ORIGINAL ARTICLE

Development and evaluation of modified release wax matrix tablet dosage form for tramadol hydrochloride

Paresh Ramesh Mahaparale, Bhanudas Shankarrao Kuchekar[1]

Department of Pharmaceutics, Padm Dr. D. Y. Patil College of Pharmacy, Sector 29, Pradhikaran, Akurdi, [1]Department of Pharmaceutical Chemistry, MAEER's Maharashtra Institute of Pharmacy, Pune, Maharashtra, India

The objective of this study was to develop modified release dosage forms of tramadol hydrochloride using wax matrix system by melt granulation method. The effect of various waxes, concentration of waxes, effect of excipients on the release profile of drug from wax matrix system was studied. Release retardant effect was observed in the order of hydrogenated vegetable oil (HVO) > compritol >precirol. This may be due to more lipophilicity imparted by HVO than any other waxy substances. It was also observed that as ratio of drug: Wax was increased, it sustained release of drug for more time. This may be due to proper embedment/entrapment of drug in sufficient wax matrix system. In case of excipients, release retardant effect was found in order of dicalcium phosphate (DCP) > microcrystalline cellulose (MCC) > lactose. DCP is insoluble which helps in release retardation of drug. MCC is hydrophilic swellable polymer which showed release of drug by swelling. Lactose is soluble excipient which get dissolved and formed channels for entry of dissolution medium and release of drug occurred by erosion mechanism. Wax matrix tablets were found to be stable.

Key words: *Melt granulation, tramadol hydrochloride, wax matrix tablet*

INTRODUCTION

Tramadol Hydrochloride is centrally acting analgesic with weak opioid agonist properties. The half-life of drug is about 5 h and needs 50–100 mg every 4–6 h.[1-3] Modified release dosage form of tramadol hydrochloride is desirable to reduce the frequency of administration and to improve patient compliance. As drug is highly water soluble, high viscosity hydrophilic polymers was not found to be sufficient to sustain the release of drug due to rapid diffusion and faster erosion of tablet matrix. Waxes due to its lipophilicity, found to be suitable matrixing agents for modified release dosage forms of drug. It offers advantages like good stability at varying pH values. Compritol 888 ATO (Glyceryl behenate), Precirol ATO 5 (Glyceryl palmitostearate), and hydrogenated vegetable oil (HVO) were used as wax substances. Liquid penetration into the matrix is the rate limiting step in such systems. Mostly, release of drug was observed by pore diffusion and erosion mechanism. Excipients such as dicalcium phosphate (DCP), microcrystalline cellulose (MCC), and lactose were used.

Address for correspondence:
Prof. Paresh Ramesh Mahaparale
Department of Pharmaceutics, Padm Dr. D. Y. Patil College of Pharmacy, Sector 29, Pradhikaran, Akurdi, Pune - 411 044, Maharashtra, India.
E-mail: pareshmahaparale@gmail.com

MATERIALS AND METHODS

Tramadol Hydrochloride was obtained as gift sample from Nicholas Piramal, Mumbai. HVO was obtained as gift sample from Emcure Pharmaceuticals, Pune. Compritol 888ATO, Precirol ATO 5 was obtained as gift sample from Colorcon Asia Pvt. Ltd., Goa. DCP, lactose, and MCC were obtained as gift sample from Signet Chemical Corporation, Mumbai.

Preparation of matrices by melt granulation method
The waxy substances such as Compritol 888 ATO, Precirol ATO 5, and HVO were separately melted in porcelain dish on a water bath maintained at constant temperature as per their melting points. Drug was gradually added to the molten wax with continuous

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stirring. The molten mass was allowed to cool and solidified at room temperature. The solidified mass was pulverized in mortar and passed through sieve no. 22. The obtained mass was compressed on 8 station tablet compression machine (CIP Machinaries, Ahmedabad) to prepare tablets.[4-6] In order to study the effect of different wax substance, ratio of wax (1:1, 1:2, 1:3), different excipients, various formulations were developed [Table 1].

The prepared melt granules were subjected for Fourier transform infrared (FTIR) study, differential scanning calorimetry (DSC) study to check for the interaction between drug and waxes. The prepared tablets were subjected for % drug content, hardness, *in vitro* drug release study.

