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Development and Characterization of Tramadol Hydrochloride Rectal Suppository

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Abstract

Tramadol is a centrally acting analgesic drug. Rectal administration of tramadol is useful in the treatment of post-operative pain or malignant pain in cases where it cannot be administered orally. Rectal suppositories of tramadol hydrochloride were prepared using different bases and polymers and the effect of different additives on *in vitro* release of tramadol hydrochloride was studied. The agar-based suppositories were non-disintegrating/non-dissolving. All the prepared suppositories were evaluated for various physical parameters like weight variation, drug content and hardness. *In vitro* release study was performed by USP type I apparatus. Addition of 10% w/w propylene glycol accelerates the release of tramadol hydrochloride significantly ($P<0.05$) as in A1, which may be due to decrease in the gel matrix of agar. In formulation A2, A3 Addition of HPMC (1%, 3% w/w) and in formulation A3 and A4 addition of PVP (1%, 3% w/w) retards the release significantly ($P<0.05$), which may be due to increase in the viscosity and gel strength of the polymer matrix. Hence, PVP, HPMC and similar polymers in higher concentration can be used to formulate sustained released suppositories. The sustained release suppositories can be prepared by addition of PVP, HPMC in agar-based suppositories.

Keywords: Tramadol, Rectal suppositories, PVP, HPMC, Agar.

Introduction

Rectal drug delivery has a number of advantages such as reduced hepatic first pass elimination of high clearance drugs, avoidance of gastric irritation associated with certain drugs in case of nausea, vomiting and when the patient is unconscious. Rectal route of administration is specifically useful for infants and children who have difficulty in swallowing oral medicine. Drug administered in suppository form can produce not only local effect but also systemic therapeutic action1. Suppositories can be prepared by using lipophilic bases like cocoa butter or by hydrophilic bases such as PEGs[1-4]. These suppositories melt or dissolve in body fluids and release the drug, but are unstable at higher temperature. Agar has been recently used as base to produce non-disintegrating/ non-dissolving suppositories, which are stable at higher temperature[5,6]. Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It is a centrally acting analgesic with a low affinity for mu opioid receptors (a class of opioid receptors with high affinity for enkephalins and beta-endorphin but low affinity for dynorphins). It consists of two enantiomers, both of which contribute to its analgesic activity via different mechanisms. (+)- Tramadol and its metabolite (+)-*O*-desmethyltramodol (M1), produced by liver *O*-demethylation, are agonists of the mu opioid receptor. (+)-Tramadol also inhibits serotonin reuptake whereas (-)-tramadol inhibits norepinephrine reuptake, to enhance the inhibition of pain[7,8]. Its use is indicated for the management of moderate to moderately severe pain including chronic pain and pain associated with molar extraction in adults[9]. Tramadol is an effective and well-tolerated agent to reduce pain resulting from trauma, renal or biliary colic, and labor, and for the management of chronic pain of malignant or nonmalignant origin, particularly neuropathic pain. Tramadol appears to produce less constipation and dependence than equianalgesic doses of strong opioids[8]. However, after intravenous and oral administration, peak concentrations are reached rapidly, and this has been associated with postoperative nausea and vomiting[10]. Thus, this limits the use of tramadol as a postoperative analgesic, especially in day surgery. Rectal administration of tramadol may be an alternative in this situation. It could be used at the same dose range as that of the oral form to maintain effective pain relief[11]. Furthermore, it is useful in the treatment of post-operative pain or malignant pain in cases where oral administration is not possible[12]. In the present study attempts were made to formulate rectal suppositories of tramadol hydrochloride with bases, as the rectal route avoids first pass metabolism and side effects.

Materials and methods

Materials

Tramadol hydrochloride was obtained as a gift sample from Sun Pharmaceutical Ltd. Ahmedabad. HPMC and PVP were purchased from Loba Chemie Pvt. Ltd., Mumbai. Propylene glycol, methyl paraben and propyl paraben were purchased from S. D. Fine Chemicals Pvt. Ltd., Mumbai, and all other chemicals used were of analytical grade and were used without any further chemical modification.

Preformulation studies[13, 14]

Physical characteristics

By visual examination, the drug was identified for physical characters like colour, texture, odour etc.

Solubility

Solubility of the drug was determined by taking some quantity of drug (about 10 mg) in the 10 ml volumetric flasks separately and added the 10 ml of the solvent (water, ethanol, methanol, 0.1N HCL, 0.1N NaOH, chloroform and 7.4 pH buffer) Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature).

