHODS

Materials

Tramadol HCl (Global Pharma Islamabad Pakistan), Ethocel 100P and 100FP (Dow Chemical Co, Midland USA), sodium hydroxide (Merck, Germany), monobasic potassium phosphate (Merck, Germany), lactose and magnesium stearate (BDH chemical, Pool England), Carboxymethyl Cellulose (CMC) and starch (Merck, Germany), hydroxypropyl methyl cellulose (HPMC K100M) (Dow chemical Co., Midland USA).

Tramadol HCl Identification

The identification and confirmation of TH

was conducted in accordance with the specifications of British Pharmacopeia (BP) ¹⁰. In this connection the melting point of the drug was determined with the use of digital melting point apparatus. The results so obtained were compared with standards given in BP ¹⁰.

Percentage Purity Determination

Before being formulated into matrix tablets, the percentage purity of TH sample was determined by comparing it with standard TH. About 50 mg of sample TH and standard TH were taken in a 100 mL flask. Twenty mL of phosphate buffer (pH 7.4) was then added to it, and after proper dissolution of the drugs in the corresponding solutions final volumes were made upto 100 mL with phosphate buffer (pH 7.4). One mL was taken from each of these solutions and diluted to 10 mL separately with the same phosphate buffer after filtration. Absorbance values of the two dilutions were recorded in triplicate by using UV Visible Spectrophotometer (UVDEC 1601, Shimadzu) at λ_{\max} 270 nm. The Eq. [1] was used for determination of percentage purity:

$$\text{Percentage Purity} = \frac{\text{Absorbance (Sample)} \times W(\text{std})}{\text{Absorbance (std)} \times W(\text{Sample})} \times 100 \quad [1]$$

where W= weight.

Formulation of Matrix Tablets

Formulations of various matrix tablets (200 mg) that were prepared during the present research are mentioned in Table 1. Ethocel 100P and its fine particle grade *i.e.* Ethocel 100FP were used. Four different drug to polymer ratios (D:P) were used *i.e.* 10:1, 10:2, 10:3, and 10:4 in both polymer's case. Each tablet contained 100 mg of TH. Lactose was used as filler and magnesium stearate was used as lubricant. In some

formulations with D:P of 10:4, 30% of the filler (lactose) was replaced with co-excipients like CMC, Starch and HPMC.

Flow Properties of the Powders & Granules and Preparation of Matrix tablets

A powder mixture must always fulfil the basic good flow requirements and the compressibility characteristics as well. For good flow the angle of repose should be measured and to determine the compressibility characteristics, Compressibility index and Hausner's ratio should be

	D:P Ratio	Tramadol HCl	Polymer	Filler (Lactose)	Lubricant (0.1%) (Mg Stearate)	Co-Excipient (30% filler)
TH-Ethocel* Tablets without Co-excipients						
Polymer Ethocel*	10:1	100 mg	20 mg	79 mg	1 mg	
	10:2	100 mg	30 mg	69 mg	1 mg	
	10:3	100 mg	40 mg	59 mg	1 mg	
	10:4	100 mg	50 mg	49 mg	1 mg	
TH-Ethocel* Tablets with Co-excipients CMC, HPMC and Starch						
Polymer Ethocel*	10:4	100 mg	40 mg	41.3 mg	1 mg	17.7 mg

Table 1. Formulations of Tramadol HCl matrix Tablets Ethocel. *: 100 P and 100 FP

measured before manufacturing of tablets. A formulation from Table 1 was selected that contains the drug to polymer ratio 10:4. This formulation was selected because it contains the maximum amount of polymer so it was predicted that it may have good flow properties and compressibility characteristics than the other formulations. All ingredients of this formulation were mixed well in a polythene bag and placed aside after tightly closing the bag. Then another physical mixture of the same formulation was prepared. In this case the ingredients (except Mg stearate) of the same selected formulation were mixed by geometric dilution method in a polythene bag. After passing this mixture through No 40 sieve was compressed to slugs (500-600 mg) by single punch machine (Erweka, Germany) using a 17 mm flat faced tooling. Then these slugs were crushed in pestle and mortar. After this Mg. stearate was added and the mixture was passed through sieve No 12 to form proper granules. Then the following tests were performed on both the mixture powder and the granules.