***In vitro* drug release study**

A standard USP XXII rotating paddle apparatus (Veego Instruments, Mumbai) was employed in the release studies at 100 rpm maintained at 37°C ± 0.5°C in 900 ml of 0.1 N HCl for 16 h.[4] Aliquot of 10 ml samples were withdrawn from the dissolution medium and replaced by the same volume of dissolution medium. Sampling interval was kept at 1, 2, 4, 8, 12, and 16 h. The samples were measured spectrophotometrically at 271 nm using UV spectrophotometer (Shimadzu 1700 PC, Japan).

The release profile of the drug was analyzed using different kinetic models such as zero order, first order, Higuchi, Hixson Crowell, and Korsmeyer–Peppas model in order to evaluate the release mechanism from matrices. Furthermore, T_{25}, T_{50}, T_{75}, and T_{90} value was determined for each formulation.[7,8] The similarity factor f_2[9,10] was calculated for all the formulations by comparing drug release profile of all formulations with marketed formulation of Tramadol HCl (Contramal SR 100 mg - Nicholas Piramal).

Stability study

The promising formulations of modified release tramadol HCl tablets were subjected for stability study.[11,12] The tablets were placed in the stability chamber maintained at 40°C ± 2°C and 75% ±5% RH for 6 months. The samples were withdrawn after 1, 3, and 6 months and evaluated for % drug content, hardness, and *in vitro* dissolution study.

RESULTS AND DISCUSSION

Compatibility study

Fourier transform infrared study

Fourier transforms infrared spectrum of pure drug, and physical mixture of drug and polymers was studied [Figure 1]. It was observed that there were no major shifts in main peaks of drug. This indicates that there was no compatibility issues of drug with waxes used.

Differential scanning calorimetry study

Differential scanning calorimetry (DSC) curves obtained for the pure drug, wax, and their formulations are shown in Figures 2 and 3. Pure drug showed a sharp melting endotherm peak at 183°C. DSC of Compritol and HVO showed single sharp endothermic peak at 76°C and 88°C, respectively. In Figure 2, DSC of melt granulated formulation showed sharp endothermic peaks at 182°C and 77°C which are corresponding to melting points of drug and compritol. In Figure 3, DSC of melt granulated formulation showed sharp endothermic peaks at 182°C and 88°C which are corresponding to melting points of drug and HVO. Presence of all peaks indicates that all ingredients were compatible with each other.

***In vitro* drug release study**

Release of drug from wax matrix tablets is reported in Table 2. Study for each formulation was carried out in triplicate. The slower drug release was observed from wax matrix tablet prepared by melt granulation method. This may be due to hydrophobicity of wax matrix system

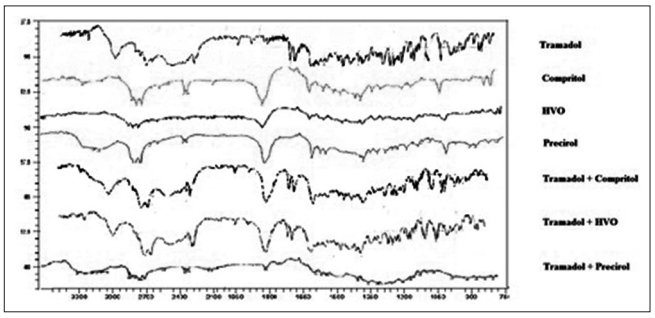

Figure 1: Drug wax compatibility study

Table 1: Formulation of tablet by wax matrix system

Formula	TM1	TM2	TM3	TM4	TM5	TM6	TM7	TM8	TM9	TM10	TM11	TM12
TM HCl	100	100	100	100	100	100	100	100	100	100	100	100
Compritol	100	200	300	-	-	-	200	200	200	100	100	100
Precirol	-	-	-	100	-	-	-	-	-	-	-	-
Hydrogenated vegetable oil	-	-	-	-	100	200	-	-	-	-	-	-
Microcrystalline cellulose	-	-	-	-	-	-	100	-	-	100	-	-
Dicalcium phosphate	-	-	-	-	-	-	-	100	-	-	100	-
Lactose	-	-	-	-	-	-	-	-	100	-	-	100
Total	200	300	400	200	200	300	400	400	400	300	300	300

