Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Preparation and Evaluation of Sustained Release Tablet of Tramadol Hydrochloride Using Rice Bran Wax

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ARTICLE DETAILS

Article history:
Received on 06 May 2013
Modified on 20 June 2013
Accepted on 23 June 2013

Keywords:
Tramadol hydrochloride,
Matrix tablet,
Rice bran wax,
Sustained release.

ABSTRACT

The objective of present work was to formulate and evaluate once a daily sustained release matrix tablet of Tramadol hydrochloride using Rice bran wax. Matrices were prepared by melt granulation technique using Rice bran wax as a release retardant. Pre-compression results revealed that granules of all formulations possessed satisfactory flow-properties and compressibility. All the tablet formulations showed acceptable Pharmacopoeial limit specifications for weight variation, drug content, hardness, thickness and friability. The *in vitro* release of drug from the formulations was studied in p^H 1.2 acidic buffers and p^H 6.8 phosphate buffer, and it was found that formulation F6 (30% of wax) exhibited good drug release pattern to provide sufficient concentration for achieving satisfactory therapeutic value for extended period of time. The formulation was optimized on the basis of acceptable tablet properties and *in-vitro* drug release. The release of Tramadol hydrochloride from the tablets was diffusion controlled and the release mechanism was non-Fickian. Stability studies (40±2°C/75±5% RH) for 3 months indicated that no appreciable difference was observed for the drug content and drug release.

INTRODUCTION

Sustained release (SR) drug delivery systems are developed to modulate the release of drug, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance [1].

The Non-bioerodible polymer and wax are commonly used as matrix forming components. The use of wax seems to have particular advantage due to chemical inertness against other materials, good stability varying at p^H and moisture levels and well established safe application in humans being [2]. Rice bran wax (RBW) is obtained from natural source (*Oryza sativa*-Family *Graminae*) and is abundantly available. It is an important by product of rice bran oil (RBO) industry.

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Chemically, the RBW is composed of esters with 46 to 60 carbon atoms, in which the most of aliphatic alcohols and aliphatic acids have 26-30 carbon atoms. Rice Bran Wax has application in a wide variety of cosmetics, and foods as a thickener, binding agent, plasticizer, coating and gelling agent [3, 4].

Tramadol hydrochloride is a synthetic opioid of the aminocyclohexanol derivative, centrally acting non-steroidal anti-inflammatory drug with weak opioid agonist properties. The half-life of Tramadol is about 5.5 h and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 h with a maximum dosage of 400 mg/day. However, its mean absolute bioavailability is only 65-70% due to the first-pass hepatic metabolism [5-7].It has been used since 1977 for the relief of strong physical pain and has been the most widely sold opioid analgesic drug in the world. Long term treatment with sustained release once daily is generally safe in patients with osteoarthritis or refractory low back pain and is well tolerated. The development of oral sustained release matrix tablets of Tramadol hydrochloride is highly useful considering the

above said facts and also the previous studies reported the oral controlled release system of Tramadol hydrochloride in the form of matrix tablets; however, there is no report on natural Rice bran wax matrix. Hence the present work was undertaken with an objective of development and evaluation of once a daily sustained release matrix system of Tramadol hydrochloride using Rice bran wax for treating osteoarthritis.

MATERIALS AND METHOD

Tramadol hydrochloride of pharmaceutical grade were obtained as gift sample from Sun Pharma Pvt. Ltd (Baroda, India), Rice bran wax was procured from Bajaj Rice Mill, Warangal (Andhra-Pradesh, India), Lactose anhydrous were kindly supplied by Zydus Cadilla Pvt. Ltd (Ahmadabad, India), Microcrystalline cellulose, Magnesium stearate and Talc were procured from Loba Chemie Pvt. Ltd (Mumbai, India). All other reagents and chemicals used were of analytical reagent grade.