Angle of Repose

It was measured by passing the powders and granules through funnel on to a Petri dish separately. The height of the heap formed and the radius of the cone was determined and thus angle of repose was determined by Eq. [2]

$$\tan\theta = \frac{h}{r} \quad [2]$$

where h is the height of the cone and r is radius of the cone base.

Hausner ratio and compressibility index

Both tests were determined by their respective equations by measuring the bulk and tapped volume of the powders and the granules. The compressibility index was determined by the following formula of Carr's compressibility percentage. Powders/granules were taken upto the volume of 100 mL in a graduated cylinder of 250 mL. These 100 mL was the bulk volume (V_o) and then the cylinder was taped on a surface until there was no change in the volume of the powder. This final volume was the taped volume (V_f) of the powder. By using Eqs. [3] and [4], Hausner ratio and compressibility Index were determined.

$$\text{Hausner Ratio} = \frac{V_o}{V_f} \quad [3]$$

$$\text{Compressibility Index} = 100 \times \frac{V_o - V_f}{V_o} \quad [4]$$

Results of the above tests on the selected formulation showed that the TH and other ingredi-

ents didn't have good flow properties and compressibility characteristics when mixed directly. So the direct compression method for preparation of matrix tablet of TH was not desired. Instead dry granulation method was used for the tablet preparation as the flow properties of the granules were satisfactory.

One hundred tablets of each formulation given in Table 1 were prepared by the same dry granulation method mentioned above. After the preparation of the dry granules they were compressed into tablets using the single punch machine (Erweka, Germany) having 8 mm tooling and concave shape.

Evaluation of Prepared Tablets

Physicochemical evaluation of the prepared tablets was carried out by performing various established physical and quality control tests like weight variation, thickness, diameter, hardness, friability and content uniformity tests. Analytical balance (Shimadzu, AX 200, Japan) was used for weight variation test. For thickness and diameter a Vernier calliper (Germany) was used. Hardness tester (Erweka Apparatus TB-24, Germany) was used for measurement of hardness of the tablets and for friability a Roche Friabilator (Erweka TA3R, Germany) was used.

In case of content uniformity, 10 tablets from each batch were pulverised using pestle and mortar. From this sample of 20 mg was taken in a volumetric flask (100 mL) and methanol was added slowly for the dissolution of the sample. And finally the volume was made up to 100 mL with methanol. The same procedure was carried out for TH powder. The absorbance of the sample and the standard were recorded using UV visible spectrophotometer at λ_{max} of 270 nm.

All these tests were carried out in triplicate with standard deviations and means calculated using Microsoft Excel.

In vitro Dissolution Studies

For *in vitro* dissolution studies, the USP method I (Rotating Basket) was used. These studies were conducted in Eight Station (Pharmatest Dissolution Apparatus (D-6312, Hainburg). Phosphate buffer (900 mL, pH 7.4) was added to 6 flasks of the dissolution apparatus. From a batch, 3 tablets were placed in separate flasks in the baskets. Temperature was maintained at 37 ± 0.5 °C and the rotation speed was fixed at 100 rpm. Samples of 5 mL of the samples were withdrawn from each flask at predetermined time points *i.e.* 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 18.0, and 24.0 h

with the help of long needled syringe. Same volume of fresh phosphate buffer (pH 7.4) which was placed at the same temperature was added in to the respective flasks after each sampling period. The same procedure was repeated for each batch. The samples were then filtered through 0.45 μm filter paper and then analysed via UV visible spectrophotometer (UVIDEC-1601 Shimadzu Japan). Absorbance values were recorded at 270 nm. The percent drug released was calculated using the standard calibration curve for TH.

