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Formulation and In Vitro Evaluation of Extended Release Oral Tablet Using Tramadol HCL

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ABSTRACT: The objective of this work was to develop extended release tablets of highly water soluble Tramadol HClusing polymers (HPMC K100M, HPMC K15M, HPMC K 4M, Carbapol 940, Chitosan, Sodium Alginate) as cost effective, non toxic easily available and suitablehydrophilic matrix system. Extended release tablet of Tramadol HCl (dose 100mg) were produced by direct compression method. After the evaluation of physical characteristics of tablets. The dissolution test was performed in phosphate buffer pH 7.4 for 08 hr. The release profile remains unchanged after one months storage oftablets. The best fit release kinetics was achieved with the zero order plot followed by the Higuchi and Korsmyer andPeppas equation. The data obtained proved that the formulations are useful for a sustained release of Tramadol HCl dueto the percentage released after 08 hr. is nearly to 100%.

Key words: - Hydroxy Propyl Methyl Cellulose, Tramadol Hydrochloride, Carbapol-940,Direct Compression,

I. INTRODUCTION

Hydrophilic matrices containing swellablepolymers are referred to as hydrogel matrices,swellable sustained release system or hydrophilicmatrix tablets. A number of polymers have beeninvestigated to develop in situ gel forming systems dueto ability of these hydrogels to release an entrappeddrug in aqueous medium and to regulate the release ofsuch drug by control of swelling and cross linking[1, 2, 3].Hydroxy Propyl Methyl Cellulose (HPMC) is thepolymer most widely used as the gel forming agent inthe formulation of sustained release dosage form.

Water penetration, polymer swelling, drug dissolution,drug diffusion and matrix erosion from these dosageform are controlled by the hydration of HPMC whichforms 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 andlevels of excipientes. The HPMC matrix can modify

The drug release rate[6]. Tramadol HCl is used in thetreatment of osteoarthritis when nonsteroidal antiinflamatory drug (NSAIDS), acetaminophen, orCox-2 inhibitors alone produce inadequate pain relief[7].After oral administration, Tramadol HCl is rapidly andalmost completely absorbed. Sustained release tabletsreach to peak concentration after 4.9hr and have abioavailability of 87%-95%. The mean eliminationhalf life is approx 5.5 hr to7 hrand requires dosing every 8 hours in order to maintain optimal relief of chronicpain[9, 10]consequently once daily extended releasetablets have been formulated. Long term treatmentwith sustained release Tramadol HCl once daily isgenerally safe in patients with osteoarthritis orrefractory low back pain and is well tolerated[11, 12]. Ithas the potential to provide patients increased controlover the management of their pain, fewer interruptionsin sleep and improved compliance[13].

II. MATERIALS AND METHOD

Materials

Tramadol Hydrochloride, Hydroxy Propyl Methylcellulose K100M, Hydroxy Propyl Methyl celluloseK15M, Hydroxy Propyl Methyl cellulose K4M, Carbapol 940, Sodium Alginate, Chitosan, Lactose, Magnesium Stearate, was obtained as laboratory sample from Micro Lab. pvt. Ltd.

Formulation of ER Tramadol HCl matrix tablet

Different tablet formulations were prepared by direct compression method. Table No.1 shows composition of each tablet formulation. All the ingredients were passed through 90µm sieve. The ingredients were accurately weighed and mixed together in a glass mortor for 10 minutes. Finally the magnesium stearate was added and mixed for additional 2 minutes. The lubricated powder blend was then compressed using 10mm standard flat faced punch on a 10 station tablet punching machine. The total tablet weight was set at 350mg. The compression pressure was adjusted during tableting of each

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formula to get tablet hardness in the range of 6 to 10 kg/cm^2.

III. EVALUATION OF TABLET BLEND

Bulk density

Method

Bulk density was determined according to USP method I. the powder sample under test was screened through sieve no. 18 and 20gm of tablet blend was accurately weighed and filled in a 100ml graduated cylinder and the powder was leveled and the unsettled volume (Vo) was noted. Bulk density (Db) was calculated in g/ml by the formula,

(Db)= M/Vo

Where, M = mass of powder taken

Vo= unsettled apparent volume

It has been stated that the bulk density values have less than 1.2 g/cm^3 indicates good packing and values greater than 1.5 g/cm^3 indicates poor packing.

