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Controlled Release Formulation of Tramadol Hydrochloride Using Hydrophilic and Hydrophobic Matrix System

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ABSTRACT

The effect of concentration of hydrophilic (hydroxypropyl methylcellulose [HPMC]) and hydrophobic polymers (hydrogenated castor oil [HCO], ethylcellulose) on the release rate of tramadol was studied. Hydrophilic matrix tablets were prepared by wet granulation technique, while hydrophobic (wax) matrix tablets were prepared by melt granulation technique and in vitro dissolution studies were performed using United States Pharmacopeia (USP) apparatus type II. Hydrophobic matrix tablets resulted in sustained in vitro drug release (>20 hours) as compared with hydrophilic matrix tablets (<14 hours). The presence of ethylcellulose in either of the matrix systems prolonged the release rate of the drug. Tablets prepared by combination of hydrophilic and hydrophobic polymers failed to prolong the drug release beyond 12 hours. The effect of ethylcellulose coating (Surelease) and the presence of lactose and HPMC in the coating composition on the drug release was also investigated. Hydrophobic matrix tablets prepared using HCO were found to be best suited for modulating the delivery of the highly water-soluble drug, tramadol hydrochloride.

KEYWORDS: tramadol, hydrogenated vegetable oil, hydroxypropyl methylcellulose, ethylcellulose, melt granulation

INTRODUCTION

Tramadol, a synthetic opioid of the aminocyclohexanol group, is a 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.[1] 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.[2] To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of tramadol is desirable. The drug is freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. The most commonly used method of modulating the drug release is to include it in a matrix system.[3] 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.[4] The drug release for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs with high water solubility, hydrophobic polymers (waxes) are suitable as matrixing agents for developing sustained-release dosage forms.[5] Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications.

In the present study, various matrix systems were designed and tested for controlled delivery of tramadol. 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 ethylcellulose as a release-retarding agent, either in the tablet matrix or when used as a coating material, on the release rate of tramadol.

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Table 1. Tramadol HCl 200 mg Tablet Formulations*

Excipients	mg/Tablet										
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
Hydrogenated castor oil	0	0	0	0	150	200	200	200	200	180	100
Ethylcellulose	0	0	10	20	0	0	5	10	20	0	0
HPMC K100	150	200	110	110	0	0	0	0	0	20	100
PVP K 90	10	10	10	10	0	0	0	0	0	0	0

* Each formulation contained tramadol hydrochloride 200 mg/tablet and magnesium stearate 8 mg/tablet. HPMC indicates hydroxypropyl methylcellulose; and PVP, polyvinylpyrrolidone.

Table 2. Coating Compositions in Water*

Coating Material	C1	C2	C3	C4	C5
Surelease	15%	14%	13%	14%	13%
HPMC 6 cps	0	1%	2%	0	0
Lactose	0	0	0	1%	2%

*HPMC indicates hydroxypropyl methylcellulose; and cps, centipoises.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride, lactose, polyvinylpyrrolidone (PVP-K90), and hydroxypropyl methylcellulose (HPMC) (6 centipoises [cps]) were obtained from Cadila Healthcare Ltd, Ahmedabad, India. Hydrogenated castor oil (Lubritab) was purchased from Dabur India Ltd (Mumbai, India). HPMC (Methocel K 100M), ethylcellulose (Ethocel), and 25% aqueous dispersion of ethylcellulose (Surelease) were purchased from Colorcon Asia Pvt Ltd (Mumbai, India).

Methods

Hydrophilic Matrix Tablets

The tablets were prepared by wet granulation technique (formulations I-IV, **Table 1**). Drug and other excipients were granulated with PVP K-90 using isopropyl alcohol as granulating agent. The mass was dried and sieved through ASTM (American Society of Testing and Materials) 20 mesh. The granules were lubricated and compressed into capsule-shaped (15.3 × 7.7 mm) tablets using 27-station rotary compression machine (CMB4 D-27, Cadmach Engg, Ahmedabad, India). Each tablet contained 200 mg of tramadol hydrochloride and other pharmaceutical ingredients as listed in **Table 1**.

