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FORMULATION AND EVALUATION OF CONTROLLED RELEASE DELIVERY OF TRAMADOL HYDROCHLORIDE USING 3^2- FULL FACTORIAL DESIGN

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ABSTRACT:Purpose: The aim of this study was to design and evaluate matrix controlled release delivery system of a highly water-soluble analgesic, Tramadol Hydrochloride, using Hydroxy Propyl Methyl Cellulose K 100 M and Xanthan Gum alone and in combination as retarding polymers.
Methods: Tablets were prepared by direct compression and wet granulation using PVP K 30 as granulating agent. HPMC and XG were used alone. Combinations were designed by using 3^2- full factorial design. Polymer concentrations were taken as variables. Dosage forms were characterized for powder properties like angle of repose, bulk density, tapped density, Carr's Index, % porosity, Void volume and tablet properties like content uniformity, weight variation, hardness, friability, thickness, % swelling, *and in vitro* dissolution. The effects by both polymers were analyzed by using factorial contour plots.
Results: The wet granulation and directly compressed tablets showed good flow property and compressibility. There was no variation in content uniformity, thickness and weight. Swelling was ranging from 11 to 30 %. Dissolution profile showed the polymer concentration dependent release up to 12 hrs. Combination of xanthan gum and HPMC was retarded the drug release for more than 12 hours.
Conclusion: For a water soluble drug single polymer like HPMC K 100 M or xanthan gum could not retard the release for longer time. But the combination of these polymers significantly retarded the release rate.
Key words: Tramadol hydrochloride, HPMC, Xanthan Gum, controlled release.

INTRODUCTION

The primary objectives of controlled drug delivery systems are to ensure safety by maintaining plasma drug concentration in therapeutic window for extended period of time, and enhancement of efficacy of treatment with improved patient compliance. So the use of such dosage forms is increasing in treatment of acute and chronic diseases. Thus, controlled drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects.[1]

Controlled release provides the most desirable dosing regimens with effective pharmacokinetic profile and pharmacodynamic response in chronic pain management. This approach prevents the patient from experiencing pain intermittently through maintenance of consistent drug input and it may alleviate the variability involved in the administration of multiple doses per day. Hence, controlled release dosage form of analgesic drugs improves patient compliance and prevents the dramatic onset of analgesia seen with immediate release dosage forms.[2-5]

Tramadol hydrochloride (TM), a synthetic opioid of amino cyclohexanol group, is a centrally acting analgesic. It is an effective centrally acting analgesic with weak opioid agonist properties. Tramadol hydrochloride has plasma elimination half life of 4-6 hrs. The usual dosage regimen is 50-100 mg every 4-6 hrs. So, to reduce the frequency of

administration and to improve patient compliance, a controlled release dosage formulation of Tramadol is desirable.[6]

Tramadol HCL is associated with certain side effects, like abdominal pain, anorexia and it may also induce psychic and physical dependence. Therefore properly designed Controlled Release Dosage Form of this drug will minimize the fluctuation in blood concentration, decreasing the risk of side effects and will show uniform pharmacological response.[7]

The aim of the present investigation was to design a controlled release dosage form of Tramadol HCl containing 150 mg of drug, using a swellable polymer matrix showing the release for more than 12 hrs. Hydrophilic matrices were selected due to their simplicity in manufacturing processes required, stability of raw material and dosage form also the cost effectiveness and broad regulatory acceptance. HPMC, a synthetic polymer and xanthan gum, a natural polymer were used alone and also in combination as release retarding agent. Combination batches were deigned by using 3^2-full factorial design.

EXPERIMENTAL

Material:

Tramadol hydrochloride was obtained from Unichem Laboratories Ltd., Mumbai as gift sample. HPMC K100 M was a gift sample from Ajanta Pharma, Mumbai. Xanthan gum, magnesium stearate and isopropyl alcohol were purchased from Loba Chemie, PVP K-30 was purchased from T – Baker lab chemicals. All other chemicals were of lab grade.

METHODS

1. Preparation of Controlled release Tablets:

Controlled release tablets of Tramadol Hydrochloride were prepared by both direct compression and wet granulation methods using two polymers viz. HPMC and xanthan gum alone and in combination.

Direct Compression Method:

The tablets were prepared by direct compression technique. Before blending of drug and other excipients, they were sifted through sieve no. 40 to remove any large particles. Drugs and other excipients were blended for 10 mins. Then, subsequently this powder mixture was blended for 5 mins with magnesium stearate. This mixture was directly compressed to get the tablets.

Wet Granulation method [8]

Drug and other excipients were sifted through sieve no. 40, blended uniformly and granulated with PVP K–30 using isopropyl alcohol as granulating vehicle. The mass was prepared and granulated through sieve no. 18. The granules were air dried for 20 mins. Lubrication with sufficient quantity of magnesium stearate was done and compressed into tablets.