Purification of Rice bran wax

The crude wax (100gm) was soxhleted with ethyl acetate (300 ml) for 30 min at 85 ^{0}C. The mixture in thimble was cooled up to 25 ^{0}C and was subjected to decolourization with 2% H_2O_2 at 90 ^{0}C for 1 h and secondary decolourization with NaOCl 15% at 100 ^{0} for 1 h. The purified wax obtained was then used for further study [8].

Preparation of matrix tablet

For the preparation of sustained release matrix tablet, rice bran wax was used in different concentrations ranges from 5% to 35%. Rice bran wax granules were prepared by melt granulation technique [9, 10], melting wax by heating at constant temperature 85-90^{0}C. Drug and diluents (Lactose anhydrous) were gradually added to the molten mass with continuous stirring. The molten mixture was then allowed to cool and solidify at room temperature and pulverized in mortar and sized through a 16 mesh sieve. The prepared granules were subjected to drying at 40^{0}C for 4 h. After drying, the granules were screened through sieve no 22 & 44 and stored for further studies. Specified quantity of magnesium stearate and talc was finally added into the granules and mixed thoroughly. The mixture was directly punched into tablets weighing about 300 mg containing 180 mg of Tramadol hydrochloride, using rotary tablet compression machine (12 stations, Karnavati, India), using 10 mm diameter concave punches. The different batches of Tramadol hydrochloride tablets were collected and stored in air tight containers. The composition of various formulations of the tablets with their codes is listed in Table 1.

Pre-compression studies of Cyproheptadine hydrochloride granules

Granules ready for compression were evaluated for flow properties like Bulk density, Tapped density, Carr's index, Angle of repose and Hausner's ratio [7, 11-13].

Post-compression studies of Cyproheptadine hydrochloride tablets

The hardness of tablets (n=6) were determined by using Tablet strength tester (Monsanto, 13-1). The Friability (n=10) of the tablets was determined using a USP-I Friabilator (EF 1W; Electrolab), and Uniformity of tablet weight (n=20) was evaluated as per Pharmacopoeial guidelines. Thickness (n=3) of the tablets was determined by using Vernier Calipers (Mitatoyo, Japan) and Drug content of the tablet was assayed in triplicate using validated UV-Spectrophotometer (Jasco, V-630) method [7,11-13].

In-vitro drug release studies

The release of drug from different batches of prepared tablets was studied by using USP dissolution apparatus type II. The dissolution medium used was 900 ml of acidic buffer of p^H 1.2 for 2 h and phosphate buffer of p^H 6.8 for 22 h. The temperature was maintained at 37°C ±0.5°C and the stirring rate was 100 rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV Spectrophotometer at 271 nm against a blank [7, 14].

Analysis of release data

The release data obtained were treated according to Zero order (cumulative amount of drug release versus time), First-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models [15].

Stability study

The stability of optimized formulations was tested according to ICH [16] guidelines. The formulations were stored at accelerated (40±2°C/75±5% RH) test conditions in stability chamber (Remi, CHM-6S) for three month. At the end of month, tablets were tested for drug content and percent drug released.

Table 1: Composition for formulation batches F1-F7 containing 5 to 35% of rice bran wax

Formulation code (mg)	F1	F2	F3	F4	F5	F6	F7
Tramadol hydrochloride	180	180	180	180	180	180	180
Rice Bran Wax	15	30	45	60	75	90	105
Lactose Anhydrous	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	300	300	300	300	300	300	300

RESULTS AND DISCUSSIONS

The Tramadol hydrochloride granules were prepared by melt granulation method. The prepared granules of different batches were evaluated for their granular size, angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio and the results are shown in Table 2. The granules have an average size in the range of 665±0.01 to 965±0.33 µm, which indicate narrow size distribution. The bulk densities of the granules were found to be in the range of 0.382±0.4 to 0.416±0.3 gm/ml. The angle of repose varied from 21.80±1.76 to 27.04±1.3^{o}, indicate good flow properties of granules. This was further supported by lower compressibility index value. The tapped densities were ranged 0.452±0.019 to 0.500±0.011 gm/ml. Hausner's ratio was found in the range of 1.12±0.36 to 1.20±0.09 and the values shows the low interparticle friction between the granules. All these results indicate that the granules possessed satisfactory flow properties and compressibility [7, 13].