Tapped density

Method

Tapped density was determined by USP method II. The powder sample under test was screened through sieve no.18 and 20 gm of tablet blend was filled in 100ml graduated cylinder of tap density tester (electrolab, ETD 1020).The mechanical tapping of the cylinder was carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the initial tapped volume (Va) was noted. Tapping was proceeded further for additional 750 times and volume was noted. The difference between two tapping

Volumes were calculated. Tapping was continued for additional 1250 tap if the difference is more than 2%. This was continued in increments of 1250 taps until differences between volumes of subsequent tapping was less than 2%. This volume was noted as, the final tapped volume (Vo).

The tapped density (Dt) was calculated in g/ml by the formula,

Dt = M/Vb

Where,

Vo = tapped volume

M = weight of sample powder

Compressibility Index and Hausner Ratio

Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such they are measures of relative importance of interparticulate interactions. In free flowing powder, such interactions are less significant and bulk and tapped density difference is close. For poorer flowing materials, this difference is greater.

a) Compressibility Index (% Compressibility)

Carr' s compressibility index i.e., % compressibility indicates the flow property and packing ability of the tablet. When the % compressibility ranges from 5 to 16, the materials have acceptable flow property and packing ability.

Compressibility Index was calculated using following equation.

Compressibility index = [(Dt-Db)/Dt] x100

Where,

Dt = tapped density

Db = bulk density

b) Hausner Ratio

The Hausner ratio indicates the flowability and packing ability of the tablet. When the Hausner ratio is close to 1, materials have acceptable flow and packing ability.

Hausner Ratio was calculated using the formula,

Hausner Ratio = Dt/Do

Where,

Dt = tapped density

Do = bulk density

Angle of repose (θ)

Method

It is a direct measure of flow property of powders. The tangent of angle repose is equal to the coefficient of friction between the particles. Angle of repose was determined using funnel to pour the powder on the surface from a fixed height of 2cm, the radius of base of a pile was measured at 5 different points and average was taken for calculating

angle of repose using following formula –

Angle of repose (θ) = $\tan^{-1}$ (h/r)

Where,

h = height of a pile (2 cm)

r = radius of pile base.

Acceptable range for angle of repose is 20^0 to 40^0.

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Evaluation of Tablet

Weight Variation

Twenty tablets were randomly selected fromeach batch and individually weighed. The average
Weight of 20 tablets wascalculated. The batch passes the test for weightvariation test if not more than two of the individualtablet weight deviates from the average weight bymore than the percentage shown in Table 2 Percentagedeviation allowed under weight variation.

Friability

Twenty tables were weighed and placed in theElectorlab friabilator and apparatus was rotated at 25rpm for 4 minutes. After revolutions the tablets werededusted and weighed again. The percentage friabilitywas 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 Monsantohardness tester. For each batch ten tablets were tested.

Content Uniformity

The Tramadol HCl matrix tablet was tested for their drug content. Twenty tablet were finely powdered 350mg of the powder was accurately weighted and transferred to 100ml volumetric flask.In volumetricflask add 100ml of phosphate buffer ph7.4. 1ml of the resulting solution was further diluted up to 100ml with phosphate buffer ph7.4 to make a solution of concentration 10µg/ml. The absorbances of the dilutions were measured against simulated phosphate buffer ph7.4 as a blank at 271nm using double beam UV visible spectrophotometer.

In-Vitrodissolution study

The dissolution study was carried out eight hour in 7.4pHphosphate buffer using USP XXIII dissolution testapparatus employing paddle stirrer. In this study one tablet containing 100 mg of Tramadol HCl was placed insidethe 900 ml dissolution medium and speed of paddlewas set at 100 rpm. Samples were (5ml) withdrawn at a particular time interval and same volume of freshmedium was replaced. The sample was analyzed fordrug content against7.4pH phosphate buffer as a blankat λmax 271 nm. The percentage drug release wasplotted against time to determine the release profile. Show in Table 4. and fig. no.1 and 2.

