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Design, Fabrication and evaluation of Metoprolol tartrate once a day Matrix tablet.

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Abstract-

The aim of present work was to formulate extended drug delivery system of Metoprolol tartrate suitable for once-a-day dosing. HPMC in various grades like K4M, K15M and K100M were screened firstly in an increasing drug to polymer ratio (1:1, 1:1.5, and 1:2) and then selected grade was combined with Carbapol-940 and also carbapol-940 combine with chitosan, sodium alginate in ratio (1:1).Pre-compression parameter of powder blend was carried out which shown the results within prescribed compendia limits. Direct compression method was adopted for the preparation of sustained release matrix tablets. The values for thickness, hardness, % friability, weight variation and content uniformity parameters were found to be within the prescribed limits and were confirmed to the pharmacopoeial requirements. The % drug release studies for combined HPMC-K4M and Carbapol-940 matrices confirmed the batch B6 (1:1) ratio at the end of 8 hours which give the 101.31% drug release. Formulation was optimized and subjected to release kinetic study and accelerated stability studies.

Keywords- Metoprolol tartrate, carbapol-940, Pre-compression, kinetic study

Introduction

Oral drug delivery system is most convenient way for drug delivery. Release of water soluble drug from the matrix system is not ease to control due to different factors such as high solubility and so dose dumping of drug. This may results to toxicity of drug. Matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behavior [1]. Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years [2]. Regular research is going on in field of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration. Natural gums are biodegradable and nontoxic, which hydrate and swell on

contact with aqueous media, and these have been used for the preparation of dosage form [3] Tramadol HCL is a rapidly and completely absorbed drug but plasma level achieved is highly variable after oral administration. Besides it also has relatively short elimination half-life (3 to 7 hours). Frequent dosing is thus necessary to maintain reasonably stable plasma concentration. However, frequent dosing results in inconvenience to the patient and leads to poor compliance. Moreover, widely fluctuating plasma concentration of the drug also results in availability of erratic amount of drug. A drug with a short half-life requires frequent dosing and this makes tramadol HCL an ideal candidate for an extended-release formulation.[4]

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. The ability of the hydrophilic polymer matrices to release drug in an aqueous medium and to regulate the release of such drug by Controlled-swelling and cross-linking makes them particularly suitable for controlled- release application

Materials and Method

Materials-

Metoprolol tartrate was provided by Alkem laboratories Ltd, Mumbai., India as a gift sample HPMC and Carbapol-940 were purchased from Alkems labs Ltd, Mumbai and Signet chemical corporation Pvt Ltd, Mumbai, India. All other chemicals and reagents used were of desired analytical grade.

Drug Interaction Studies

IR spectra of pure Tramadol hydrochloride and polymers viz. hydroxymethycellulose (K4M, K15M, and K100M), sodium alginate, carbapol 940 and chitosan were taken separately. Then to know if there is any interaction between drug and polymer, IR spectra of Tramadol hydrochloride and other polymers were taken in combination [5].

Pre-compression parameters

Bulk density

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 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 [6-8],

(Db)= M/Vo

Where, M = mass of powder taken

Vo= unsettled apparent volume

Tapped density

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).

Compressibility Index and Hausner Ratio

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

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)

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

Formulation Studies

Selection of Release Retarding Agent

The release retarding agents play a central role in the formulation of sustained release matrix tablet. The objective of present study was to develop matrix sustained-release tablets of Tramadol hcl using suitable hydrophilic matrix system.

Thus, in the present study, firstly different batches of tablets were prepared by taking various viscosity grades of hydroxymethylcelluolse, i.e. K4M, K15M and carbapol- 940. All the agents were added in various concentrations of drug to polymer ratio. The grade of hydroxymethylcellulose among all these, who will give the results as per the U.S.P. specifications for 8 hours dosing of Tramadol hydrochloride will be selected and utilized for further studies.

Table no. 1: Composition of tablet formulation

	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
Weight	350	350	350	350	350	350	350	350	350	350

Evaluation of Tablets

Sustained release matrix tablets thus prepared were evaluated for following parameters:-

Hardness

Tablets require a certain amount strength or hardness and resistance to friability to withstand mechanical shock of handling in manufacturing, packaging and shipping.

