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Formulation Development and Evaluation of Compressed Mini-Tablets of Tramadol HCl as a Biphasic Drug Delivery System.

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ABSTRACT

Mini tablets are defined as tablets with a diameter of 3 mm or less. In compressed mini -tablet system mini tablets acts as a multiple unit dosage form in a single unit dosage forms. Tramadol hydrochloride is BCS class I drug selected for the biphasic delivery system. The weighed amount of fast releasing component placed in the die along with mini-tablets compressed in to the single tablets by using 12 mm punch. The weight of the compressed mini-tablets was 750 mg. Two different ratios of fast releasing component and mini-tablets were prepared. The results show that the release profile is strongly dependent on the number and polymer composition of mini-tablets. The results of testing both HPMC and EC indicate that the HPMC release the drug with in the 8 hours but the EC containing formulations shows the sustained release upto 12 hours. Hydrophilic matrix of HPMC could sustain the drug release only upto 8 hours. It is evident that a hydrophobic matrix of EC is a better system for sustained delivery of a highly water soluble drugs like Tramadol hydrochloride for prolonged period. The 6 number of mini-tablets containing compressed mini-tablet formulation (CMT4) shows better sustained release, *f*2 value and the other characteristics, compare to the CMT3 (containing 12 mini-tablets).

Keywords: Mini-tablet, f2 value, Compressed mini-tablet, Hydrophilic & Hydrophobic polymers, Matrix tablets.

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INTRODUCTION

Mini tablets are defined as tablets with a diameter of 3 mm or. In compressed mini tablet system mini tablets acts as a multiple unit dosage form in a single unit dosage forms. Multiple unit dosage form which has definite advantages over single unit dosage forms. These advantages are less risk of dose dumping, less inter and intra subject variability, high degree of dispersion in the digestive tract thus minimizing the risks of high local drug concentrations.

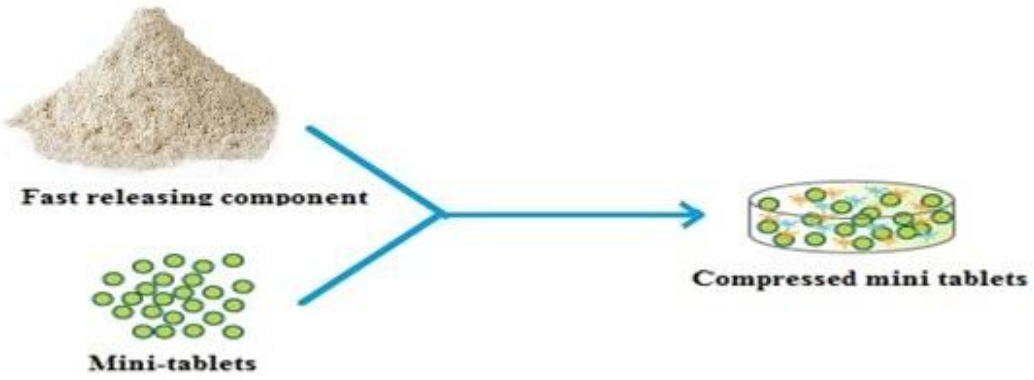

Figure 1: Mini-tablets delivered as a tablet

Tramadol hydrochloride is BCS class I drug (high solubility, high permeability). Because of high solubility and high permeability of drug its therapeutic index, duration of action, half-life (5.5 hrs) very less although it showing more toxic effects because of more drug concentration. Multiple dose administration at intervals of 6 hours is difficult for a patient suffering from postoperative or cancerous pain leading to patient noncompliance. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of Tramadol hydrochloride is desirable to overcome such problems in present work compressed mini-tablet system was select as a method to control the drug release [1-12].

METHODS [13-24]

Preparation of the Compressed Mini-Tablets

The composition of mini-tablets and compressed mini-tablets of the different formulations was given in the Tables 1 & 2.

Preparation of fast release component

The fast releasing component consist of drug along with super disintegrant and excipients. Sodium starch glycolate was used as a super disintegrant. Required amount of drug, super disintegrant, excipients were taken and blended.

Preparation of min-tablets

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The mini-tablets were prepared by using two different polymers individually. The formulations contain HPMC K100M and Tramadol hydrochloride was taken 1:1 ration and EC and Tramadol hydrochloride was taken 1:5 ratios. The mini-tablets were prepared by direct compression method by using 3 mm curved punch.

