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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF TRAMADOL HCL

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ABSTRACT: The objective of this work was to develop sustained release tablets of highly water soluble Tramadol HCl using polymers (HPMC K100M, HPMC K15M, HPMC K 4M) as cost effective, non toxic easily available and suitable hydrophilic matrix system. Sustained release tablet of Tramadol HCl (dose 50mg) were produced by wet granulation method. After the evaluation of physical characteristics of tablets. The dissolution test was performed in 0.1 N HCl for two hr. and phosphate buffer pH 6.8 for ten hr. The release profile remains unchanged after three months storage of tablets. The best fit release kinetics was achieved with the zero order plot followed by the Higuchi and Korsmyer and Peppas equation. The data obtained proved that the formulations are useful for a sustained release of Tramadol HCl due to the percentage released after 12 hr. is nearly to 100%.
Key words: - Hydroxy propyl methyl cellulose, Tramadol hydrochloride, Microcrystalline cellulose.

INTRODUCTION

Hydrophilic matrices containing swellable polymers are referred to as hydrogel matrices, swellable sustained release system or hydrophilic matrix tablets. A number of polymers have been investigated to develop in situ gel forming systems due to ability of these hydrogels to release an entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and cross linking[1, 2, 3]. Hydroxy Propyl Methyl Cellulose (HPMC) is the polymer most widely used as the gel forming agent in the formulation of sustained release dosage form. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from these dosage form are controlled by the hydration of HPMC which forms a gel barrier through which the drug diffuses[4, 5]. The adjustment of the polymer concentration, the viscosity grade and the addition of different types and levels of excipientes. The HPMC matrix can modify the drug release rate[6]. Tramadol is used in the treatment of osteoarthritis when nonsteroidal antiinflamatory drug (NSAIDS), acetaminophen, or cox-2 inhibitors alone produce inadequate pain relief[7]. After oral administration, Tramadol is rapidly and

almost completely absorbed. Sustained release tablets reach to peak concentration after 4.9hr and have a bioavailability of 87%-95%. The mean elimination half life is approx 6 hours[8] and requires dosing every 6 hours in order to maintain optimal relief of chronic pain[9,10] Consequently once daily extended release tablets have been formulated. Long term treatment with sustained release Tramadol once daily is generally safe in patients with osteoarthritis or refractory low back pain and is well tolerated[11, 12]. It has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep and improved compliance[13].

MATERIALS AND METHOD

Materials

Tramadol Hydrochloride, Hydroxy Propyl Methyl cellulose K100M, Hydroxy Propyl Methyl cellulose K15M, Hydroxy Propyl Methyl cellulose K4M, Lactose, Microcrystalline cellulose (Avicel pH 101), PVP K 30, Magnesium Stearate, Talc was obtained as laboratory sample from Merck chemicals pvt. Ltd

Formulation of SR Tramadol HCl matrix tablet

Weight accurately Drug with HPMC K100M and HPMC K15M, HPMC K4M, lactose and microcrystalline cellulose, pass through 40 no. sieves and mix it properly for 3 to 5 minutes in a steel tub. Prepare binder solution by dispersing PVP K30 in isopropyl alcohol. Granulation of above mixture is done by prepared binder solution by kneading up to granulation end point is obtained (Dough mass) .Pass the dough mass through 12 mess and keep it in a tray dryer for drying and finally keep the loss on drying (LOD) up to 2-3 %.Remove the dried granules from oven and pass through 20 mess sieve to get optimum size granules. Lubrication is done by using Magnesium stearate and talc previously passed through 60 mess sieve of the granules for 3 to 4 min. in a steel tub and then in polybag.Compression is done by suing 16 station single rotary CADMACH machine by using 6.3 mm standard concave circular punch.

Evaluation of Granules[14]

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 graduated cylinder was closed with lid, set into the density determination apparatus . The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the following formulas,

Bulk density = W/V_o

Tapped density = W/V_f

Where

V_o =initial Volume

V_f = final Volume

Compressibility index

The Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interaction, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner Ratio. The compressibility index and Hausner ratio may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped})as follows :

Compressibility index = $\rho_{tapped} - \rho_{bulk} / \rho_{tapped} \times 100$

Hausner ratio = $\rho_{tapped} / \rho_{bulk}$

Loss on drying

Drying time during granulation was optimized depending LOD value. LOD of each batches were tested at 105 c for 2.5 minutes by using "Sartorius" electronic LOD apparatus.

Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\theta = h/r$

$\theta = \tan^{-1} h/r$

Where

h = height of pile

r = radius of the base of the pile

θ = angle of repose

Evaluation of Tablet[14]

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in Table 3 Percentage deviation allowed under weight variation

Table 3.

Percentage deviation allowed under weight variation test.	
Average weight of tablet (X mg)	Percentage deviation
X< 80 mg	10
80 < X < 250 mg	7.5
X > 250 mg	5

Friability

Twenty tables were weighed and placed in the Electorlab friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

% F = { 1- (Wt/W)} x 100

Where %F= friability in percentage

W = Initial weight of tablet

Wt = weight of tablet after revolution

Hardness

Hardness was measured using Monsanto hardness tester. For each batch ten tablets were tested.

Dimension

Twenty tables were randomly selected from each batch and there thickness and diameter was measured by using digital vernier calipers

Drug Content of Tramadol HCL by HPLC

Accurately weigh of 100 mg of Tramadol HCl reference Standard into a 100.0 ml volumetric flask, dissolve in methanol and dilute to volume. Accurately weigh an amount of tablet powder, equal to 100mg of Tramadol HCl, into a 100.0 ml volumetric flask, and add methanol to volume. Stirr during one night to allow the tramadol to dissolve. Centrifuge and inject (20 µl) the clear solution and % drug content of the filtrate was recoded at λmax of 271 nm with help of HPLC

***In-Vitro* dissolution study**[15]

The dissolution study was carried out first two hour in 0.1N HCl and another ten hour in 6.8pH phosphate buffer using USP XXIII dissolution test apparatus employing paddle stirrer. In this study one tablet containing 50 mg of tramadol was placed inside the 900 ml dissolution medium and speed of paddle was set at 100 rpm. Samples were (10ml) withdrawn at a particular time interval and same volume of fresh medium was replaced. The sample were analyzed for drug content against 0.1N HCl for first two hour and for another ten hour 6.8pH phosphate buffer as a blank at λmax 271 nm . The percentage drug release was plotted against time to determine the release profile.

Kinetic Study[16,17]

Further to understand the order and mechanism of drug release the data was subjected to various kinetic equations and plotted according to zero order, Higuchi and Korsymere's Peppas equation. The kinetic values obtained from different plots are listed in table no.5

STABILITY STUDY [18]

The batch T6 was selected as an optimum batch and the stability study was carried out at accelerated condition. Of 40°C/75 % RH condition for a period of three month.

Method

Ten tablets were individually wrapped using aluminum foil and packed in ambered color screw cap bottle and put at above specified condition in incubator for three months. After three month tables were evaluated for content uniformity and in- vitro drug release.

Observation

The results of stability study after three month are given in Table 7 & 8 the plot of cumulative % drug release v/s Time (hr) depicted as Fig. 3

Drug content: Comparative content uniformity of the tablet after three month stability.

RESULTS AND DISCUSSION

The sustained release tablet of Tramadol Hydrochloride were prepared by wet granulation method, They were evaluated for weight variation, drug content, friability, hardness, and thickness for all batches (T1 to T8). No significant difference was observed in the weight of individual tablets from the average weight. Tablet weights of all batches were found within recommended pharmacopoeia limits. The data of uniformity of content indicated that tablets of all batches had drug content within pharmacopoeia limits. The hardness of tablets of all batches is in acceptable limits. All the formulation showed % friability less than 1% that indicates ability of tablets to withstand shocks, which may encounter. No significant difference was observed in the thickness of individual tablet from the average weight. In Kinetic assessment the data was plotted according to Zero order shows R^2 (0.7467 to 0.9456) suggested the rate of drug released was followed zero order for HPMC batches. The data was fitted with Higuchi with R^2 (0.9907 to 0.9944) indicating the mechanism was diffusion controlled. To known the preciously whether the fickian and non-fickian. Release mechanism, the data was fitted to Korsmeyer's Peppas equation. It shows the n value lies in between 0.42 to 0.59 which indicates the fickian and non-fickian release or anomalous.