Drug Release Kinetics

The kinetic models which were applied to the *in vitro* dissolution data of the matrix tablets of TH are as consigned in Eqs. [5] to [9].

$$\text{Zero order Kinetics }^{11}: \\ W = K_1 t \quad [5]$$

$$\text{First order kinetics }^{11}: \\ \ln(100 - W) = \ln 100 - K_2 t \quad [6]$$

$$\text{Higuchi Kinetics }^{12}: \\ W = K_4 t^{1/2} \quad [7]$$

$$\text{Hixson Crowell kinetics }^{11}: \\ (100 - W)^{1/3} = 100^{1/3} - K_3 t \quad [8]$$

$$\text{Korsmeyer Peppas kinetics }^{13}: \\ M_t / M_\infty = K_5 t^n \quad [9]$$

The n value (diffusional exponent) in the Korsmeyer Peppas kinetic model describes the mechanism of the drug release from the matrix tablets. If $n > 0.89$ then Super case II or Zero order release Kinetics will be observed. If $n = 0.45$ then drug is released with a Fickian diffusion mechanism from the matrix tablets and when $0.45 < n < 0.89$ then release of drug will be of anomalous or non-Fickian diffusion mechanism.

Difference Factor (f_1) and Similarity Factor (f_2)

Difference factor (f_1) and similarity factor (f_2) were adopted by FDA centre for drug evaluation and research (CDER) ¹⁴ for assessing the similarity between two *in vitro* dissolution profiles. In our study the f_1 and f_2 were determined for all formulations by comparing the release profile of test matrix tablets with that of the standard Tramadol HCl immediate release capsules (purchased from market).

Difference factor f_1 is used for the calculation

of percent difference between the two dissolution profile at each time point and relative error between the two curves.

The similarity factor f_2 is a logarithmic reciprocal square root transformation of the sum of squared error and is measurement of the similarity in the percent dissolution between the curves ¹⁴. Formulas for Difference factor f_1 and similarity factor f_2 are given by Eqs. [10] and [11].

$$f_1 = \left\{ \frac{3 |R - T|}{\sqrt{3R}} \right\} C 100 \quad [10]$$

$$f_2 = 50 \log \left\{ \frac{1 + 1/n \sum_{i=1}^n (R_i - T_i)^2}{\sum_{i=1}^n (R_i - T_i)^2} \right\}^{0.5} \times 100 \quad [11]$$

If f_1 value is 0 and f_2 value is 100 then it means that the test and reference profiles are identical but as f_1 value increases and f_2 value decreases the dissimilarity between the profiles increases ¹⁵. According to FDA proposal two dissolution profiles will be considered similar if f_2 ranges between 50 and 100 and the f_1 values lies between 0-15.

RESULTS AND DISCUSSION

Melting point determination method was used for the identification of TH according to British Pharmacopeia 10. The recorded melting point of TH was 185 ± 1.5 °C which complied with the acceptability set out in the BP. The percentage purity of TH calculated was $99 \pm 0.5\%$.

Flow properties of Powders and Granules

The angle of repose, compressibility index and Hausner's ratio of the mixture of the powders of selected formulation was 47 ± 2 °, 28 ± 1.35 and 1.42 ± 0.05 , respectively. These results didn't comply with USP limits ¹⁶ and showed a poor flow and compressibility properties of the simple mixture of the ingredients hence direct compression method cannot be used. Contrary to the above results angle of repose, compressibility index and Hausner's ratio of the prepared granules of the same formulation was 29 ± 1.3 °, 28 ± 1.35 and 1.10 ± 0.03 , respectively which were within official USP limits ¹⁶ and indicated good flow properties of the granules. These results indicate dry granulation method can be used for the tablet preparation as the flow properties of the granules were satisfactory.

Physicochemical Evaluation

All tablets were smooth and elegant in appearance. The acceptable ranges of diameter and thickness are 4-13 mm and 2-4 mm, respec-

tively. The USP range for hardness and friability is 5-10 kg/cm³ and 0.8%, respectively, and the drug content uniformity's USP limits are 90-110%¹⁶. The prepared matrix tablets in this research work had a diameter ranging between 8 ± 0.01 to 8 ± 0.05 mm. Thickness of the prepared matrix tablets was 2.7 ± 0.03 to 2.7 ± 0.06 mm. Hardness ranged between 6.9 ± 0.13 to 7.8 ± 0.23 Kg/cm². Friability of the prepared tablets was 0.15 ± 0.01 % to 0.37 ± 0.03%. The content uniformity was 99 ± 0.05 to 102 ± 1.2. These results showed that all the physicochemical tests of the prepared matrix tablets were within the limits.

In Vitro Drug Release Profile

Ethocel 100 P was used along with its finely milled 100FP form at four different drug to Polymer ratios (10:1, 20:2, 10:3, and 10:4) in this research work.