Table 1: composition of mini-tablet formulations

COMPOSITION (Mg)	FORMULATION CODE			
	MT1	MT2	MT3	MT4
Tramodol hydrochloride	12	12	15	15
HPMC K 100M	12	12	-	-
EC	-	-	9	9
Number of mini-tablets	12	6	12	6

Preparation of compressed mini-tablets

The biphasic delivery system was prepared by using fast releasing component and mini-tablets. The weighed amount of fast releasing component placed in the die along with mini-tablets compressed in to the single tablets by using 12 mm punch.

The weight of the compressed mini-tablets was 750 mg. Two different ratios of fast releasing component and mini-tablets were prepared (462/288 and 606/144).

Table 2: Composition of Biphasic Compressed Mini-Tablet Formulations

COMPOSITION (Mg)	FORMULATION CODE			
	CMT 1	CMT 2	CMT 3	CMT 4
Fast release component (Weight/biphasic system)				
Tramadol hydrochloride	120	180	120	180
Avicel pH 102	337	420	337	420
Sodium starch glycolate	5	6	5	6
Prolonged release component				
Number of mini-tablets/biphasic system	12	6	12	6
Mini-tablet composition (Weight/mini-tablet)				
Tramodol hydrochloride	12	12	15	15
HPMC K 100M	12	12	-	-
EC	-	-	9	9

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Figure 2: Mini-tablets.

Figure 3: Compressed mini-tablet.

FRACTURE SURFACES OF THE COMPRESSED MINI-TABLETS.

Figure 4: CMT1 (12 mini-tablets)

Figure 5: CMT2 (6 mini-tablets)

Characterization of Tablets

The properties of the mini-tablets, compressed mini-tablets such as Thickness, Hardness, and Friability, Weight variation, Drug content uniformity and *Invitro* release kinetic studies were studied.

Statistical Analysis

Statistical evaluation of the different properties of the formulations was performed, using the one-way analysis of variance (ANOVA), along with the Tucky post test. For this purpose GraphPad Instat software version 3.0.1 was used.

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Comparison of Dissolution Profiles by Using Similarity Factor *F2* Value

To describe the properties of the similarity factor (*f*2) as a measure for assessing the similarity of two dissolution profiles. In general, a single point dissolution test does not characterize the dosage form completely, and therefore the dissolution profile and dissolution profile comparison is recommended in recently released guidances by the agency. For the post-approval changes such as: The similarity factor *f*2 as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products (Mukesh et al., 2002).

RESULTS

Physical Evaluation Parameters of Mini-Tablets

Tramadol hydrochloride mini tablets were evaluated for various physical parameters namely thickness, hardness, friability, weight variation, etc.

Thickness

The thickness of HPMC and EC mini-tablets are respectively 0.96±0.11 mm and 0.81±0.05 mm.

Hardness test

The hardness of HPMC and EC mini-tablets are respectively 3.62±0.02 Kg/cm^2 and 3.91±0.01 Kg/cm^2.

Friability test

The percentage friability of HPMC and EC mini-tablets are respectively 0.806% and 0.718%.

Weight variation test

The percentage weight variations for all formulations are performed. Both the formulations passed weight variation test as per the pharmacopial limits of 10%.

Drug content uniformity

Drug content uniformity of HPMC and EC mini-tablets shows 99.68±0.13% and 99.76±0.24%.

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***In vitro* drug release characteristics of mini-tablets**

The min-tablets were prepared by using drug with HPMC and EC, *in vitro* drug release studies were carried out in trial (n=3) basis. Total two formulations were studied by dividing into 12, 6 mini-tablets of HPMC (MT1, MT2) and 12, 6 tablets of EC (MT3, MT4) individually.