Table 1. ***Formulation of Batch T1 to T8***

Ingredients (mg)/tablet	Formulation No.							
	T1	T2	T3	T4	T5	T6	T7	T8
Drug	50	50	50	50	50	50	50	50
HPMC K 100M	-	-	8	10	8	8	10	10
HPMC K 15 M	10	15	5	-	-	3	4	6
HPMC K4 M	8	3	5	8	10	7	4	2
Lactose	21	21	21	21	21	21	21	21
Micro crystalline cellulose	20	20	20	20	20	20	20	20
PVP K 30	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3
Mg. Stearate	2	2	2	2	2	2	2	2
Total Weight	120	120	120	120	120	120	120	120

Table 2. ***Technological characterization of formulated Tramadol HCl powder blend****

B.No	Bulk density	Tapped density	Loss on Drying in %	Compressibility Index	Hausner Ratio	Angle of Repose(^{o})
T1	0.442 ±. 0.024	0.506 ± 0.014	1.7 ± 0.011	12.65 ± 0.015	1.14 ± 0.014	27^{o}±3
T2	0.486 ± 0.018	0.556 ± 0.026	1.2 ± 0.014	12.59 ± 0.022	1.14 ± 0.016	30^{o}±2
T3	0.529 ± 0.016	0.593 ± 0.021	1.5 ± 0.018	10.79 ± 0.021	1.12 ± 0.014	27^{o}±3
T4	0.512 ± 0.019	0.574 ± 0.025	1.4 ± 0.016	10.80 ± 0.019	1.12 ± 0.018	29^{o}±2
T5	0.544 ± 0.022	0.601 ± 0.022	1.4 ± 0.011	9.48 ± 0.014	1.10 ± 0.019	28^{o}± 2
T6	0.539 ± 0.017	0.586 ± 0.021	1.3 ± 0.013	8.02 ± 0.016	1.09 ± 0.021	26^{o}±3
T7	0.499 ± 0.018	0.564 ± 0.016	1.8 ± 0.017	11.52 ± 0.024	1.13 ± 0.022	27^{o}±3
T8	0.523 ± 0.018	0.602 ± 0.017	2.2 ± 0.012	13.12 ± 0.021	1.15 ± 0.017	26^{o} ±3

***All values are mean ± S.D. for n=3**

Table 4. ***Evaluation of tablets T1-T8***

B.No	Weight Variation (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg)	Friability (%)	Drug Content (%)
T1	120±0.97	6.21±0.03	2.34±0.05	5.50±0.50	0.62	101.65
T2	120±0.68	6.20±0.03	2.32±0.03	5.60±0.50	0.62	98.22
T3	120±0.05	6.23±0.02	2.33±0.04	5.40±0.30	0.42	103.99
T4	120±0.01	6.19±0.04	2.32±0.03	5.50±0.40	0.49	99.55
T5	120±0.84	6.22±0.03	2.31±0.04	5.30±0.50	0.65	96.98
T6	120±0.36	6.21±0.03	2.34±0.04	5.50±0.50	0.53	100.83
T7	120±0.14	6.20±0.02	2.32±0.03	5.60±0.30	0.67	96.42
T8	120±0.15	6.23±0.02	2.33±0.03	5.40±0.50	0.53	96.89

***All values are mean ± S.D. for n=3**

Table 5. ***Dissolution Profile of batch no. T1- T8***

B.No	Time in Hours (cumulative percentage drug release)						
	1	2	4	6	8	10	12
T1	44.32	70.46	92.03	101.53	-	-	-
T2	46.67	68.32	15.66	93.77	101.82	-	-
T3	30.12	44.74	62.05	72.31	81.30	89.12	96.34
T4	25.65	43.09	49.94	63.54	72.27	78.99	93.68
T5	29.80	36.24	56.90	71.82	84.42	100.3	-
T6	27.27	3.13	55.85	68.31	80.16	93.01	99.98
T7	14.32	23.43	36.20	51.63	60.43	65.72	74.81
T8	12.40	20.26	35.42	47.38	59.42	62.23	70.62

Table 6. ***Kinetic treatment of dissolution data for batch T1 - T8***

B. Code	Time in Hours (cumulative % drug release)			Release exponent (m)
	Zero order	Higuchi	Korsmeyer's	
T6	0.9381	0.9984	0.9993	0.53

Table 7. ***Drug content of optimized batch T6 kept for stability***

Time	Weight Variation (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg)	Friability (%)	Drug Content (%)
Initial	120±0.36	6.21±0.03	2.34±0.04	5.50±0.50	0.53	99.55
After three month	120±0.25	6.21±0.03	2.34±0.04	5.50±0.50	0.51	98.84

***All values are mean ± S.D. for n=3**

Table 8. ***Dissolution profile of optimized batch T6 kept for stability***

S.N	Time (hrs)	Cumulative % release	
		Initial	Three month
0	0	0	0
2	1	27.04	26.53
3	2	39.19	37.13
4	4	55.85	55.59
5	6	68.31	66.86
6	8	80.16	78.87
7	10	93.01	92.52
8	12	99.98	99.24