Tablets prepared by melt granulation were subjected to various evaluation tests, such as Thickness, Uniformity of weight, Drug content, Hardness and Friability, and the results are presented in Table 3. The tablet weight was within the prescribed limits as per official requirements and it was varied between 300.6±4.6 to 301.6±3.8 mg. Hardness of tablets was found to be in the range 3.0±0.52 to 4.2±0.24 kg/cm^2, indicate to have better binding properties of granules. Another measure of tablet strength is friability. In the present study the percentage friability for all the formulation was below 1%, indicating that the friability is within the prescribed limits. Drug content was uniform within the prepared batches and ranges between 98.59±0.32 to 99.57±0.63 %. From post-compression studies, it is clear that the above said factors showed acceptable Pharmacopoeial limit specifications [7, 13].

The *in vitro* release was studied in acidic buffer pH 1.2 for 2 h and in phosphate buffer p^{H} 6.8 for 22 h. The drug release from the matrix tablet is based on the porosity of tablets which is due to penetration of water into matrix system. The matrix tablets formulations F1, F2, F3, F4, F5, F6 and F7 containing 5%, 10%, 15%, 20%, 25%, 30% and 45% of carnauba wax showed 96.8±0.61% , 96.8±0.14%, 91.6±0.86%, 95.6±0.60%, 97.1±0.65%, 98.2±0.82% and 90.4±0.74% drug released at the end of 8, 10, 12, 18, 22, 24 and 24 h respectively. It was found that the cumulative percentage drug release of the formulations F1, F2 and F3 are faster than formulation F4, F5, F6 and F7 which showing the slowest release. Drug release was inversely proportional to the amount of rate retarding polymer present in the matrix system i.e. the rate and extent of drug release increases with decrease in total polymeric content of the matrix [17]. Increasing Rice bran wax concentration decreased initial burst release and retards further drug release from the matrix tablets observed in formulations F6 and F7. Among all formulations, F6 containing 30% of Rice bran wax showed 98.00% drug release in 24 h, which indicated that this concentration of wax can be used as an effective matrix former, to retard the release of Tramadol hydrochloride for long period of time i.e. up to 24 h. The selected formulation F6 was subjected to stability study as per ICH guidelines. Table 4 and Fig. 1 presented the percent cumulative drug release and *in-vitro* drug release profile of tablet formulations respectively.

The *in vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to Zero order, First order, and Higuchi and Peppas models in order to determine the mechanism of drug release. The results of linear regression analysis data i.e. regression coefficients are summarized in Table 5.

Table 2: Results of pre-compression studies

Formulation code	Parameters					
	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Car's index (%)	Hausner's Ratio	Angle of repose (^{o})	Particle size (µm)
F1	0.416±0.38	0.500±0.011	16.80±1.9	1.20±0.09	27.04±1.3	665±0.01
F2	0.400±0.13	0.476±0.23	15.96±1.0	1.19 ±0.56	25.64±1.1	795±0.04
F3	0.384±0.07	0.454±0.045	15.41±1.76	1.18 ±0.65	23.57±1.31	825±0.12
F4	0.414±0.035	0.474±0.049	12.64±0.74	1.14 ±0.76	21.80±1.76	855±0.02
F5	0.386±0.32	0.472 ±0.58	12.60 ±1.3	1.23±0.34	25.55±1.24	905±0.05
F6	0.402±0.29	0.452±0.019	12.01±1.89	1.13±0.19	22.60±1.43	938±0.54
F7	0.382±0.41	0.484±0.033	11.70±0.32	1.12 ±0.36	24.62±1.83	965±0.33