The release of Tramadol hydrochloride from the mini-tablets was studied in 900 ml of 0.1 N HCl (pH 1.2) for 2 hrs and in pH 6.8 phosphate buffer upto 12 hrs as dissolution mediums using USP XXIII paddle dissolution apparatus at 50 rpm and $37^0 \pm 0.5^0$ C. Drug content was determined by UV-Visible spectrophotometer at 271 nm. Cumulative percentage of drug release was calculated by using an equation obtained from a standard curve. The dissolution studies were performed 3 times for a period of 12 hrs and mean values were calculated. The results of studies were shown in table 3

Table 3: **Comparative *In Vitro* Drug Release Of All Mini-Tablet Formulations.**

Time (min)	Cumulative % drug release*			
	MT1	MT2	MT3	MT4
0	0	0	0	0
30	16.46±1.00	15.18±1.06	12.06±0.56	19.48±0.93
60	28.13±1.13	26.00±1.00	20.80±0.84	24.86±0.59
120	43.64±0.40	43.83±0.97	31.30±1.63	30.31±0.62
180	56.31±1.17	55.00±1.05	44.81±0.91	40.73±0.69
240	65.18±0.92	64.50±0.15	52.06±0.40	46.66±0.90
300	71.37±1.24	70.42±0.44	59.34±1.11	53.18±0.91
360	83.77±2.11	83.78±1.19	65.18±1.62	61.71±0.88
420	89.40±0.59	91.37±0.93	75.48±1.26	72.40±1.46
480	96.31±1.14	98.12±0.31	82.24±0.36	80.11±0.46
600	-	-	88.73±0.94	88.64±0.53
720	-	-	93.73±1.29	96.13±0.77

*Each value represents the mean±S.D. of three experiments

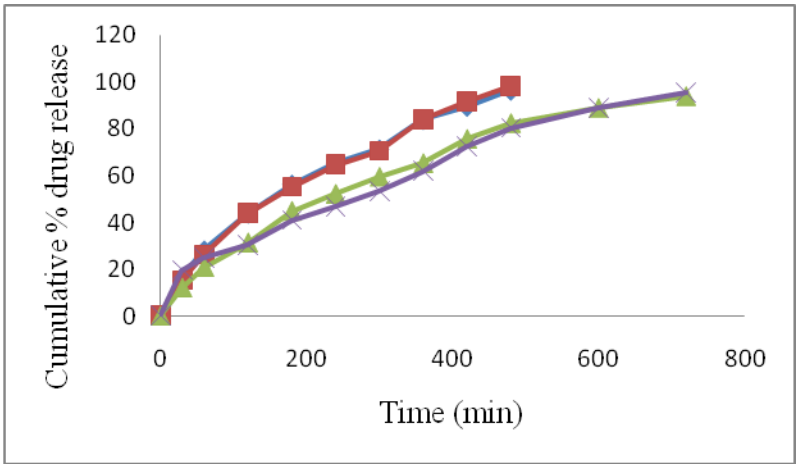

Figure 5: Comparative *In vitro* drug release patron of MT1 (), MT2 (), MT3 () and MT4 ().

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Table 4: Kinetic Values Of Mini-Tablet Formulations.

Formulation Code	Zero order plot	First order plot	Higuchi's plot	Koresmeyer/Peppa's plot		Mechanism of drug release
	R^2	R^2	R^2	n	R^2	
MT1	0.952	0.931	0.993	0.624	0.995	Non-Fickian release
MT2	0.961	0.874	0.989	0.661	0.994	Non-Fickian release
MT3	0.935	0.984	0.989	0.656	0.994	Non-Fickian release
MT4	0.959	0.936	0.980	0.528	0.972	Non-Fickian release

Physical Evaluation Parameters of Compressed Mini-Tablets

Tramadol hydrochloride compressed mini tablets were evaluated for various physical parameters namely thickness, hardness, friability, weight variation, etc.

Thickness

The thickness of all formulations ranged from 6.14±0.15 mm to 6.22±0.08 mm.

Hardness test

The hardness of all batches ranged from 3.33±0.28 Kg/cm^2 to 4.08±0.14 Kg/cm^2 .

Friability test

The percentage friability of all batches ranged from 0.263% to 0.798%.

Weight variation test

The percentage weight variations for all formulations are performed. All the formulations passed weight variation test as per the pharmacopeia limits of 5%.

Drug content uniformity

Drug content uniformity all batches ranged from 98.34±0.23 to 99.29±0.62.