Preliminary Batches: -

The tablets were prepared by using HPMC K100 M and Xanthan gum. The Polymers were used in three concentrations. The drug: Polymer ratios used for tablet formulation were 1:1, 1:0.75 and 1:0.5. The batches were coded as A1-A3 for HPMC (direct compression) and B1 to B3 for xanthan gum (by Wet Granulation).

3^2 Factorial Design for combination batches [9, 10] **-**

The combination of polymers was made according to a two factors and three levels factorial design. The variable factors selected were concentrations of both polymers with three levels of concentrations. The batches were assigned codes as C1 to C9. The design is depicted in Table No.1 and 2.

MEASUREMENT OF MICROMERITIC PROPERTIES OF GRANULES[11-13]

The flow properties of prepared granules were investigated by measuring the bulk density, tapped density, Carr's index and packing factor. The bulk and tapped densities were measured in a 50 ml graduated measuring cylinder. The sample contained in the measuring cylinder was tapped mechanically by means of constant velocity rotating cam. The initial bulk volume and final tapped volume were noted from which, their respective densities were calculated. The angle for the granules of each formulation was determined by the funnel method suggested by Neumann. % Porosity of granules is the ratio of void volume to the bulk volume of packing. It was calculated by the formula

$$\varepsilon = \frac{Vb - V_p}{Vb} = 1 - \frac{Vp}{Vb}$$

Where ε = = Porosity
Vb = Bulk volume
Vp = True volume

EVALUATION OF TABLET PROPERTIES [11]:

Tablets prepared from granules and powder blends were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, thickness and in-vitro drug release.

1. Drug content uniformity

Twelve randomly selected tablets were weighed and powdered. A quantity of powder equivalent to 50 mg of Tramadol hydrochloride was taken. It was shaken with 70ml of water for 15 min. and then diluted to 100 ml with water. It was filtered through Whatman filter paper no. 41. 1 ml of this

solution was withdrawn and final volume was made 10 ml with distilled water. Absorbance was measured spectrophotometrically at 268 nm using SHIMDZU UV – 1700 spectrophotometer

2. Weight variation:

Uniformity of weight was determined by USP method. Twenty tablets were selected randomly and weighed. Average weight of the tablet was determined. These tablets were weighed individually and the weight variation was determined.

3. Tablet hardness:

The resistance of tablets to breakage, under conditions of storage, transportation or handling before usage depends on its hardness. The hardness of tablet of each formulation was checked by using Erweka tester in terms of Newton.

4. Friability:

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 100 revolutions, tablets were weighed and percentage loss in tablet weight was determined.

5. Thickness:

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Erweka Tester. It was determined by checking ten tablets from each formulation.

6. % Swelling property: [14]

% Swelling is determined by soaking tablet of each formulation in 50 ml of distilled water in Petri dish. The swelling is measured diametrically using Vernier caliper at intervals of 15 min for 1 hr. Percent swelling index is calculated by following formula,

$$\% \text{ Swelling Index} = \frac{Dt - Di}{Di} \times 100$$

Where,

Dt = diameter after time‘t’

Di = initial diameter of tablet

7. In vitro dissolution studies[15] **:**

In vitro Dissolution study was performed at 37ºC using Type II (paddle) Dissolution Test Apparatus USP XXI MODEL (Veego DA-6D Tablet dissolution test apparatus). 900 ml of distilled water was used as dissolution medium. Study was carried out for 12 hours at 50 rpm. 5 ml Aliquot was taken at each time interval. Samples were analyzed spectrophotometrically at 268 nm using SHIMDZU UV – 1700 spectrophotometer. $T_{50\%}$, $T_{80\%}$, n and k values were used to compare the dissolution kinetics of different batches.

Release Kinetics

Data obtained from in vitro release studies were fitted to various kinetics equations[10] to find out the mechanism of drug release from tablets. The rate constants were also calculated for the respective models.

RESULTS AND DISCUSSION

Powder Properties:

The angle of repose before and after lubrication for all formulations fell within the range of $25\text{-}33^0$ indicating good flow properties. The lubrication with magnesium stearate showed decrease in angle of repose suggesting improvement of flow characteristics. Carr’s index values are below 20 which indicate excellent flowability[12]. Granules prepared by wet granulation (B1- B3) show very less Carr’s index compared with directly compressible powders. Table No. 3 illustrates the bulk density, tapped density, Carr’s index, % porosity values of all formulations.

