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Research Article

APPLICATION OF CHITOSAN TO MODULATE HPMC-EC BASED CONTROLLED RELEASE TRAMADOL MATRIX SYSTEM

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Abstract

Tramadol hydrochloride, highly water soluble drug was chosen as candidate drug for formulation of controlled release drug delivery owing to its undesirable side effects like abdominal pain, anorexia which were likely to happen after administration of conventional drug delivery of tramadol. The objective of present study was to design and investigate the performance of hydrophilic and hydrophobic matrix system in controlling release of tramadol. Moreover the effect of Chitosan and its water soluble form as release retarding agent was investigated as polymeric matrix systems accompany the problem of initial burst release. Polymers such as HPMC and ethyl cellulose were used and controlled release tablets were prepared by direct compression. Further they were subjected to evaluation of flow properties, tablet properties *and in vitro* dissolution. All the batches depicted improvement in flow property and compressibility. It was observed that all the batches had uniform thickness and reflected uniform behaviour during compression process. In, in-vitro drug release studies, the drug release was found to be completed within 10 hours. Further addition of ethyl cellulose was found to control the drug release to certain extent. All formulations without Chitosan and water soluble Chitosan gave initial burst release followed by steady state release. However incorporation of Chitosan and water soluble Chitosan impaired the initial burst release indicating better and more controlled drug release. Thus Chitosan and water soluble Chitosan could be best suited to modulate HPMC-EC based controlled release Tramadol matrix system with minimal burst and maximal controlled release.

Keyword: Tramadol HCl, HPMC, Ethyl cellulose, Chitosan, water soluble Chitosan.

Introduction: Tramadol hydrochloride, 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 has been

proved to be effective in both experimental and clinical pain without causing serious cardiovascular or respiratory side effects. The half-life of the drug is about 5.5 hours and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hours with a maximum dosage of 400 mg/day. But, Tramadol HCL is associated with certain side effects, like abdominal pain, anorexia and it may also induce psychic and physical dependence. So, a controlled release dosage formulation of Tramadol is desirable to reduce the frequency of administration and to improve patient compliance [1] by minimizing the fluctuations in blood concentration, and thereby decreasing the risk of side effects and showing uniform pharmacological response. [2]

For drugs like Tramadol HCL having high water solubility, a mix of hydrophilic and hydrophobic polymers are suitable as matrixing agents for developing sustained-release dosage forms [3]. Hydrophilic polymer matrix systems are advantageous for their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance [4]. Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications.

But most of the polymeric matrix systems studied for controlled drug release show the problem of initial burst release and need the process of coating which is rather costlier and time consuming complicated process needing sophisticated instruments [2]. So aim of the present study was to formulate controlled release matrix system of Tramadol HCL without any initial burst release.

In the present study, various matrix systems were de-signed and tested for controlled delivery of tramadol HCL. The objectives of the study were (1) to investigate the performance of hydrophilic and hydrophobic matrix systems in controlling the release of this freely soluble drug, and (2) to investigate the effect of Chitosan and its water soluble form as a release-retarding agent controlling burst release.

Materials and methods:

Materials:

Tramadol hydrochloride was obtained from Unichem Laboratories Ltd., Mumbai, India as gift sample. Chitosan and Water Soluble Chitosan were gift sample from Mahatani Chitosan Pvt. Ltd., Ahmedabad, India. HPMC K 100M and ethyl cellulose were purchased from Colorcon Asia Pvt Ltd Mumbai, India. All other chemicals, solvents and reagents were of analytical grade.

Preparation of Controlled release Tablets:

Controlled release tablets of Tramadol Hydrochloride were prepared by direct compression using two polymers viz. HPMC and ethyl cellulose. Before blending of drug and other excipients, they were sifted through sieve no. 20. Drugs and other excipients were blended for 10 mins. Then, subsequently this powder mixture was blended for 5 mins with magnesium stearate, Aerosil and Micro Crystalline Cellulose (MCC). This mixture was directly compressed to get the tablets. Preparation of different batches and concentrations of drug, polymer and excipients used in the batches is depicted in table 1. [5]

Table-1: Preparation of different batches.

Batches	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**
Tramadol	300	300	300	300	300	300	300	300
HPMC	117	130	117	130	80	50	80	50
EC	32.5	32.5	45.5	45.5	35.5	20.5	35.5	20.5
Chitosan	---	---	---	---	60	90	---	---
WSC	---	---	---	---	---	---	60	90
Magnesium Stearate	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Aerosil	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25
MCC	190.75	177.75	177.75	190.75	164.75	141.75	164.75	141.75

Evaluation of tablets [6]

The flow properties of prepared powdered mixtures 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 of repose of the prepared granules was determined by the funnel method suggested by Neumann.

The prepared tablets were evaluated for weight variation, hardness, thickness, friability, and drug content. Pfizer hardness tester was used for the determination of hardness. In weight variation test twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture was recorded. In this work, for each formulation the hardness of 6 tablets was evaluated. The crown-to-crown thicknesses of ten tablets from each batch were determined using vernier calipers. The Friability of the tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (1- W0 / W) \times 100$$

Where, W0 is the weight of the tablets before the test and W is the weight of the tablets after the test. For determination of drug content at least three tablets from each formulation were weighed individually, pulverized, and diluted to 250ml with sufficient amount of phosphate buffer pH 6.8. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 268nm.