***In vitro* drug release characteristics of compressed mini-tablets**

The compressed min-tablets were prepared by using drug with HPMC and EC, *in vitro* drug release studies were carried out in trial (n=3) basis for total four formulations (CMT1, CMT2, CMT3, CMT4). The release of Tramadol hydrochloride from the compressed mini-tablets was studied in 900 ml of 0.1 N HCl for 2 hrs and in pH 6.8 phosphate buffer upto 12 hrs as dissolution mediums using USP XXIII paddle dissolution apparatus at 50 rpm and 37^0±0.5^0 C and

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drug content was determined by UV-Visible spectrophotometer at 271 nm. The results of studies were shown in table 6.

Table 6: Comparative *In Vitro* Drug Release Of All Compressed Mini-Tablet Formulations

Time (min)	Cumulative % drug release			
	CMT1	CMT2	CMT3	CMT4
0	0	0	0	0
5	11.37±0.50	14.64±1.00	19.96±0.57	9.32±0.63
10	14.31±0.26	20.71±0.78	25.2±1.08	15.38±0.62
15	20.73±0.33	25.00±1.10	28.5±0.90	20.94±1.89
20	24.88±1.22	28.25±0.81	33.0±0.68	27.31±1.30
25	32.72±1.33	36.78±1.34	40.50±0.63	34.89±1.35
30	39.26±1.30	52.14±1.01	48.60±1.07	40.13±1.67
60	52.15±2.47	59.64±0.62	57.60±1.15	50.68±1.97
120	58.29±0.42	72.50±0.62	66.13±0.33	58.10±1.90
180	61.36±0.79	76.78±1.32	69.30±0.66	66.73±0.69
240	68.52±1.37	79.28±1.72	72.90±1.08	69.64±0.28
300	77.04±0.77	82.50±0.68	76.50±1.00	73.50±2.34
360	81.11±0.93	87.85±1.72	78.73±1.66	75.18±0.91
420	86.25±0.89	91.42±1.12	81.00±1.00	81.32±0.46
480	88.97±0.70	99.28±0.94	82.00±0.66	85.69±1.46
600	97.15±0.98	-	86.10±0.78	90.06±0.84
720	-	-	90.00±1.22	94.82±1.09

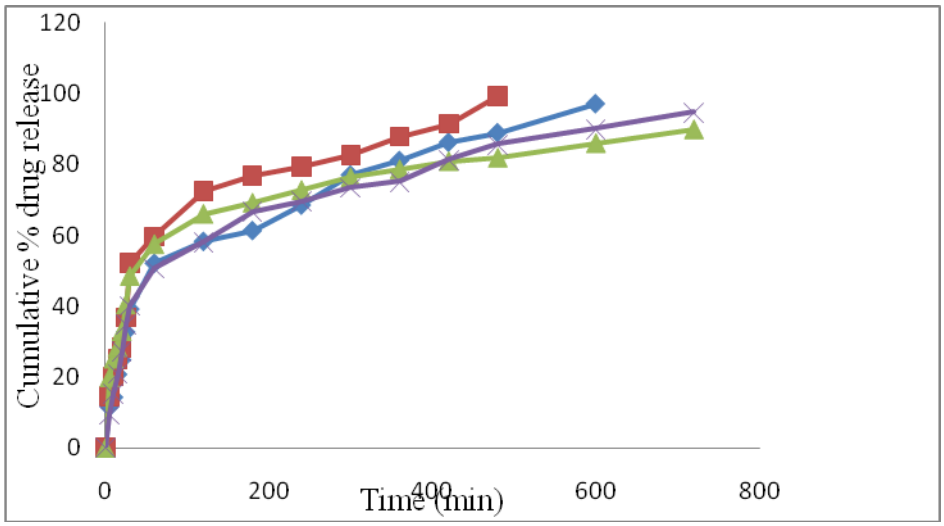

Figure 6: Comparative *In vitro* drug release patron of CMT1 (), CMT2 (), CMT3 (), CMT4 ().

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Table 7: **Kinetic Values Of Compressed Mini-Tablet Formulations.**

Formulation code	Zero order plot	First order plot	Higuchi's plot	Koresmeyer-Peppa's plot		Mechanism of drug release
	R^2	R^2	R^2	n	R^2	
CMT1	0.844	0.953	0.960	0.425	0.952	Non-Fickian release
CMT2	0.781	0.937	0.921	0.397	0.936	Non-Fickian release
CMT3	0.707	0.910	0.885	0.293	0.949	Fickian release
CMT4	0.793	0.970	0.939	0.412	0.929	Non-Fickian release

Comparison of Dissolution Profiles by Using Similarity Factor *F2*

The comparison of dissolution values of pre change batch (min-tablets) and post change batch (compressed mini-tablets) shows the similarity as given in the table 8.