Tablet Properties of All Formulations

Tablets were prepared by both techniques namely direct compression (A1 – A3 and C1 – C9) and wet granulation (B1 – B3). All the formulations were evaluated for various parameters. The % deviation in weights of tablets was $\pm$ 5 % which is within the range according to USP. This shows uniform die fill during tablet compression. The tablets were analyzed for potency. The drug content uniformity was in range of 95-105% showing uniform distribution of drug in matrix. As there was no much variation in thickness of tablets in each formulation, it shows that granules and powder blends were consistent in particle size and uniform behavior during compression process. The hardness of tablet was measured on Erweka hardness tester. The hardness was in range of 100 – 280 N. The two factors i.e. high value of hardness and absence of disintegrant in formulation, indicate that tablet will not disintegrate in gastrointestinal tract and release the drug slowly by diffusion process. Friability was found to be 0.2 – 0.6 %. As friability was below 0.8 % tablets in each formulation can withstand the mechanical shocks. Observations are shown in Table No. 4.

3. % Swelling Index

Table No. 5 shows the % swelling index was initially more up to 30 mins but then swelling was slowed down. This occurs because, at first hydration of polymer at surface take place fastly so the swelling is more but afterwards the diffusional path length is increased causing slow penetration of water and slow swelling of polymer. The gel layer thickness depends on water penetration, polymer chain disentanglement and mass transfer in water. After some time when

diffusion path is more, water penetrates slowly and there is little change in gel thickness because water penetration and chain disentanglement rates are similar.

4. *In-Vitro* Dissolution Studies

Fig.1 shows, Tramadol release from tablets containing HPMC K100M. At lower concentration % release was more. As concentration of polymer increases the release rate was retarded. At higher concentration there was no much variation in drug release. Fig.2 depicts, the effect of xanthan gum on drug release from matrices, increasing the concentration of xanthan gum in matrix showed some what retardation of drug release. Fig. 3 shows the drug release profile of tablets with combination of xanthan gum and HPMC K 100 M. The combinations of polymers significantly retard the release for more than 12 hrs. As the concentration of HPMC K100 M increased the release rate decreased. An increase in the polymer i.e. HPMC K100M and Xanthan gum concentration causes the increase in viscosity of gel and also the formation of gel layer with longer diffusional path. This may decrease the effective diffusion coefficient of drug and therefore there is reduction in drug release rate.

All the formulations showed the initial burst in release rate. This may be due to the drug release from surface and the time needed for the formation of an efficient gel layer capable of controlling water penetration and drug diffusion.

Release Kinetics:

Formulations B1, B2, B3, C5 and C6 showed Fickian type drug release as values of 'n' that is diffusional exponent are less than 0.45. Other formulations show non-Fickian drug release as the value of 'n' is more than 0.45 and less than 0.89 [13].

Effect of Polymer Concentration on T_{50} :

The effect of Polymer Concentration on T_{50} is shown in Fig. No. 4 The factorial equation shows good coefficient of correlation (0.8). Both the factors affect the release but at initial part of dissolution profile HPMC K100 M concentration can be viewed as more significant factor in sustaining the drug release.

The factorial equation for t_{50} is as follows,

Y=

$$4.67 + 0.556\,X_1 + 0.758\,X_2 - 0.507\,X_1^2 + 0.069\,X_2^2 - 0.055\,X_1X_2$$

Effect of Polymer Concentration on T_{80}:

The effect of Polymer Concentration on T_{80} is shown in Fig.No.5 The factorial equation shows good coefficient of correlation (0.8). In case of T_{80} both the factors are significant and affect the release in similar manner this may be due to HPMC K100 M get hydrated faster than xanthan gum. Hence the initial release rate was more retarded with increasing concentration of HPMC K100 M. So that the xanthan gum showed Peppas type of release profile that is initial burst followed by tailing off, while formulations containing HPMC K100 M showed matrix type release profile.

The factorial equation for t_{80} is as follows,

Y=

$$12.91 + 1.43\,X_1 + 1.46\,X_2 - 1.94\,X_1^2 + 0.13\,X_2^2 - 0.209\,X_1X_2$$

Summary and Conclusion

The aim of present investigation was formulation and evaluation of controlled release matrix tablets for Tramadol HCl that gives drug release for more than 12 hours which will be effective for pain management.

Matrix tablets of Tramadol showed the release over a period of more than 12 hrs. The formulations C1 to C8 that is having combination of xanthan gum and HPMC K 100 M retarded the drug release for more than 12 hours. For a water soluble drug single polymer like HPMC K 100 M or xanthan gum could not retard the release for longer time. But the combination of these polymers significantly retarded the release rate. The factorial equations showed that there was influence of HPMC K 100 M on the release rate of Tramadol from Tablet formulations. As concentration of HPMC K 100 M increased the drug release rate was decreased. It was observed that formulations C1 to C8 showed the drug release for prolonged duration than marketed preparation of Tramadol. (Tramazac^R Cadila)

Further work should be done to reduce the initial burst release by coating the tablets and studying the drug release profiles. Also the formulations prepared need to be studied for the long-term/ accelerated stability studies, and in vivo bioequivalence performance.