In vitro Dissolution study was performed at 37ºC using Type II (paddle) Dissolution Test Apparatus USP XXI MODEL (LABINDIA Tablet dissolution test apparatus). 900 ml of distilled water was used as dissolution medium. Study was carried out for 16 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. Evaluation has been done in triplicate.

Results and Discussion

Various physical parameters evaluated for blended powders were found within official limits. Carr's index values were below 20 which indicated excellent flowability [7]. A Hausner ratio of <1.25 indicated powder's free flowing nature [7]. The results of evaluation of micromeritic properties are displayed in table 2.

Table-2: Evaluation of Powder Properties.

Batches	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio	Angle of Repose ± S. D.
A1	0.49±0.03	0.55±0.05	10.90	1.122	29.12±0.81
A2	0.47±0.18	0.54±0.14	12.72	1.148	26.38± 0.72
A3	0.52±0.12	0.6±0.13	13.33	1.153	25.12± 0.71
A4	0.48±0.04	0.56±0.07	14.28	1.166	28.37± 0.23
A5	0.52±0.07	0.59±0.07	11.86	1.134	26.21± 0.16
A6	0.50±0.11	0.55±0.05	9.09	1.1	31.10± 0.82
A7	0.46±0.08	0.51±0.09	9.80	1.108	29.53± 0.12
A8	0.48±0.07	0.54±0.13	11.11	1.125	29. 78± 0.23

It was found that the tablets were of an average weight of 650 mg ± 5% and 600 mg ± 5% which is within the limits of the percentage deviation allowed by Indian Pharmacopoeia 2010 for tablets weighing 325 mg or more.

The values of thickness (mm) for the tablets of different formulation are given in table 2. From the results it may be inferred that the deviation in thickness is within ± 5%. This is tolerable for the normal manufacturing practices. The thickness may vary with no change in weight due to difference in the pressure applied to the tablets, wear and tear on length of punches as well as on the speed of tablet compression. Less variation in thickness of tablets in each formulation showed that particles and powder blends were consistent in particle size and displayed uniform behaviour during compression process.

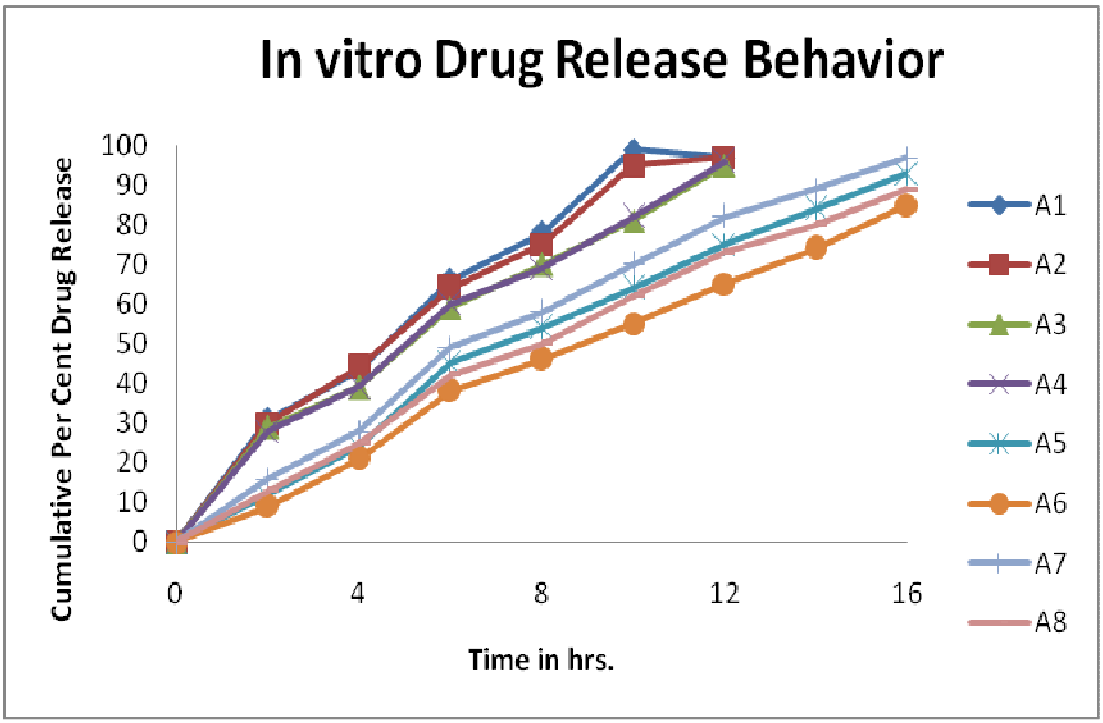
The percentage friability of the tablets depicted that the greater the hardness of the tablets the lesser is the percentage friability. As the hardness of the tablets was increased gradually there was a markable decrease in the percentage friability in all formulations. The possible reason for this result might be that at high compressional

force the particles were packed strongly together and there was low degree of crumbling during friability.