Note: Mean of 3±SD

Table 3: Results of post-compression studies

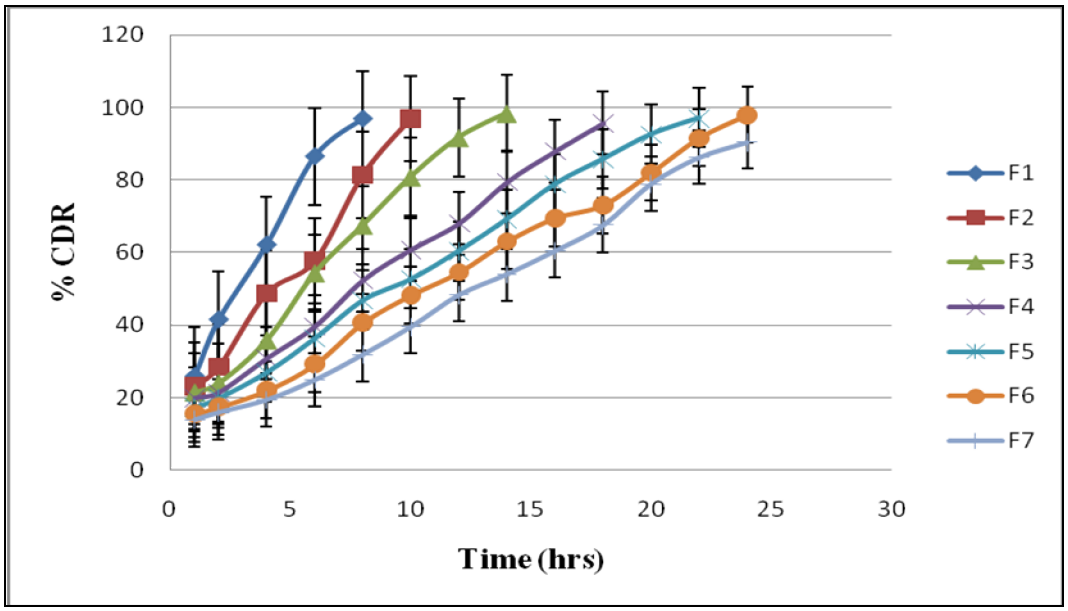
Formulation code	Weight variation[a](mg)	Thickness[b] (mm)	Hardness[c] (kg/cm^2)	Friability[d] (%)	Drug content[e] (%)
F1	301.4±1.5	3.76±0.052	3.0±0.52	0.13±0.67	98.87±0.45
F2	301.3±3.6	3.82±0.047	3.2±0.18	0.49±0.56	99.15±0.25
F3	301.5±4.5	3.72±0.050	3.3±0.55	0.19±0.56	98.73±0.85
F4	300.7±4.2	3.80±0.052	3.6±0.50	0.16±0.78	99.43±0.32
F5	301.6±3.8	3.65±0.052	3.8±0.32	0.23±0.69	98.59±0.32
F6	301.4±2.6	3.72±0.042	4.0±0.42	0.26±0.23	99.57±0.63
F7	300.6±4.6	3.66±0.052	4.2±0.24	0.17±0.64	99.29±0.67

Notes: [a]Test performed on number of tablets weighing not less than 2 gm, [b]Mean of 3±SD, [c]Mean of 6±SD, [d]Test performed on 20 tablets and [e]Mean of 3±SD.