Hardness was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying the force. Mean of three values with standard deviation for each formulation was taken.[9-10]

% Friability Studies

Friability is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of tablets were placed in the friabilator and tumbled in a friabilator (model, Roche, Bombay) for 4 min at 25 rpm. The tablets then were dedusted, and the loss in weight caused by fracture or abrasion was recorded as percentage friability. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

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

Where,

% F = friability in percentage

Wo = initial weight of tablet

W = weight of tablet after test

The % friability study was carried out in triplicate manner and the averages of the three determinations were taken for the evaluation purpose.

Thickness Measurement

The sample was selected randomly from each batch and thickness was measured using Vernier caliper**.**

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 50ml volumetric flask. Then volume was made up with 0.1N HCL and shaken for 10min. to ensuser complete solubility of drug. The mixture was centrifuged (Type: 2000, clements, Rydalmere, Australia) and 10ml of the supernatant liquid was diluted 20 times with 0.1N HCL, and after centrifugation the absorbance was determined spectrophotometrically at 271nm.[11-13]

***In-vitro* Release Profile Study of Formulated Tablets**

In vitro drug release studies were carried out using USP 25 (Type II) apparatus in 900ml of dissolution medium maintained at 37 ± 1^0C at a speed of 100 rpm. Phosphate buffer ph7.4 was used as dissolution medium to avoid the effects of pH change on the solubility of tramadol hydrochloride as it decreases with the increasing pH. Aliquots of 5ml were withdrawn at predetermined time intervals using calibrated pipette during at 8 hours period and filtered. An equivalent amount of fresh dissolution medium, maintained at 37 ± 1^0C was added after withdrawing each sample to maintain the sink conditions. The drug concentrations in the sample analyzed spectrophotometrically (double beam UV, simadzu) at 271nm.[15-17]

Result and discussion-

Drug Interaction Studies

This compatibility study or interaction study was done using Fourier transformed infrared spectroscopy. IR spectra of pure tramadol hydrochloride and polymers were taken along with both in the combinations.

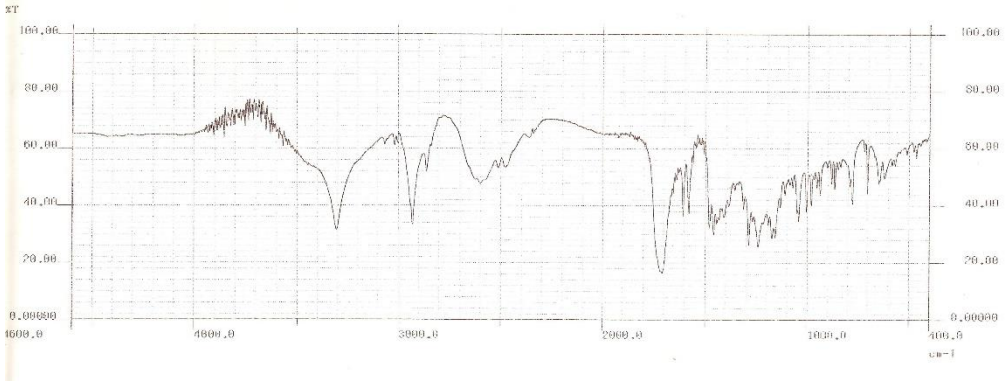

Fig No. 1: FTIR of Tramadol Hydrochloride

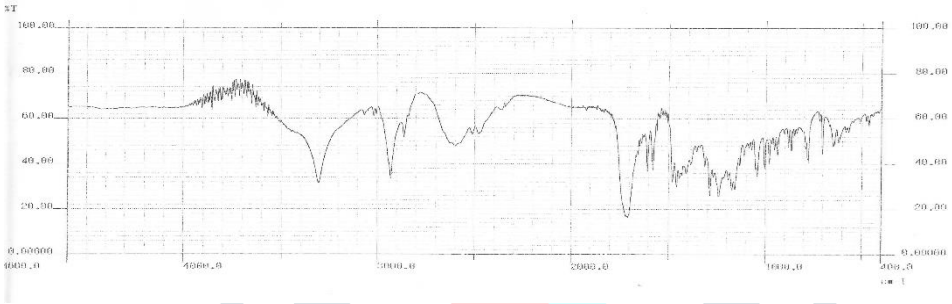

Fig No. 2: FTIR of Tramadol Hydrochloride Physical mixture.