The drug content uniformity was in range of 95-105% showing uniform distribution of drug in matrix. These values were under the limit of B.P. (1988) as described by Tramadol tablets i.e. ±5%.

Fig 1 shows in vitro drug release behaviour of all the formulations. In this work, HPMC K-100M was used as a hydrophilic matrixing agent because it forms a strong viscous gel on contact with aqueous media, which may be useful in controlled delivery of highly water-soluble drugs. As only hydrophilic matrix was not suitable for controlling release of water soluble drug, ethyl cellulose was incorporated in the hydrophilic matrix. The matrices released the drug up to 10-12 hours only. Incorporation of ethyl cellulose was found to control the drug release to some extent, which could be attributed to the decreased penetration of the solvent molecules in the presence of hydrophobic polymer leading to decreased diffusion of the drug from the matrix [8, 9]. In an attempt to prolong the release of drug, the concentration of HPMC and EC was increased. An increase in concentration of HPMC did not significantly prolong the drug release. But increase in EC concentration did significant impact but to a lower extent. With all four formulations, an initial burst release of the drug followed by a steady-state release. The reason might be suggested as drug release from surface and the time required for the formation of an efficient gel layer which is capable of controlling water penetration and drug diffusion through matrix [10].

Fig-1: The results of in vitro drug release studies from formulations.



This burst effect in which a large drug volume is quickly released into the body can be dangerous to the body as higher concentration might be responsible for untoward effects. In addition to that, amount of drug in the matrix system would get reduced and purpose of controlled drug delivery would not be achieved.

Table-3: Evaluation of Tablet Properties.

Batches	Hardness (kg/cm2)	Thickness (mm)	Weight(mg)	Friability (%)	Drug content* (%)
A1	180	5.89±0.31	648±0.36	0.49	97.54±0.24
A2	178	5.86±0.05	649±0.87	0.62	98.45±0.26
A3	182	5.88±0.10	651±0.58	0.52	99.70±0.12
A4	207	5.89±0.08	676±0.26	0.30	99.21±0.28
A5	215	5.87±0.07	647±0.87	0.25	101.23±0.14
A6	240	5.82±0.08	611±0.96	0.26	102.12±0.23
A7	256	5.86±0.13	647±0.16	0.21	97.26±0.15
A8	265	5.87±0.11	612±0.39	0.13	99.34±1.03

Table 4 depicts mechanism of drug release. It was observed that batches A1, A5 and A6 followed zero order drug release, while all the remaining batches followed peppas model of drug release. The best fit model was confirmed by observing the R values and the model which gave maximum R value was selected as best fit model. $T_{25,}$ T_{50}, and T_{99} values clearly give the pattern of drug release. T_{25} values of 2.0,1.6,1.7 and 1.8hrs for A1, A2, A3 and A4 respectively indicate burst release which is significantly reduced to 3.7 , 4.4 hrs for A5 , A6 and 3.2, 3.8 hrs for A7 and A8 batches respectively; depicting significant role of Chitosan and Water Soluble Chitosan. Incorporation of Chitosan and water soluble Chitosan in matrix, drastically impaired the initial burst release (A5 to A8). It was minimum for A5 and A6 batches showing 12% and 9% respectively. The initial decrease in the drug release could be due to prevention of penetration of water into the matrix system.

Table-4: Evaluation of different dissolution parameters.

Batch codes	Best fit model for drug release	R value	T_{25} (hrs)	T_{50} (hrs)	T_{99} (hrs)
A1	Zero order	0.9923	2.0	4.6	9.8
A2	Peppas	0.9943	1.6	4.3	11.4
A3	Peppas	0.9911	1.7	4.8	13
A4	Peppas	0.9925	1.8	4.8	12.8
A5	Zero order	0.9943	3.7	7.8	15.9
A6	Zero order	0.9971	4.4	9.0	18
A7	Peppas	0.9952	3.2	6.9	14.9
A8	Peppas	0.9972	3.8	8.0	16.6

Further, comparisons of drug release between A5-A6 and A7-A8 batches indicated that if concentration of Chitosans increased effect on controlling burst and in vitro drug release is also increased. An increase in the polymer concentration caused 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 was overall reduction in drug release rate.

The results of the dissolution studies indicated that incorporation of water-soluble Chitosan aided in the overall drug release due to its more hydrophilic nature than Chitosan. The combinations of polymers significantly retarded the release for more than 16 hrs along with control over burst drug release.

Conclusion

Tablets prepared by direct compression method were found to have good tablet as well as flow properties. The objective of controlled drug release was found to fulfil with use of HPMC. Moreover addition of ethyl cellulose did significant impact on drug release of tramadol. However the 'burst release' limitation of controlled drug delivery was improved with the use of Chitosan and water soluble Chitosan. Both these polymers significantly improved the drug release pattern by impairing the burst effect but Chitosan was found to be significantly better. Thus the

potential of Chitosan or water soluble Chitosan will be helpful in formulation of controlled drug delivery systems avoiding limitations of burst release.

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