Table 4: *In vitro* dissolution data for formulations F1-F7

Time (h)	% Cumulative drug release						
	F1	F2	F3	F4	F5	F6	F7
1	26.2±0.12	23.20±0.34	21.5±0.36	19.8±0.48	17.1±0.51	15.4±0.14	13.9±0.09
2	41.5±0.24	28.5±0.28	24.7±0.71	21.3±0.63	19.7±0.97	17.3±0.93	15.9±0.29
4	62.1±0.46	48.8±0.41	35.8±0.61	30.7±0.77	26.9±0.29	22.1±0.10	19.3±0.83
6	86.4±0.39	57.6±0.57	54.3±0.26	39.5±0.95	36.3±0.13	29.1±0.71	24.8±0.78
8	96.8±0.61	81.3±0.42	67.5±0.15	52.3±0.30	46.7±0.43	40.6±0.46	31.8±0.88
10	-	96.8±0.14	80.8±0.58	60.7±0.37	52.6±0.56	48.2±0.72	39.5±0.54
12	-	-	91.6 ±0.86	68.4±42	60.4±0.54	54.5±0.85	48.3±0.35
14	-	-	-	79.3±0.73	69.2±0.32	63.2±0.69	54.1±0.55
16	-	-	-	87.8±0.58	78.9±0.43	69.5±0.55	60.4±0.84
18	-	-	-	95.6±0.60	85.8±0.41	73.1±0.21	67.5±0.59
20	-	-	-	-	92.6±0.39	82.8±0.71	78.9±0.69
22	-	-	-	-	97.1±0.65	91.6±0.62	86.2±0.62
24	-	-	-	-	-	98.2±0.82	90.4±0.74

Note: Mean of 3±SD



n=3, Error bars indicate standard deviation.

Figure 1: The *in-vitro* drug release profile of Tramadol hydrochloride from tablet formulations F1 to F7

Table 5: Release kinetic of tramadol hydrochloride tablet formulations

Formulation code	R^2				
	Zero order	First order	Higuchi	Korsmeyer Peppas	Korsmeyer Peppas (n)
F1	0.958	0.946	0.979	0.930	0.5623
F2	0.959	0.947	0.990	0.942	0.5337
F3	0.962	0.934	0.994	0.954	0.5911
F4	0.971	0.954	0.989	0.937	0.5655
F5	0.961	0.963	0.996	0.934	0.5693
F6	0.979	0.972	0.997	0.967	0.5753
F7	0.965	0.952	0.992	0.966	0.5681

The R^2 values obtained from Zero order equation for F-1, F-2, F-3, F-4, F-5, F-6 and F-7 were 0.958, 0.959, 0.962, 0.971, 0.961, 0.979 and 0.965 respectively. The R^2 values obtained from first order equation for F-1, F-2, F-3, F-4, F-5, F-6 and F-7 were 0.946, 0.947, 0.934, 0.954, 0.963, 0.972 and 0.952 respectively. The best linearity values found in Higuchi's equation plot were 0.979, 0.990, 0.994, 0.989, 0.996, 0.997 and 0.992 respectively, indicating the release of drug from matrix as a square root of time dependent process based on diffusion. The n values for Korsmeyer and Peppas equation (F-1, F-2, F-3, F-4, F-5, F-6 and F-7) were found to be 0.56, 0.53, 0.59, 0.56, 0.57 and 0.56 respectively, indicating non Fickian (anomalous) release, coupled diffusion. Thus, it was proposed that these formulations delivered their active compounds by coupled diffusion and erosion [15].

The selected formulation F6 was subjected to stability study as per ICH guidelines. There was no significant difference in the drug content and drug release before and after stability studies (Table 6).

Table 6: Accelerated Stability Study Analyzed Data (40±2°c/75±5% Rh)

Stability	Drug content (%)	Drug release (%)
Initial	99.70±0.98	97.57±2.15
1 month	99.49±1.23	97.40±1.68
2 month	99.23±1.54	97.25±1.72
3 month	99.09±0.86	96.94±1.44

Note: Mean of 3±SD

CONCLUSION

The study reveals that, the release of water soluble Tramadol hydrochloride was sustained in concentration 30 % w/w of carnauba wax in order to retard the drug release up to 24 h. The drug released depends on concentration of rice bran wax. The drug release was diffusion controlled and release the release mechanism was non-Fickian. From the present study it may concluded that Tramadol hydrochloride can be formulated as sustained release drug delivery system with Rice bran wax.

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