Principal peaks at wave numbers 1284, 1601, 1042, 1238, 1575, 702 cm^{-1} tramadol hydrochloride .Interpretation of drug-polymer interaction was done by viewing the similar FTIR peaks in the various blends of the drug with polymer and was interpreted that no drug interaction was observed.

Pre-compression parameters

The bulk density and tapped density values were lies in between 0.430 to 0.476 g/cm^3 and 0.526 to 0.555 g/cm^3 i.e. less than 1.2, indicates good packing. The values of % compressibility, Hausner ratio and angle of repose were lies in between 8.71% to 15.35%, 1.1 to 1.18 and 25^0-12' to 35^0-22', respectively indicates acceptable flow property and also good packing ability. Therefore, the tablet blend might be used for the preparation of extended release matrix tablets. Results are shown in table no.

Table No. 2 : Evaluation of Physical Properties of Powder Blend

Formulation	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility (%)	Hausner Ratio	Angle of Repose (θ)
B1	0.476	0.555	14.23	1.16	26^0-15’
B2	0.454	0.526	13.64	1.15	27^0 -20’
B3	0.434	0.5	13.2	1.15	25^0-12’
B4	0.430	0.508	15.35	1.18	31^0-20’
B5	0.482	0.528	8.71	1.1	26^0-06’
B6	0.470	0.548	14.23	1.17	32^0-24’
B7	0.442	0.502	11.95	1.14	30^0-15’
B8	0.436	0.496	12.1	1.14	35^0-22’
B9	0.476	0.526	9.55	1.16	28^0-18’
B10	0.422	0.472	10.59	1.12	29^0-12’

Post compression Evaluation of Tablets

Hardness values for Formulation were ranged from 6.2 to 9.4 kg/cm^2 which indicate good strengths of the tablets. Friability values for Formulation were in the range of 0.60% to 0.84%, which is less than 1.0%.The thickness of all the tablets were in the range of 4.34mm to 4.49mm, which was as desired. It indicates all the tablets have good strength to withstand the mechanical stresses. The assay values for the determination of content uniformity of all formulations were within the range of 98.97% to 101.31%.As per the general pharmacopoeial requirements a tablet weighing more than 324mg should have weight variation deviation not more than ± 5.0%. No formulation was found to have weight variation.

Table No. 3: Tablet Evaluation Tests for Formulation

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

In-vitro drug release for Formulation

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 & Carabol 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 Table of Test 2 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).

Table 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

Drug Release Kinetic Studies

The release mechanism of tramadol hcl from most optimized formulation batch B6 was studied by fitting the data obtained from in-vitro release studies into zero-order, first order, Higuchi, korsmeyer-peppas and Hiixon-crowell models. The values of correlation coefficient (r) are given in Table 5.

On the application different release models, it was found that the optimized formulation batch B6 follows the Korsmeyer-peppas model. The value of ‘n’ was found to be 0.5082 means it follows non-fickian diffuasion. Which coincides with swelling erosion study i.e.drug release was controlled by an intermediate of both diffusion and erosion mechanism. The formulation batch B6 follows the komeyer peppas order release which show constant drug release rate with time.

Table 5 : r values of various models for formulation batches.