Melting point

A small quantity of powder was placed into a fusion tube. That tube was placed in the melting point determining apparatus (Chemline) containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

FTIR spectroscopy

The concentration of the sample in KBr should be in the range of 0.2% to 1 %. The pellet is a lot thicker than a liquid film, consequently a decrease concentration in the sample is required (Beer's Law). For the die set that you'll be the usage of, about 80 mg of the mixture is wanted. Too excessive of an attention causes typically difficulties to obtain clean pellets. FTIR spectra of the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolution.

Determination of λ_{max} of tramadol HCl

Tramadol, 100 mg, was accurately weighted into a 100 ml volumetric flask, dissolved in phosphate buffer of pH 6.8 and the volume was made up with phosphate buffer of pH 6.8. Pipette 1 ml of this solution into a 10 ml volumetric flask with phosphate buffer of pH 6.8 as the volume and marks it as stock. Prepare an appropriate dilution to bring the concentration down to 2.5-17.5µg/ml. The resulting solution is scanned with a UV spectrophotometer (UV-1700 Shimadzu corporation, Japan) in the range of (200-400 nm) to determine the absorption maximum (λ max). Concentration vs. absorbance was shown on a graph.

Preparation of tramadol hydrochloride rectal suppository

Agar suppositories were prepared by molding method[15], dissolving methyl and propyl paraben in hot water and then drug along with other additives like propylene glycol, HPMC, PVP was added and mixed well. Finally, agar was incorporated by maintaining the temperature at 75-80°C and mixed thoroughly. The molten mass was poured into previously calibrated stainless-steel mould of 1g and allowed to set. The details of all formulations are tabulated in Table 1. All the prepared suppositories were packed in polyethylene laminated foil pouches.

Table 1: Formulations of tramadol hydrochloride rectal suppositories

Ingredients (%w/w)	Formulation codes				
	A0	**A1**	**A2**	**A3**	**A4**
Tramadol hydrochloride	5	5	5	5	5
Agar	10	10	10	10	10
Propylene glycol	-	10	10	10	10
Methyl paraben	0.03	0.03	0.03	0.03	0.03
Propyl paraben	0.02	0.02	0.02	0.02	0.02
HPMC	-	-	1	3	-
PVP	-	-	-	-	1
Water qs	100	100	100	100	100

Evaluation

Prepared suppositories were visually inspected. Randomly selected suppositories were cut longitudinally and the surfaces were examined with naked eye. For determination of weight uniformity, twenty suppositories were weighed individually and the average weights were determined[16]. No suppositories should deviate from average weight by more than 5% except two, which may deviate by not more than 7.5%. The drug content for agar suppositories was determined by soaking individual suppository in water for 30 min, broken with spatula, vortexed for 5 min, filtered, diluted to 50 ml with distilled water, and then tramadol hydrochloride was estimated by Shimadzu UV/visible spectrophotometer at 271 nm. The hardness of the prepared suppositories was tested using Monsanto hardness tester. Hardness test or breaking strength test was carried to determine the tensile strength of the suppositories to access whether they will be able to withstand the hazards of packing and transporting[17]. USP tablet disintegration apparatus was employed to measure the melting range of suppositories[18]. The time taken for the entire suppositories to melt/disperse was measured when immersed in water bath maintained at constant temperature of 37±0.5^{0}C. For *in vitro* dissolution studies an Electrolab USP XXIII dissolution apparatus was used[19]. The dissolution medium was 900 ml of distilled water, maintained at 37±0.5^{0}C. The suppository was placed in the metal basket and maintained at 50 rpm. Ten millilitres of sample was withdrawn at different intervals of time (10, 20, 30, 45, 60, 90, 120, 180, 240 min) and absorbance was measured at 271 nm.

Results and Discussions

The melting point of tramadol hydrochloride (pure drug) was found to be 180-183°C. Tramadol hydrochloride was freely soluble in water, methanol and ethanol, soluble in chloroform and PBS 6.8. Identification of tramadol hydrochloride was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification Figure 1. The calibration curve of tramadol