TM: Tramadol, HCl: Tramadol hydrochloride

Table 2: Dissolution data of tablet prepared by melt granulation method

Cumulative % drug released (average* [*n*=3]±SD)												
Time (h)	**TM1**	**TM2**	**TM3**	**TM4**	**TM5**	**TM6**	**TM7**	**TM8**	**TM9**	**TM10**	**TM11**	**TM12**
1	18.66±1.43	17.25±1.26	11.91±1.19	31.33±1.62	20.63±2.29	13.17±1.15	15.00±1.37	18.38±1.01	23.16±1.65	27.95±2.02	33.30±1.30	25.42±1.93
2	31.25±1.71	18.57±1.04	14.29±2.02	44.90±1.55	24.94±2.89	16.70±1.87	18.41±2.03	23.51±1.58	28.21±2.79	38.39±2.33	40.00±1.63	36.25±2.25
4	45.96±2.18	26.63±2.34	18.01±1.42	62.30±2.78	34.68±1.34	19.75±1.48	26.61±2.64	31.09±1.67	36.33±1.34	51.98±1.40	52.63±2.58	53.90±1.69
8	65.73±1.33	40.67±1.49	28.09±1.47	81.40±2.11	47.81±1.86	25.91±2.09	43.83±2.38	45.04±2.49	55.85±1.56	68.73±2.24	65.15±2.72	80.90±2.29
12	78.69±2.02	55.23±1.62	37.22±1.89	95.63±1.94	58.69±2.03	32.22±1.23	56.23±1.59	58.69±2.37	67.88±2.07	82.04±1.75	75.23±1.47	95.63±2.67
16	94.00±1.14	67.88±1.07	47.22±2.56	99.22±1.22	71.42±2.67	42.22±1.65	70.82±1.84	71.22±1.26	82.66±1.92	97.23±1.11	90.25±1.04	101.2±0.92
f_2	42.68	24.61	17.55	77.06	28.51	16.67	25.31	27.24	34.24	53.10	48.04	58.22
Percentage dissolution Time (h)												
T_{25}	1.5	3.7	6.8	<1	2.0	7.7	3.6	2.4	1.2	<1	<1	<1
T_{50}	4.4	10.5	>10	2.8	9.1	>16	10.1	9.3	5.5	3.8	3.7	3.6
T_{75}	9.3	>16	>16	5.8	>16	>16	>16	>16	14.0	10.1	12.0	7.1
T_{90}	15.1	>16	>16	10.6	>16	>16	>16	>16	>16	14.2	16.0	10.8
Best fit model	Matrix	Matrix	Matrix	Matrix	Matrix	Peppas	Matrix	Matrix	Matrix	Peppas	Peppas	Peppas
Diffusion exponent '*n*'	0.582	0.457	0.432	0.467	0.425	0.452	0.565	0.443	0.453	0.431	0.362	0.562

TM: Tramadol, SD: Standard deviation. *n=3

which hinders entry of dissolution medium in matrix giving retardation in release of drug.[4,13]

Effect of wax type on release profile of the drug from wax matrix tablet

When drug and wax substances were used in 1:1 ratio and prepared by melt granulation method, it was observed that HVO sustained the release of drug for more time [Figure 4]. This may be due to a more hydrophobicity imparted by HVO to matrix system. Dissolution media take more time for entry into the tablet and hence diffusion and dissolution of the drug was found to be less. Release retardation effect was found to be in order of HVO >compritol >precirol.[4,13,14]

Figure 2: Differential scanning calorimetry study of tramadol HCl, compritol and melt granulated formulation

Figure 3: Differential scanning calorimetry of tramadol HCl, hydrogenated vegetable oil and melt granulated formulation

Figure 4: Effect of wax type on release profile of drug

Effect of drug: Compritol ratio on release profile of the drug

When ratio of drug: Compritol was increased from 1:1, 1:2, 1:3, the release retardant effect was found to increase [Figure 5]. This may be due to drug dispersed in more amount of wax substance which imparts more hydrophobicity to the formulation. Dissolution media cannot enter easily in matrix system; hence, it takes more time for diffusion and dissolution of drug from wax matrix system having more ratio of drug: wax.[6,15]

Effect of excipients on release profile of the drug

Excipients like DCP (insoluble filler), MCC (swellable), lactose (soluble filler) was used as an excipient in wax matrix system. Sustained release wax matrix tablets of compritol and HVO prepared with lactose showed faster release [Figures 6 and 7]. This may be due to the formation of pores or channels due to dissolution of lactose. Along with the dissolution of lactose tablet also gets eroded and hence release was found to be faster. Wax matrix tablets containing MCC as an excipient showed somewhat faster release as compared to DCP as an excipient. This may be due to slight swelling property of MCC that causes crack formation which creates channel for entry of dissolution medium and causes dissolution of drug. DCP has retarded release of drug due to its insoluble tendency. The release of drug from wax matrix tablet without excipient showed more sustained release effect than wax matrix tablet containing excipient. In wax matrix system, drug is uniformly and molecularly dispersed in wax system. When the granules are compressed drug remains in contact with wax. Presence of excipients in wax matrix system disturbs the integrity of tablet. In both wax matrix system of compritol and HVO, it was observed that as concentration of lactose in wax matrix system increases, it increases release of drug.[4,6,15]