Table 8: **Similarity Factor *F2* Values.**

S. No	Comparison	*f*2 value	Dissolution profile
1.	MT1 and CMT1	64.81	similar
2.	MT2 and CMT2	67.72	Similar
3.	MT3 and CMT3	79.75	Similar
4.	MT4 and CMT4	78.50	Similar

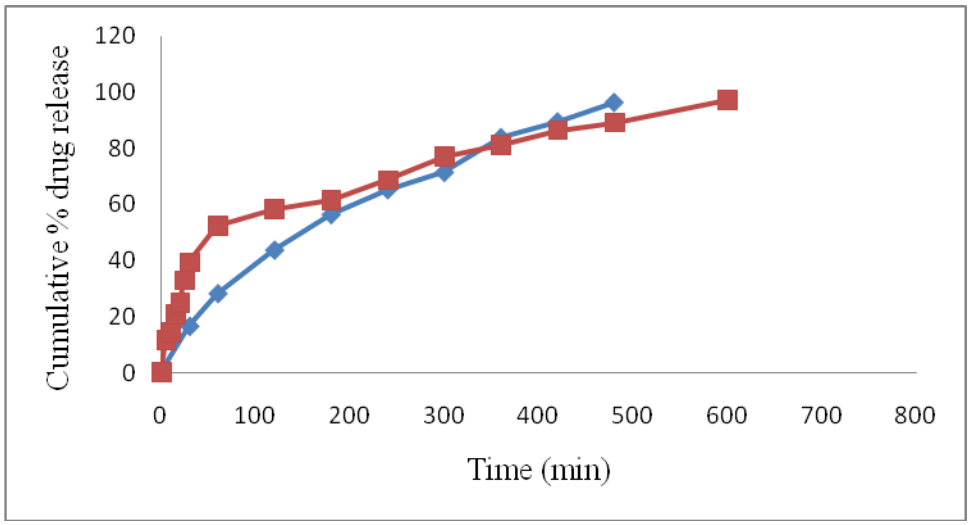

Figure 7: Comparative *In vitro* drug release patron of MT1 (), CMT1 ().

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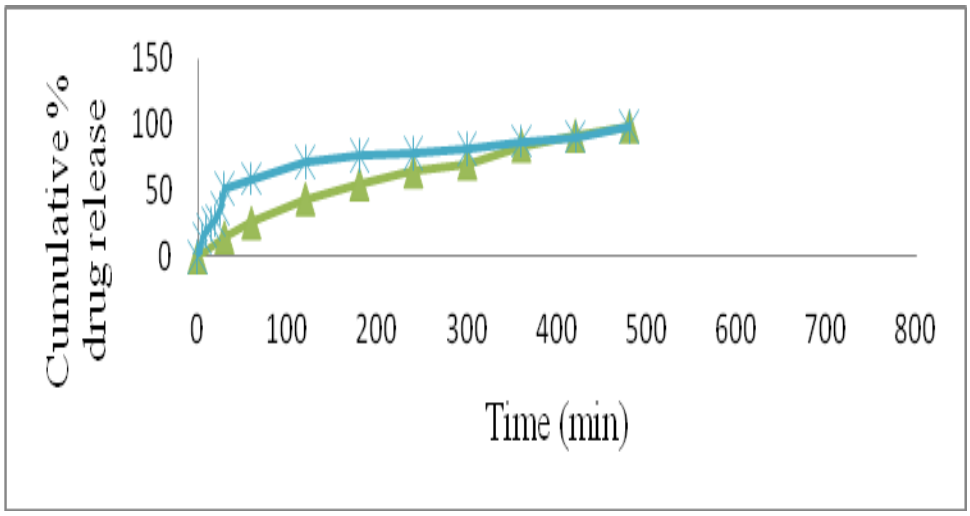

Figure 8: Comparative *In vitro* drug release patron of MT2 (), CMT2 ().