Figure 1: *In vitro* dissolution profile for T6

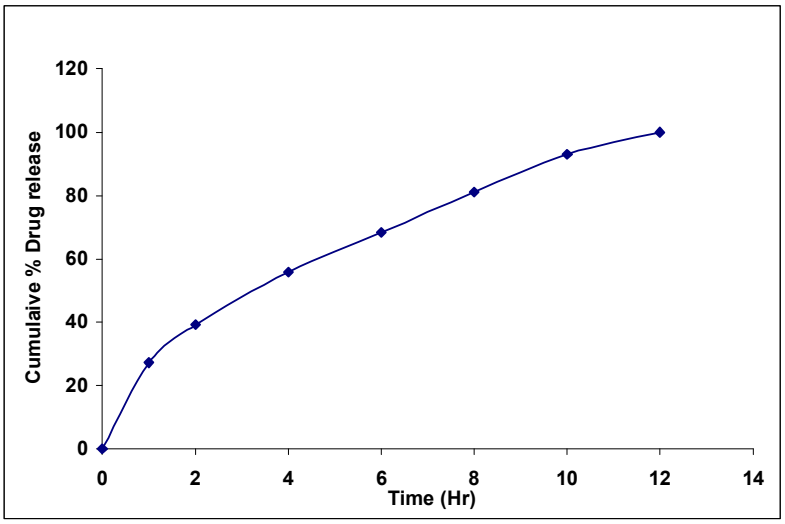


Figure 2: *In vitro* dissolution profile for T1 to T8

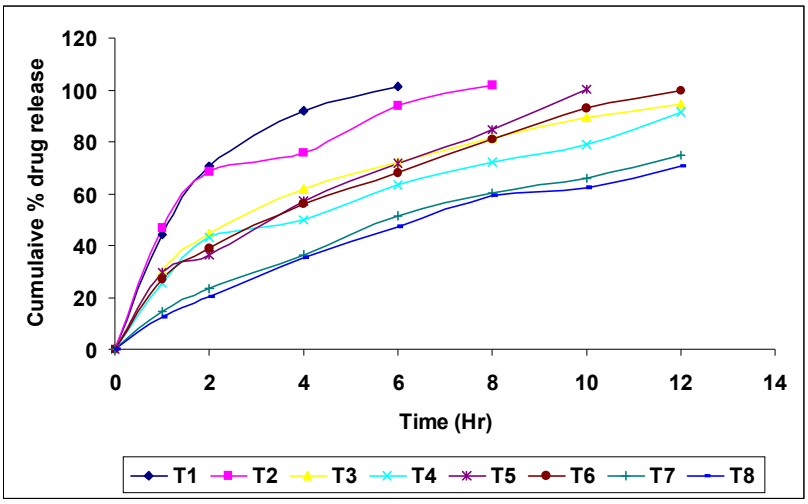
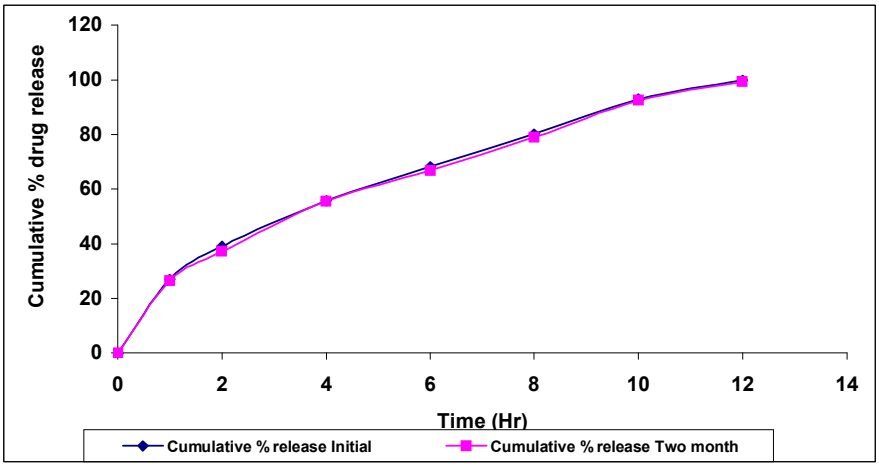


Figure 3: *in vitro* dissolution profile for T6 and stabilized batch



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