Hydrophobic Matrix Tablets

The formulations of matrices are listed in **Table 1** (formulations V-IX). Drug, hydrogenated castor oil (HCO), and ethylcellulose were mixed homogeneously; the blend was then heated (85°C-90°C) in a water bath (model SW 23, Julabo Labortechnik GMBH, Seelbach, Germany) with continuous agitation. The molten mass was allowed to cool at room temperature. The congealed solid mass was then sieved, lubricated, and compressed.

Tablets with combination of hydrophilic and hydrophobic matrix polymers were prepared as follows (formulations X-XI, **Table 1**). Drug and HCO granules were prepared by melt granulation technique as described above and HPMC was then added extragranularly. The blend was mixed manually in a polybag, lubricated, and then compressed.

Coating

The effect of ethylcellulose coating on the release rate of tramadol from hydrophobic matrix tablet was studied. Tablets of batch VI were selected for coating with ethycellulose (Surelease, **Table 2**). The effect of channeling agents, such as lactose and HPMC (6 cps), in the coating formulation on the drug release pattern was

also studied (**Table 2**). The tablets were coated using laboratory coater (model GAC-250, Gansons Ltd, Mumbai, India) under controlled conditions.

Weight Variation and Hardness Determination

To study weight variation, 20 tablets of each formulation were weighed using a Mettler-AE 200 balance (Mettler Toledo GMBH, Greifensee, Switzerland). For each formulation, the hardness of 10 tablets was measured using a hardness tester (model 6-D, Dr Schleuniger Pharmatron, Manchester, NH).

In Vitro Release Studies

In vitro dissolution studies were carried out using USP apparatus type II (model 2100C, Distek Inc, North Brunswick, NJ) at 50 rpm. The dissolution medium consisted of degassed demineralized water (DM) (900 mL), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by online UV-visible spectrophotometer (8453, Agilent Technologies, Singapore) at 271 nm using Chemstation software (Agilent Technologies, Singapore). It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate (6 tablets in each set), and the mean values were plotted versus time with SD of less than 3, indicating the reproducibility of the results.

RESULTS

All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation and hardness. **Figure 1** depicts the effect of HPMC K-100 M on the tramadol release from hydrophilic matrices. Increasing the concentration of HPMC in the matrix did not alter the drug release profile significantly.

Figure 2 shows the effect of ethylcellulose on tramadol release from hydrophilic matrix system. Incorporation of ethylcellulose in hydrophilic matrix retarded the release rate of tramadol. The release rate of tramadol from hydrophobic matrix of HCO is shown in **Figure 3**. Use of ethylcellulose in wax-based system also resulted in retardation of drug release (**Figure 4**). The effect of combination matrix (HCO and HPMC K-100M) on drug release rate is shown in **Figure 5**. The drug release rate was faster from the hydrophilic matrix systems when compared with hydrophobic HCO matrix. Application of Surelease coating further decreased the drug release (**Figure 6**). Incorporation of lactose or HPMC (6 cps) in Surelease coating composition aided in the initial release of the drug (**Figure 6**).

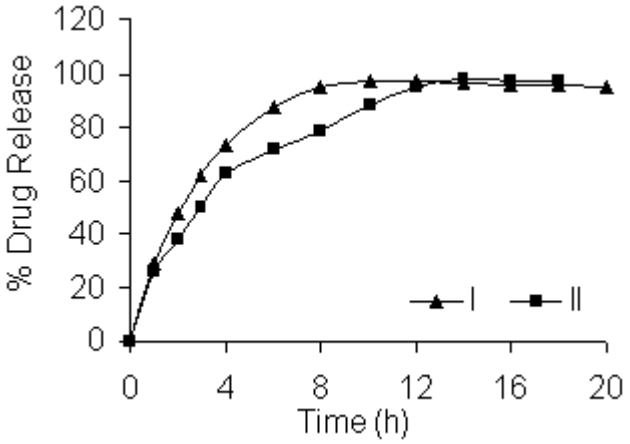

Figure 1. Effect of HPMC on tramadol release from hydrophilic matrix system prepared by wet granulation as per Table 1. Dissolution test in DM water using USP apparatus type II at 50 rpm and 37°C (n =18).