STABILITY STUDY

The Batch B6 was selected as an optimumbatch and the stability study was carried out at Accelerated condition. Of 40°C/75 % RH condition for a period of one month. Show in Table 6.

IV. RESULT AND DISCUSSION

The sustained release tablet of TramadolHydrochloride were prepared by wet granulation Method, They were evaluated for weight variation,drug content, friability, hardness, and thickness for all batches (B1 to B10).All the formulations were subjected to in-vitro dissolution studies. The results revealed that formulations with the drug – polymer Used HPMC K4M, in ratio B1 (1:0.5), B2 (1:1) ratio, B3(1:1.5) ratio and B4 (1:2) which showed a drug release rates from 60.10 to 97.88% and those of Polymer used carbapol-940 and HPMC K4M B5(1:1) ratio, B6(1:1) ratio, B7(1:1.5) ratio which have displayed drug release rates in the range of 83.86% to 101.31 % over a period of 08 hours. This indicates that as the polymer concentration increased, the drug release rate was found to be retarded.The drug polymer used HPMC K15M & Carbpol 940 B8 (1:2) ratio, B9 (1:1) ratio, B10 (1:1) ratio which shows a drug release rates from 85.86% to 101.31%.As formulation B6 containing HPMC K4M and carbapol-940 shown 101.31 % cumulative drug release pattern, which was according to the Acceptance given in USP-NF 2007 for the 08 hours dosing of Tramadol Hydrochloride and correlation coefficient (r^2) value 0.9617 this batch was chosen for the further studies in the ratio of 1:1 (Drug: Polymer)

V. CONCLUSION

- In the above view of findings it can be suggested that hydroxypropylmethylcellulose (HPMC) when combined with the hydrophilic semisynthtic gums i.e. carbapol-940 shows the synergistic effects and hence can be utilized as matrix forming agent to prolong the release of tramadol hcl.
- The overall frequency of administration of a drug candidate like tramadol hcl was successfully reduced to 2 times a day, which

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generally requires dosing in 3 to 4 times a day in conventional tablet dosage form.

- The improved patient convenience might thus be obtained by the administration of such a dosage form with minimal blood level fluctuations.

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Table No. 1: FORMULATION CHART

(Composition of Tramadol HCl matrix tablet in milligrams/tab.)

	Formulation Batch									
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**
Drug	100	100	100	100	100	100	100	100	100	100
HPMC K4M	50	100	150	200	50	25	50	– –	– –	– –
HPMC K15M	– –	– –	– –	– –	– –	– –	– –	200	50	25
HPMC K100M	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –
Carbapol 940	– –	– –	– –	– –	50	75	100		50	75
Chitosan	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –
Sodium Alginate	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –
Lactose	196.5	146.5	96.5	46.5	146.5	146.5	96.5	46.5	146.5	146.5
Mg. Sterate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total Weight	350	350	350	350	350	350	350	350	350	350

Table no. 2Weight variation tolerance for uncoated tablets

Average Weight of Tablet (mg)	**Maximum % Deviation Allowed**
130 mg or less 130mg to 324mg More than 324mg	10.0% 7.5% 5.0%

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Tablet no. 3Evaluation Tests for Formulation Batch

Formulation	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Content Uniformity (%)	Weight Variation Test (mg)
B1	6.5	0.69	4.44	98.97	362.25
B2	6.8	0.72	4.46	99.76	349.50
B3	6.5	0.60	4.42	98.98	350.62
B4	7.3	0.77	4.49	99.35	348.84
B5	8.3	0.65	4.34	98.99	350.42
B6	6.2	0.84	4.44	101.31	351.60
B7	7.6	0.79	4.47	99.65	348.82
B8	8.0	0.63	4.43	100.40	349.66
B9	9.4	0.78	4.46	99.12	352.92
B10	7.2	0.70	4.47	99.26	348.10