Effect of Particle Size of Ethocel on the Release Profile TH

Fig. 1 shows the release profile of TH from Ethocel matrices and explains the effect of particle size of Ethocel on the release rate of TH from the matrix tablets. Tablets having Ethocel 100P as the rate controlling agent exhibits a faster release rate as compared to that of the matrices having finely milled Ethocel 100 FP. Thus the use of Ethocel FP Premium polymers extends TH release more efficiently than the conventional granular form of the polymer. This shows that the particle size of the polymer has a role in controlling the release rate. As the particle size is decreased so will be the porosity decreased and the drug will be entrapped for a longer time in the matrix. Our results are in con-

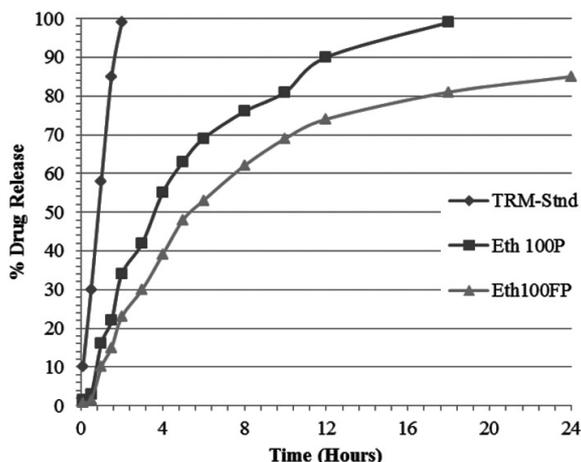


Figure 1. Release profile of Tramadol HCl from matrix tablets having drug to polymer ratio 10:4.

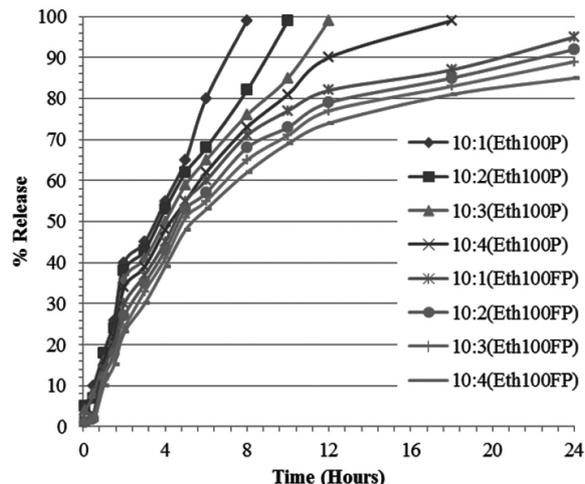


Figure 2. Dissolution Profile of Tramadol HCl from various formulations.

firmation to the results of Shefaat *et al.*⁸ and Akhlaq *et al.*¹⁷.

Effect of Drug to Polymer ratio on the Release Profile of TH

Fig. 2 shows the % drug release verses time graph at different drug to polymer ratios of TH of granular grade of Ethocel (100P) and finely milled form (100FP). The drug to polymer ratios were 10:1, 10:2, 10:3, and 10:4. The graph clearly shows that as the concentration of either of the polymer is increased, the release rate will decrease. The formulation having polymer Ethocel 100P at D:P of 10:2 showed 100% of the drug released after 9 h. The percent drug released from Ethocel 100P at a D:P of 10:4 was 100% after 18 h. Similarly in the case of Ethocel 100FP, as the polymer concentration increases, there was a decrease in drug release rates.

This effect of the D:P ratio may be due to a reason that at higher concentration of Ethocel the matrix may be stronger compared to the formulation containing low amount of the polymer. The matrix tablets with higher amount of Ethocel would allow less water or solvent penetration through the micropores and that will result in a slower release rate. Our findings are in confirmation with those of Velasco *et al.*¹⁸ and Shefaat *et al.*⁸. Khan & Maiden¹⁹ reported that a matrix with higher polymer ratios would cause decrease in size and an increase in the diffusional path length.