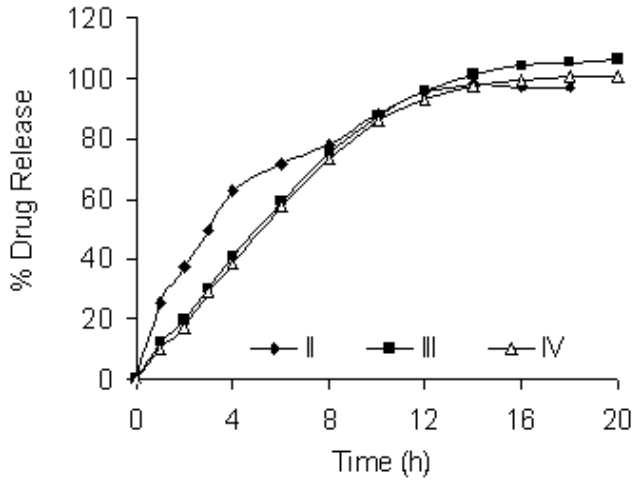

Figure 2. Effect of ethylcellulose on tramadol release from hydrophilic matrix system prepared by wet granulation as per Table 1. Dissolution test in DM water using USP apparatus type II at 50 rpm and 37°C (n = 18).

DISCUSSION

Tramadol is a synthetic, centrally acting analgesic agent with 2 distinct synergistic mechanisms of action. It is both a weak opioid agonist with selectivity for the μ receptors and a weak inhibitor of the reuptake of noradrenaline and serotonin. Its limiting side effects in the treatment of acute and chronic pain are reported to be less intense and less frequent.[6-7] Multiple dose administration at intervals of 6 hours is difficult for a pa-

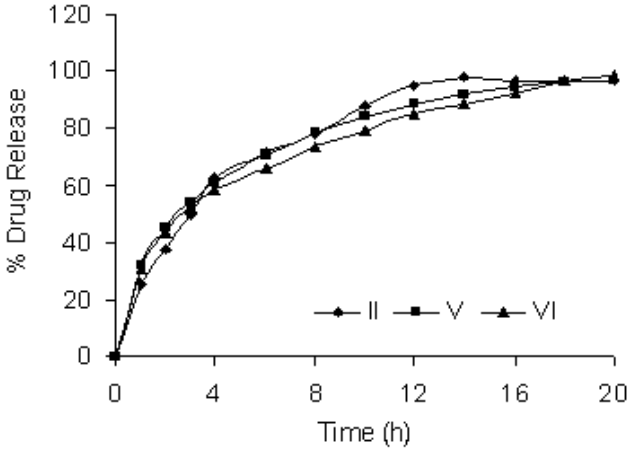

Figure 3. Effect of HCO on tramadol release from hydrophobic matrix system prepared by melt granulation as per Table 1. Dissolution test in DM water using USP apparatus type II at 50 rpm and 37°C (n = 18).

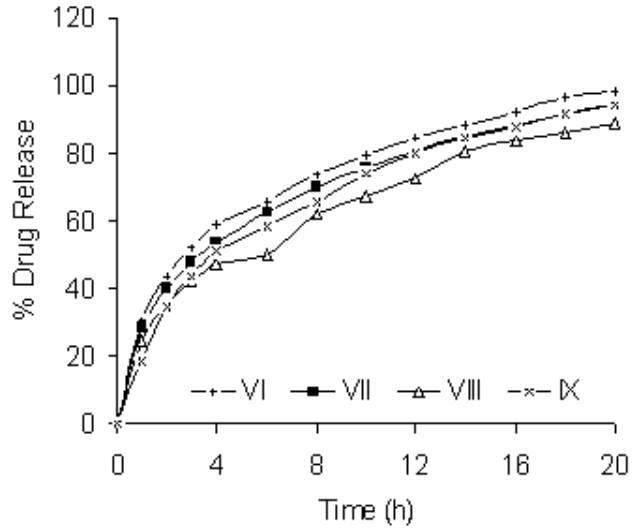

Figure 4. Effect of ethylcellulose on tramadol release from HCO matrix system prepared by melt granulation as per Table 1. Dissolution test in DM water using USP apparatus type II at 50 rpm and 37°C (n = 18).