Batch N0.	Zero-order(r)	First--order(r)	Higuchi model (r)	Hixon-crowel cube root (r)	Komeyer peppas(r)	Release exponent (n)
B1	0.8999	0.9560	0.9808	0.9540	0.9895	0.4561
B2	0.8425	0.9193	0.9841	0.8965	0.9895	0.3782
B3	0.9412	0.9793	0.9916	0.9698	0.9895	0.5293
B4	0.9184	0.9433	0.9736	0.9380	0.9895	0.4961
B5	0.9180	0.9731	0.9921	0.9706	0.9895	0.4660
B6	0.9381	0.9384	0.9637	0.9537	0.9895	0.5087
B7	0.9794	0.9900	0.9728	0.9938	0.9895	0.6898
B8	0.9352	0.9761	0.9908	0.9824	0.9895	0.5248
B9	0.9629	0.8785	0.9948	0.9400	0.9895	0.4201
B10	0.8555	0.9233	0.9818	0.9068	0.9895	0.4268

Accelerated Stability Studies

The stability studies were carried out on optimized formulation i.e. batch B6 The formulation were stored at 50^0C for one month (30days). After 30 days, samples were withdrawn and retested for thickness, hardness, drug content and *in-vitro* drug release studies.

Table No. 6 : Parameters studied on batch B6 formulation before and after stability

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%

Table no. 22 showed that there were no considerable changes in thickness, hardness and drug content of batch B6 formulation before and after accelerated stability study. Also table no.6 and Fig. no. 3 showed that there was hardly any difference between dissolution profile of batch B6 formulation before and after stability study. Hence matrix tablet prepared were found to be stable.

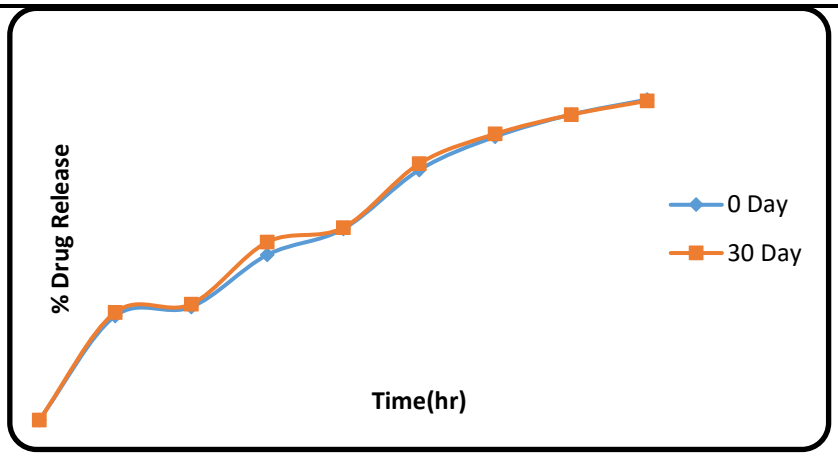

Fig. No 3: In vitro Dissolution profile of formulation batch B6 before and after stability study

Similarity Factor (F_2)

A statistical comparison of dissolution data was carried out using a model independent method (F_2). The results were illustrated in Table No. 26.

Table No. 7: Table indicating calculation of similarity factor (F_2)

Time (min)	Rt	Tt	Rt-Tt	(Rt-Tt)^2
1	34.55	33.95	0.6	0.36
2	47.97	36.72	11.25	126.5625
3	56.24	50.36	5.88	34.5744
4	64.13	60.61	3.52	12.3904
5	77.45	77.45	0	0
6	85.11	85.11	0	0
7	94.99	92.4	2.59	6.7081
8	100.17	101.31	1.14	1.2996
∑	**560.61**	**537.91**	**24.98**	**181.895**
Number of points		**9**		
F1	**4.46**			
F2	**66.84**			

Similarity factor was calculated by comparison of Batch B6 formulation batch in-vitro release with marketed product release profile. Similarity factor (F_2) of optimized formulation batch B6 was found to be **66.84.** This value indicated that the in-vitro release of Batch B6 were closely similar to that of marketed tablet release profiles.

Conclusion

In the above view of findings it can be suggested that hydroxypropylmethylcellulose (HPMC) when combined with the hydrophilic semisynthetic 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 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. The release retardant materials are cheap, readily available, safe, having wide regulatory acceptance and easy to handle for economic point of view. It may beneficial to adopt such simple technology for the commercial production of sustained release matrix tablets.

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