Effect of Different Co-Excipients on the Release Profile of TH from the Matrix

Co-excipients like HPMC, Starch and CMC

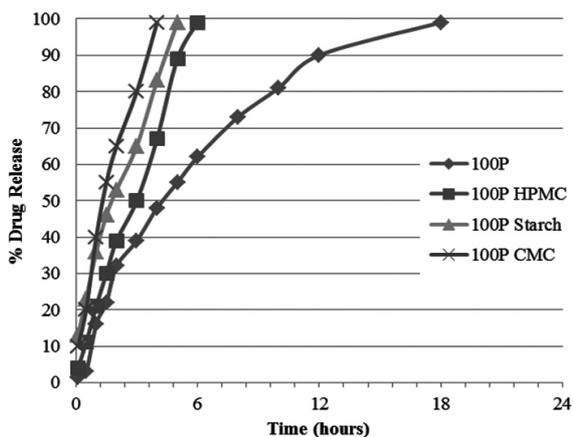


Figure 3. Dissolution profile of Tramadol HCl from matrix tablets having Polymer Ethocel 100P.

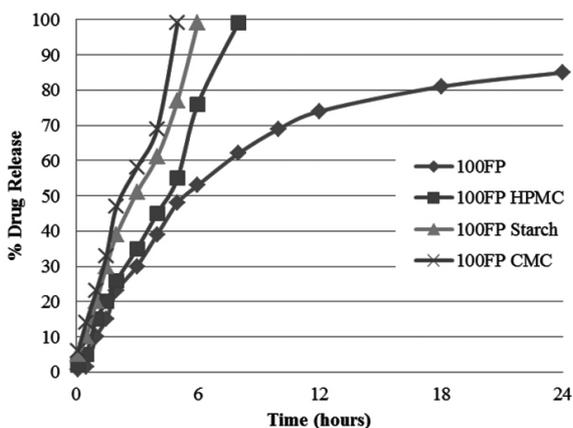


Figure 4. Dissolution profile of Tramadol HCl from matrix tablets having Polymer Ethocel 100FP.

was added to matrix tablets formulation by replacing 30 % of the filler (Table 1). The drug to polymer ratio was 10:4. Figs. 3 and 4 show the effect of the different co-excipients (HPMC, Starch and CMC) on the release profile of TH from the matrix tablets containing Ethocel 100P and 100FP Premium respectively. These figures show a comparison between the %drug release without the co-excipients and with co-excipients. Both these figures show that there was a great change in the release rate when the Co-Excipients were added: e.g. in Fig. 3, 100 % of drug released from the matrix tablets having Ethocel 100 Premium as the rate controlling agent in more than 12 h but when the co-excipients like HPMC, starch and CMC were added to the formulation, nearly 100 % of the drug released within 3-4 h. Similar results can be seen with Ethocel 100FP Premium.

As HPMC can create osmotic pressure within

the matrix system due to which water penetrates into the matrices. This may be the cause of higher release rate of TH from the matrix tablets when HPMC was used as co-Excipient. Similar results were reported by Gohal *et al.*²⁰ and Khan & Zhu⁷. These authors also claimed that HPMC in small quantity can act as a channelling agent and can increase the release rate.

Starch is insoluble in water. This water insoluble nature of starch might have caused non uniformity of the polymeric material around the drug due to which membranes may have been distorted and resulted in a quick release of drug from the polymer. Starch is water swellable in nature which also might be a reason for the fast release rate^{7,8}.

The reason for faster release behaviour from the matrix tablets when CMC was used as Co-Excipient may be attributed to the lower viscosity of CMC that cause low swellability and fast dissolution and erosion of the diffusion gel layer²¹. Shah & Jarwoski²² showed that the fast release from CMC may be due to its disintegrating property. Khan & Zhu⁷ attributed this effect of CMC to its water soluble properties due to which CMC may break up the polymeric membrane around the drug because of the creation of osmotic forces within the matrices.

Figs. 3 and 4 also showed that release rate from the matrix tablets containing HPMC were somewhat slower than those that contained Starch and CMC. This extended release might be due to the less hydration capacity of HPMC^{9,23}.