tient suffering from postoperative or cancerous pain leading to patient noncompliance. Tramadol is rapidly absorbed after single and multiple doses, and the presence of food increased the bioavailability.[8-9] Tramadol with all evident advantages was proved to be a suitable candidate for development of a controlled-release dosage form.[10] Various techniques were developed for controlled delivery of tramadol hydrochloride. Monoolein-water systems containing tramadol HCl were developed.[11] Tramadol was complexed with sulfonic acid cation-exchange resin by a column method and microencapsulated by spray drying technology for a better release pattern.[12]

HPMC, which is commonly used in hydrophilic matrix drug delivery systems, is mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. The hydration rate of HPMC depends on the nature of these substituents. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropyl content. The solubility of HPMC is pH independent.[13] In the present study, 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. In an attempt to prolong the release of drug, the concentration of HPMC was increased. An increase in concentration of HPMC did not significantly prolong the drug release (**Figure 1**). Faster release of the drug from the hydrophilic matrix was probably due to faster dissolution of the highly water-soluble drug from the core and its diffusion out of the matrix forming the pores for entry of solvent molecules. Further, ethylcellulose was incorporated in the hydrophilic matrix. The matrix could release the drug up to 14 hours only. Incorporation of ethylcellulose 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 (**Figure 2**).

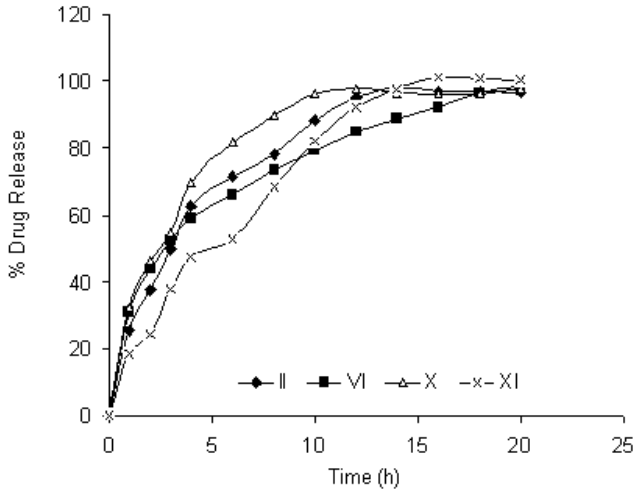

Figure 5. Effect of combination of hydrophilic (HPMC) and hydrophobic (HCO) matrixing polymers on release rate of tramadol. Granules were prepared by melt granulation with HCO as per Table 1, and HPMC was added extragranularly. Dissolution test in DM water using USP apparatus type II at 50 rpm and 37°C (n = 18).

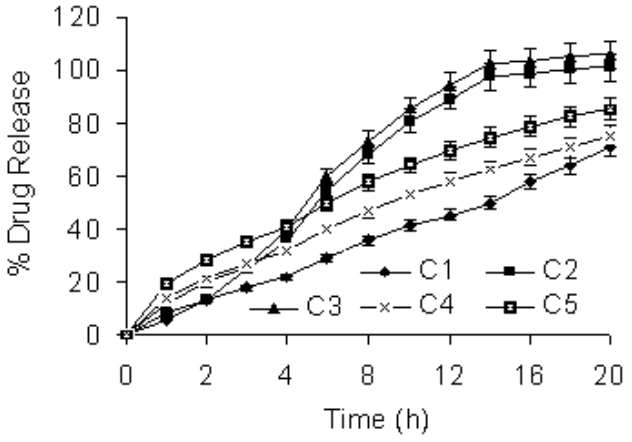

Figure 6. Effect of coating composition on tramadol release from hydrophobic (HCO) matrix system prepared by melt granulation. Dissolution test in DM water using USP apparatus type II at 50 rpm and 37°C (n = 18).