hydrochloride was found to be linear in the concentration range of 2.5-17.5 µg/ml at 271nm Figure 2. All the suppositories were free from pits, fissures and cracks. The longitudinal section of the suppositories was plain and clear. The results of different evaluation parameters are shown in Table 2. The weight variation study for all the suppositories were found to be within the acceptable range of <5%, which indicates that calibration of mold was perfect. All the prepared suppositories showed uniformity in drug content and were within the permissible range (97% to 105%) indicating uniformity of drug dispersion in suppositories. The suppositories should have good mechanical strength for handling and transportation. All the suppositories were having good mechanical strength in the range of 1.50 to 2.00 kg/cm^2 showing optimum hardness. Dissolution study of agar-based suppositories indicated that the suppository does not disintegrate, melt or dissolve in the dissolution medium but remains intact. The drug diffuses out from the hydrophilic matrix with time. It was observed that more than 50% of the drug was released from A0 formulation within 60 min. Addition of 10% w/w propylene glycol accelerates the release of tramadol hydrochloride significantly (P<0.05) as in A1, which may be due to decrease in the gel matrix of agar. In formulation A2, A3 addition of HPMC (1%, 3% w/w) and in formulation A3, A4 addition of PVP (1%, 3% w/w) retards the release significantly (P<0.05), which may be due to increase in the viscosity and gel strength of the polymer matrix. Hence, PVP, HPMC and similar polymers in higher concentration can be used to formulate sustained released suppositories Table 3.

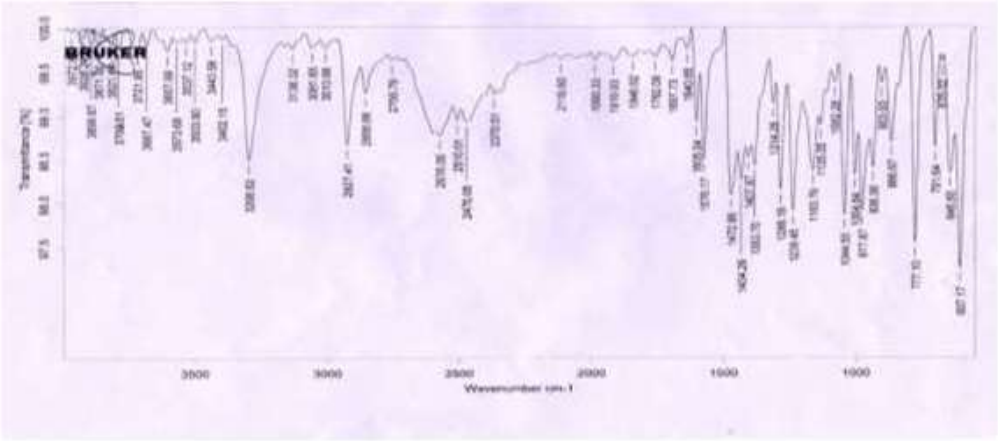

Figure 1: FT-IR spectrum of pure drug (Tramadol hydrochloride)

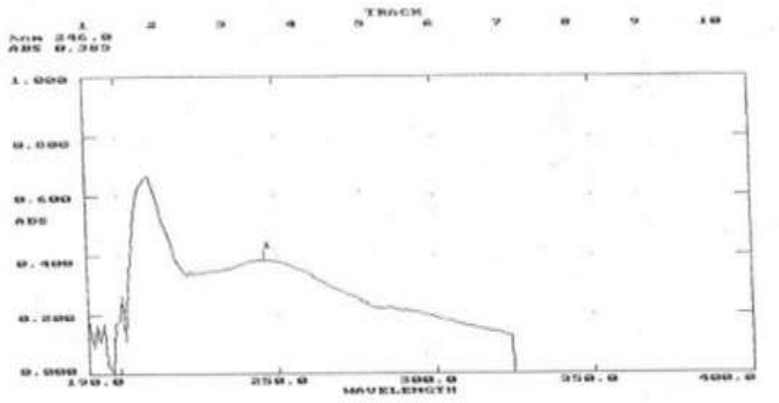

Figure 2: Wavelength maxima of tramadol hydrochloride in PBS 6.8

Table 2: Evaluation of suppositories for various parameters

Formulation code	Drug content* (%)	Weight variation ±SD (g)	Hardness* (kg/cm2)
A0	97.55	1.008±0.04	1.50
A1	97.00	0.997±0.04	2.00
A2	98.10	0.998±0.03	2.00
A3	101.30	1.001±0.01	2.00
A4	105.00	1.002±0.02	2.00

Table 3: *in vitro* release of tramadol hydrochloride from suppositories

Time (Min)	% Drug Release				
	A0	**A1**	**A2**	**A3**	**A4**
40	30	60	45	20	50
80	40	72	55	30	59
120	50	78	60	35	62
160	60	80	65	40	65
200	65	82	70	45	68
240	70	85	75	55	70

Conclusion

In conclusion, tramadol hydrochloride suppositories prepared using bases showed a rapid and almost complete release of the drug from their bases. Rectal administration of tramadol in addition to oral and intravenous administration may be an alternative route for the treatment of pain.

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