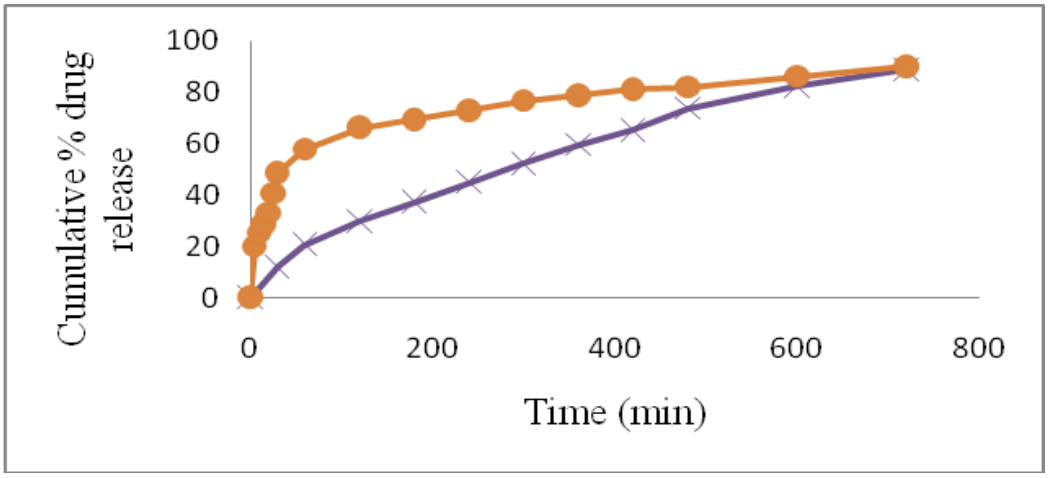

Figure 9: Comparative *In vitro* drug release patron of MT3 (), CMT3 ().

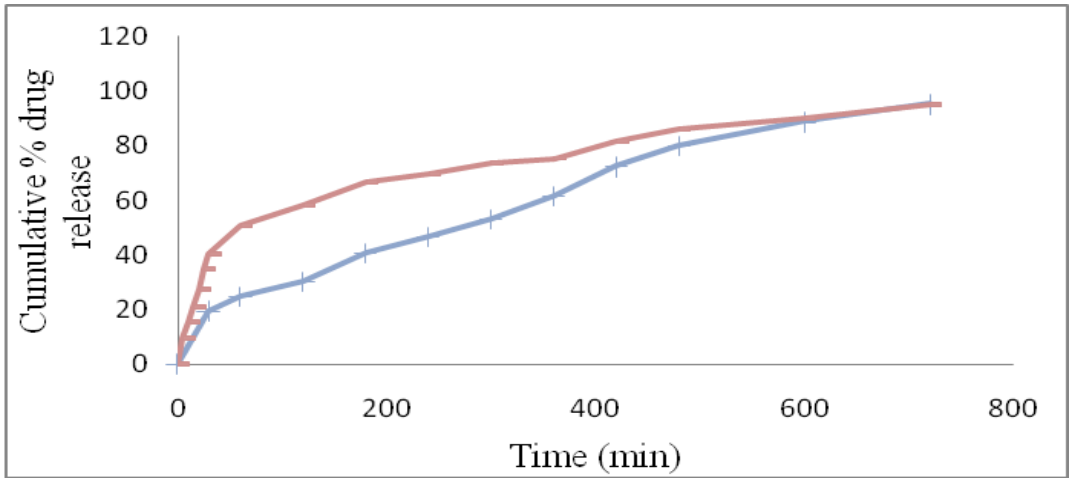

Figure 10: Comparative *In vitro* drug release patron of MT4 (), CMT4 ().

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CONCLUSION

In conclusion the results show that the release profile is strongly dependent on the number and polymer composition of mini-tablets. The results of testing both HPMC and EC indicate that the HPMC release the drug with in the 8 hours but the EC containing formulations shows the sustained release upto 12 hours. Hydrophilic matrix of HPMC could sustain the drug release only upto 8 hours. It is evident that a hydrophobic matrix of EC is a better system for sustained delivery of a highly water soluble drugs like Tramadol hydrochloride for prolonged period. The 6 number of mini-tablets containing compressed mini-tablet formulation (CMT4) shows better sustained release, *f*2 value and the other characteristics, compare to the CMT3 (containing 12 mini-tablets).

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