Because the hydrophilic matrix system could control the release only up to 14 hours, a hydrophobic matrix system using HCO was investigated. HCO is a white to slightly yellow fine powder obtained by hydrogenation of castor oil using a catalyst. HCO has been used in formulation technology as a sustained-release coating material and hardening agent.[14] When tablet components are compressed, HCO forms a thin coating on the surface of the drug particles; thus, HCO may function as a binder. Physical mixing of drug with HCO to obtain the prolonged release was described by Yonezawa et al.[15] In the present study, the matrix system was developed by melt granulation technique. The tramadol release rate was slower compared with the hydrophilic matrix system (**Figure 3**). The slow release of the drug could be due to the formation of a uniform coating on individual drug particles by the hydrophobic polymer during melt granulation. It was reported that, in designing the controlled drug delivery device, the melt granulation technique is better compared with matrices prepared by direct compression of physical mixture of the polymer with the drug.[16] Initial burst release (32% in the first hour) from the matrix could probably be attributed to the dissolution of drug from the surface of the tablet. Further, penetration of the solvent molecule was hindered due to hydrophobic coating of the HCO on the drug particle leading to slow drug release for a prolonged period. Ethyl cellulose has been used as a release retardant polymer in controlled-release matrix dosage forms.[17] Presence of hydrophobic polymer along with the wax matrix was found to reduce the drug release further (**Figure 4**), possibly due to the reduction in the penetration of the solvent molecules into the system because of the hydrophobic nature of ethylcellulose present on the surface of the tablet.

In the present study, another approach of combination of hydrophilic (HPMC) and hydrophobic (HCO) matrixing polymer in controlling the release rate of tramadol was also examined. The release profile of the drug was found to be significantly rapid (**Figure 5**). Surprisingly in the dissolution medium, the tablet was found to swell and burst out the drug. This result could be attributed to the presence of both HPMC, which rapidly takes up the water molecules leading to swelling, and HCO, which repels the water molecules, resulting in separation of the formulation components. From the dissolution data, one can conclude that the combination of hydrophilic and hydrophobic polymer matrices is not suitable in the development of a controlled-release dosage form for water-soluble drugs.

Application of film coating is the simplest approach to mask the bitter taste of the drug. With a dual objective of taste masking and controlling the initial burst release, it was decided to coat the tablets with Surelease (aqueous dispersion of ethylcellulose). Surelease is used as a rate retardant polymer in wide array of formulations. Pellets coated with Surelease containing HPMC were found to increase the drug release from the pellets.[18] Incorporation of hydrophilic excipients such as HPMC in the coating formulation was found to facilitate the drug release from the hydrophobic coating materials.[19] To evaluate the effect of coating on drug release, tablets of formulation VI were coated with Surelease (15% aqueous dispersion). Application of Surelease coating drastically impaired the initial burst release (**Figure 6**). The initial decrease in the drug release after coating could be due to prevention of penetration of water into the matrix system. To aid the initial drug release, hydrophilic excipients such as lactose or HPMC were incorporated in the coating composition. The results of the dissolution studies indicated that incorporation of water-soluble excipients aided in the initial drug release. Moreover it was observed that one could control the initial drug release by altering the amount of lactose or HPMC in the coating composition (**Figure 6**). HPMC and lactose are hydrophilic excipients, and their incorporation in the hydrophobic coating causes the formation of channels/pores for entry of water molecules. By changing the amount of such excipients in the coating formulation, one can judiciously control the initial drug release to a desired level.

CONCLUSION

Hydrophilic matrix of HPMC could not control the tramadol release effectively for more than 12 hours. It is evident from the results that a hydrophobic matrix prepared by HCO is a better system for controlled delivery of a highly water-soluble drug like, tramadol hydrochloride. Surelease coating with water-soluble excipients (HPMC 6 cps and lactose) proved to be useful as a functional coating to control the drug release along with masking the bitter taste of the drug.

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