Release Kinetics of Tramadol HCl- Ethocel Matrix Tablets

For the interpretation of the release of TH from the prepared matrix tablets Eqs. [5-9] were used. Table 2 shows the *n* values for the power law of the formulated matrix tablets⁹ and rate constants, *r*² for zero, first order, Higuchi and Hixon Crowels equations. The formulations showed diffusional exponent value *n* between 0.631 and 0.504 for tablets without co.excipients and tablets having co-excipients have *n* values less than 0.45. This is an indication that the formulations without the co.excipients followed non-Fickian anomalous release (*n* = 0.46-0.89). It is therefore clear that the drug is released by diffusion coupled with swelling and erosion mechanism^{7,9}. Table 2 indicates that formulations having TH and Ethocel 100FP with a drug to polymer ratio of 10:4 showed the best release kinetics as this formulation has the highest value of *n* (0.631).

D:P ratio	Zero order	First order	Higuchi	Hixon Crowell	Korsmeyer	
	R1	R2	R3	R4	R5	n
Controlled release tablets of TH -Ethocel® 100P						
10:1	0.8875	0.4926	0.9890	0.9940	0.9893	0.522
10:2	0.9894	0.5874	0.9963	0.9977	0.9886	0.514
10:3	0.87563	0.4893	0.9850	0.9456	0.8993	0.538
10:4	0.8775	0.6893	0.9945	0.9843	0.8991	0.501
Controlled release tablets of TH -Ethocel® 100FP						
10:1	0.8923	0.7786	0.9757	0.9891	0.9894	0.611
10:2	0.91293	0.7982	0.9784	0.9935	0.9675	0.601
10:3	0.9639	0.8653	0.9812	0.9783	0.9958	0.532
10:4	0.9658	0.6923	0.9182	0.9893	0.9896	0.631
Controlled release tablets of Tramadol -Ethocel® 100P (D:P= 10:4)						
HPMC	0.7643	0.8738	0.8339	0.7628	0.8374	0.433
Starch	0.1584	0.8829	0.4720	0.3529	0.4922	0.138
CMC	0.1394	0.8748	0.3028	0.5627	0.5022	0.193
Controlled release tablets of Tramadol -Ethocel® 100FP (D:P= 10:4)						
HPMC	0.7672	0.8328	0.8384	0.9738	0.9473	0.432
Starch	0.4145	0.752	0.3442	0.4933	0.6542	0.231
CMC	0.2432	0.752	0.2481	0.534	0.7932	0.254

Table 2. Drug Release kinetics of Tramadol HCl matrix tablets Applying Dissimilarity Factor f_1 and Similarity Factor f_2 .

S/No	Polymer	D:P Ratio	Co-Excipients	f_1 value	f_2 value
1	Ethocel 100 P	10:1	-	67.38	12.28
2	Ethocel 100 P	10:2	-	67.29	13.54
3	Ethocel 100 P	10:3	-	65.21	18.02
4	Ethocel 100 P	10:4	-	64.22	15.67
5	Ethocel 100 FP	10:1	-	70.38	14.91
6	Ethocel 100 FP	10:2	-	70.27	16.28
7	Ethocel 100 FP	10:3	-	73.91	13.27
8	Ethocel 100 FP	10:4	-	72.91	15.52
9	Ethocel 100 P	10:4	HPMC	48.19	24.98
10	Ethocel 100 P	10:4	Starch	24.28	43.00
11	Ethocel 100 P	10:4	CMC	19.37	45.24
12	Ethocel 100 FP	10:4	HPMC	49.53	23.09
13	Ethocel 100 FP	10:4	Starch	31.75	36.76
14	Ethocel 100 FP	10:4	CMC	25.82	38.09

Table 3. f_1 and f_2 values for different formulations of Tramadol HCl matrix tablets.

While comparing the release profiles of TH matrix tablets the reference conventional formulations, the values of f_1 were higher than 15 (Range 0-15), and the values of f_2 were less than 50, that clearly indicates the difference between the release profiles of drug from the test and the reference standard formulation. The formulation having Co-excipients have higher f_2 and lower f_1 values but still in the dissimilar range. The values of f_1 and f_2 values for the various formulations are given in Table 3.

CONCLUSION

The matrix tablets prepared in this research work showed an extended release profiles with Ethocel 100 P and 100FP. The decrease in the particle size and increase in the amount of polymer results in a more extended release of the drug. Thus Ethocel 100 Premium and 100FP Premium can be successfully used as rate controlling agents for Tramadol HCl. Moreover, the matrix tablets with different co-excipients showed an enhanced drug release rates.

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