Stability study

Stability study was carried out as per ICH stability guidelines on selected formulations [Table 3]. Formulations were selected on the basis of f_2 factor, cumulative percentage drug release after 16 h. The parameters like percentage drug content, hardness and cumulative percentage drug release were measured. One of the best formulations, TM4 was selected for stability study. Slight change in color and appearance of the tablet was found. Tablet became pale yellow in color and surface became rough. This may be due to the effect of temperature which affects wax present in tablet.

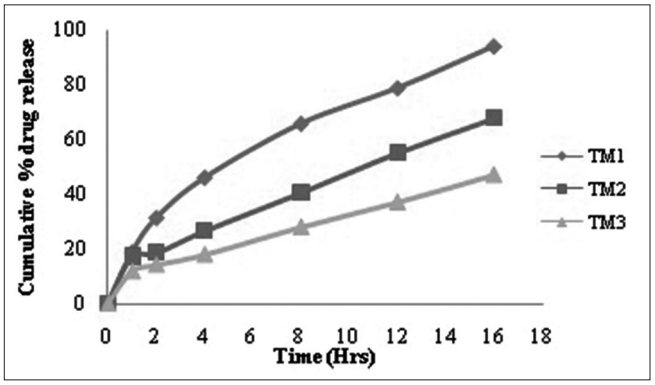

Figure 5: Effect of drug: Compritol ratio on release profile of drug

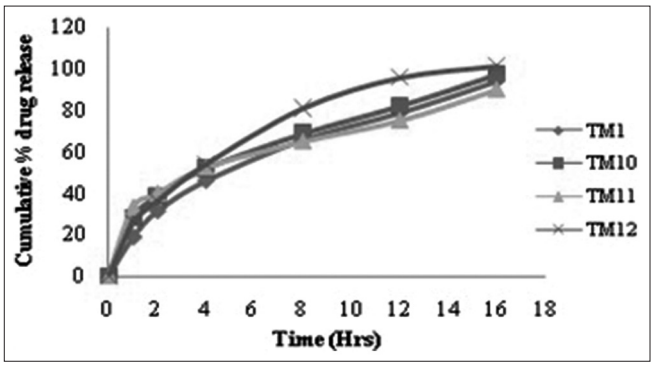

Figure 6: Effect of excipients on release profile of drug from compritol matrix (1:1)

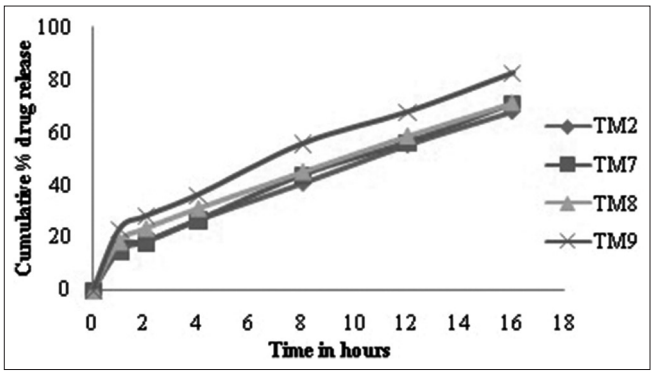

Figure 7: Effect of excipients on release profile of drug from compritol matrix (1:2)

Table 3: Stability study of selected formulations

Formulation code	Time in months	Percentage drug content*	Hardness*	Cumulative % drug released (average* [*n*=3]±SD)			
				1 h	4 h	8 h	16 h
Wax matrix (TM4)	Initial (0)	98.12±0.55	6.2±0.56	25.42±2.09	53.9±1.11	80.90±2.51	101.23±1.08
	1	97.88±0.72	6.3±0.27	26.23±1.72	53.85±1.78	81.12±2.00	99.85±0.79
	3	97.45±1.08	6.3±0.56	26.56±1.42	55.39±1.37	81.56±1.61	99.23±0.97
	6	97.32±0.82	6.3±0.56	27.12±1.17	56.26±2.02	83.13±1.19	99.12±1.09

SD: Standard deviation, TM: Tramadol. *n=3

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