Tablet no. 4 Cumulative % Drug Release of Formulation

		Cumulative Percent Drug Released								
		Formulation Code								
Time	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**
1	41.99	31.05	22.64	20.25	36.93	33.95	22.34	37.23	33.95	33.95
2	48.86	39.76	29.32	26.06	46.49	36.72	33.17	50.05	42.64	46.20
3	61.25	48.37	37.11	33.87	55.95	50.36	46.53	59.78	53.30	52.42
4	81.11	49.86	46.27	35.14	67.35	60.61	55.64	77.89	59.15	66.76
5	82.69	58.31	52.41	47.75	79.20	77.45	67.84	85.60	66.39	64.64
6	90.04	73.90	62.82	52.40	85.11	85.11	75.56	92.35	71.22	77.88
7	94.99	83.26	64.77	55.84	90.96	92.40	81.46	95.85	84.05	82.04
8	97.88	79.64	70.12	60.10	95.59	101.31	83.86	101.31	85.86	96.78

Tablet no.5 Kinetic treatment of dissolution data for batch optimized Batch B6

Batch N0.	Zero-order(r)	First--order(r)	Higuchi model (r)	Hixon-crowel cube root (r)	Komeyer peppas(r)	Release exponent (n)
B6	**0.9381**	**0.9384**	**0.9637**	**0.9537**	**0.9895**	**0.5087**

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Tablet no.6Parameters studied on batch B6 formulation before and after stability study:

Parameters	Before stability study	After stability study
Thickness (mm)	4.44	4.43
Hardness (Kg/cm^2	6.2	6.2
Drug content (%)	101.59%	100.2%

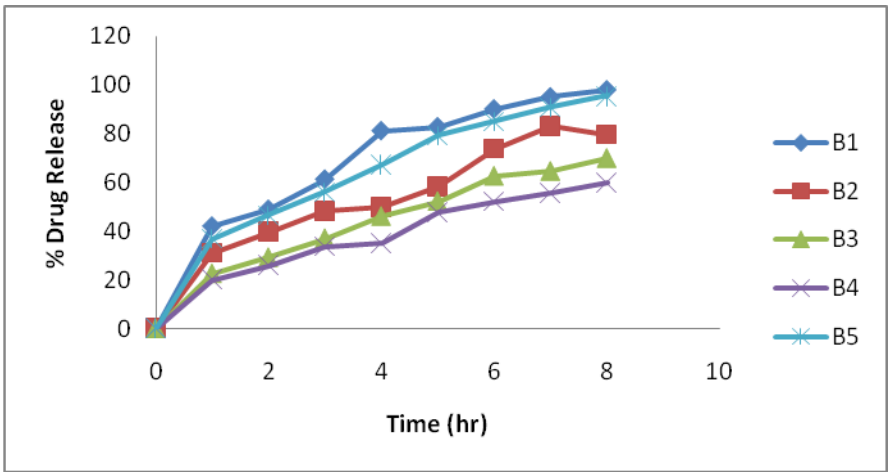

Fig. no. 1In-vitro dissolution of formulation B1 to B5

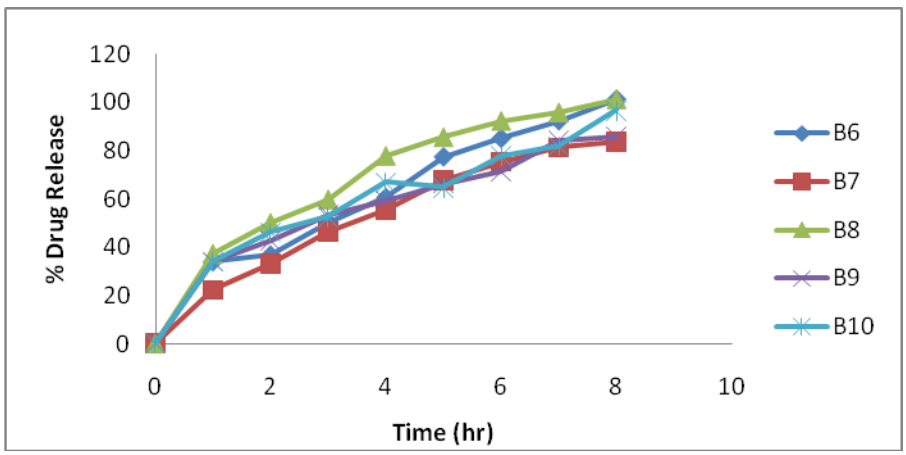

Fig. no. 2 In-vitro dissolution of formulation B6 to B10

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