Table 1: Factorial Design for Preparation of Batches

Batch Code	Variable levels in Coded form	
	X_1	X_2
C1	-1	-1
C2	-1	0
C3	-1	+1
C4	0	-1
C5	0	0
C6	0	+1
C7	+1	-1
C8	+1	0
C9	+1	+1

Table 2: Translation of Coded Values to Actual Values

Variable levels	Low (-1)	Medium (0)	High (+1)
X_1 = Concentration of Xanthan gum (%w/w)	0.5	0.75	1
X_2 = Concentration of HPMC K100 M (%w/w)	0.5	0.75	1

Table No. 3: Powder Properties

Batch Code	Angle of repose (degree)		Bulk density (g/cc)	Tapped Density (g/cc)	Carr's Index	Void Volume (cc)	% Porosity
	Unlubricated	Lubricated					
A1	30.2	29.07	0.465	0.488	4.877	1	25
A2	33.74	31.21	0.362	0.383	5.742	1.5	34
A3	32.08	30.96	0.652	0.702	7.726	1.1	27.5
B1	29.76	25.26	0.371	0.378	1.890	0.5	12
B2	27.11	25.89	0.370	0.377	1.885	0.5	10
B3	30.07	25.96	0.388	0.399	2.792	0.7	19
C1	30.83	29.72	0.460	0.502	9.027	1.8	30
C2	30.96	29.16	0.487	0.515	5.660	1.1	22
C3	32.12	30.32	0.440	0.465	5.574	1.2	24
C4	30.02	28.85	0.422	0.453	7.241	1.6	27
C5	32.12	30.19	0.462	0.494	6.915	1.4	28
C6	32.82	30.15	0.417	0.441	5.732	1.3	26
C7	34.41	33.58	0.462	0.496	7.446	1.5	30
C8	32.94	29.37	0.417	0.439	5.268	1.2	24
C9	32.04	31.38	0.372	0.391	5.082	1.3	26

Table No. 4: Tablet Properties

Batch Code	Average weight (mg)	Thickness (mm)	% Drug Content	Hardness (Newton)	% Friability
A1	305.21	4.38	97.93	111	0.48
A2	266.82	4.28	99.03	104	0.52
A3	228.90	3.46	99.73	102	0.55
B1	320.12	3.85	99.38	176	0.44
B2	282.68	3.45	100.79	114	0.49
B3	238.71	2.93	101.49	107	0.53
C1	458.62	6.12	102.2	192	0.25
C2	416.73	5.5	102.9	215	0.23
C3	379.82	5.16	103.6	184	0.28
C4	415.18	5.47	101.85	280	0.27
C5	378.28	5.06	101.14	170	0.32
C6	338.38	4.54	98.14	156	0.36
C7	376.58	5.01	102.55	265	0.26
C8	336.21	4.55	100.79	175	0.31
C9	304.08	4.11	100.44	155	0.37

Table No. 5: Swelling Profile

Batch Code	% Swelling of tablets			
	15 min	**30 min**	**45 min**	**60 min**
A1	18	23.66	30.11	30.55
A2	11.18	25.22	28.44	29.11
A3	15.66	21.22	24.33	24.88
B1	21.00	22.44	25.33	31.55
B2	18.55	25.55	28.66	31.33
B3	13.33	25.00	25.77	31.00
C1	11.22	23.33	28.66	31.55
C2	11.66	24.11	25.33	29.33
C3	11.77	22.22	28.44	29.55
C4	17.77	26.88	32.77	33.44
C5	17.55	26.33	30.44	30.88
C6	12.00	20.00	27.88	30.88
C7	20.66	28.33	30.33	31.00
C8	15.77	22.44	30.44	31.11
C9	15.88	26.77	29.77	30.22

Table No. 6: n, k, T_{50} and T_{80} values in Dissolution profile

Batch Code	n	K	T 50	T 80
A1	0.547	24.13	3.78	8.91
A2	0.484	24.63	4.21	11.38
A3	0.463	31.28	2.75	7.58
B1	0.417	35.05	2.34	7.22
B2	0.388	36.36	2.27	7.61
B3	0.323	47.02	1.20	5.15
C1	0.482	23.01	4.97	12.72
C2	0.501	21.65	5.27	13.51
C3	0.462	26.32	4.00	11.04
C4	0.508	19.99	6.04	15.47
C5	0.434	27.82	3.85	11.35
C6	0.445	26.21	4.26	12.19
C7	0.505	23.45	4.47	11.45
C8	0.492	25.88	3.82	9.78
C9	0.448	32.17	2.67	7.62

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