

Research Article

Preparation and Evaluation of Sustained Release Matrix Tablets of Tramadol Hydrochloride Using Glyceryl Palmitostearate

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Abstract

Purpose: To prepare oral sustained release matrix tablets of a highly water soluble drug, tramadol hydrochloride, and to evaluate the effect of concentration of the hydrophobic polymer content and method of preparation on drug release.

Methods: The tablets were a mixture of both tramadol hydrochloride and glyceryl palmitostearate (GP) prepared by melt granulation (MG1, MG2, MG3 and MG4 in ratios 1:1, 1:2, 1:3 and 1:4, respectively) or by direct compression (DC, 1:2 ratio). The hardness of the tablets was measured. Drug/GP interaction was determined by FT-IR spectroscopy while drug release from the matrix tablets was studied using USP II dissolution apparatus. The release data were subjected to different models in order to evaluate their release kinetics and mechanisms.

Results: The hardness of the tablets was in the range of 5.30 ± 0.36 - 6.50 ± 0.10 kg/cm². FT-IR spectra showed that there was no clear interaction between the drug and the glyceride. Of the formulations (MG1 to MG4) prepared by melt granulation, MG4 showed the most suitable sustained release, 58.4 ± 1.1 % in 12 h ($p < 0.05$). Drug release (98.2 ± 0.2 % in 8 h) was highest for DC which was prepared by direct compression. Also, drug release mechanism for the formulations was by Fickian diffusion.

Conclusion: Glyceryl palmitostearate is a suitable matrix-forming agent to sustain the release of a water-soluble drug such as tramadol hydrochloride. Melt granulation was a better technique for formulating the product than direct compression.

Keywords: Tramadol hydrochloride; Glyceryl palmitostearate; Melt granulation; Direct compression; Sustained release.

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INTRODUCTION

A sustained-release dosage form is defined as “any drug or dosage form modification that prolongs the therapeutic activity of the drug” [1]. The primary objectives of sustained drug delivery are to ensure safety and enhancement of efficacy of drug with improved patient compliance. This delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above the minimum effective concentration and below the minimum toxic level for an extended period of time. Thus, sustained drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects [2].

Glycerides are a family of excipients which have generated considerable interest in the preparation of oral dosage forms. Some glycerides such as Precirol ATO 5 (glyceryl palmitostearate) can be used for the preparation of sustained release dosage forms [3]. The esterification of glycerol by long chain fatty acid gives them a pronounced hydrophobic character with a low HLB value of 2 [4]. Several techniques including melt granulation [5], melt pelletization [6], hot melt extrusion [7] and hot melt coating [8] have been used to obtain sustained release dosage forms from glycerides-based formulations. Melt granulation is a solvent-free process which involves the use of a substance that melts at a relatively low temperature. This substance can be added in the molten form over the substrate or in the solid form, which is then heated above its melting point. The substance acts as a liquid binding agent, and the technique does not require the use of organic solvents. Moreover, in melt granulation drying is not necessary and thus, the process is less consuming in terms of time and energy compared to other methods [9]. Sustained release matrix tablets have been produced with Precirol ATO 5 by various methods including melt granulation

[10], hot melt extrusion [11] and melt pelletization [6].

Tramadol Hydrochloride (TH), a synthetic opioid of the aminocyclohexanol group, is a centrally acting analgesic. The melting point of GP and tramadol hydrochloride (TH) is 52 – 55 and 180 – 184 °C, respectively. Therefore, TH is a thermally stable drug and melt granulation technique should not affect the thermal stability of the drug. It was approved by United States Food and Drug Administration (US FDA) in 1995 and has been proved to be effective in both experimental and clinical pain without causing serious cardiovascular or respiratory side effects [12]. It has a plasma elimination half-life of 4 - 6 h with a usual dosage regimen of 50-100 mg every 4 - 6 h. Therefore, to reduce frequency of administration and improve patient compliance, a sustained release dosage formulation of tramadol is desirable. The drug is associated with certain side effects, such as abdominal pain and anorexia, and may also induce psychic and physical dependence. Therefore, a properly designed sustained release dosage form of the drug should also minimize fluctuation in blood concentration, reduced risk of side effects and show uniform pharmacological response [13].

Hydrophobic matrix tablets have previously been produced to yield sustained tramadol formulations using hydrogenated castor oil and ethyl cellulose [14], and glyceryl behenate [15]. Various monoolein-water systems have been tested in this regard [16] while the drug has also been complexed with a sulfonic acid cation-exchange resin in a microencapsulation process using a spray-drying method [17]. The objective of the present study was to prepare oral sustained release matrix tablet of a highly water soluble drug by melt granulation using glyceryl palmitostearate, and to evaluate the effect of the concentration of the glyceride on the release of the drug. Such a sustained release formulation, if achieved, would be

substantially more affordable than those previously developed.

EXPERIMENTAL

Materials

Tramadol hydrochloride was a gift from Neon Laboratories Ltd, Mumbai, India while glyceryl palmitostearate (Precirol ATO 5) was obtained free of charge from Gattefosse Corp, France. Concentrated hydrochloric acid, sodium hydroxide and potassium dihydrogen phosphate were also obtained free of charge from Fine Chemicals Ltd, Mumbai, India.

Preparation of tramadol hydrochloride matrix tablets

Melt granulation method

The matrix tablets were composed as shown in Table 1. Glyceryl palmitostearate (GP) melted in a porcelain dish over a water bath maintained at 75 °C for 3 min and tramadol hydrochloride (TH) was gradually added with continuous stirring until uniformly mixed. The molten mixture was allowed to cool and solidify at room temperature crushed in a mortar and passed through a 1190 µm aperture sieve. The granules were compressed into 8 mm diameter flat-faced tablets using a press (single punch, semiautomatic, model 999, Shimadzu Corporation, Kyoto, Japan) at a force of 1 ton.

Table 1: Composition of tramadol hydrochloride matrix tablets

| Tablet code | Drug: polymer ratio | Total weight (mg) |
|-------------|---------------------|-------------------|
| MG1 | TH: GP (1:1) | 200 |
| MG2 | TH: GP (1:2) | 300 |
| MG3 | TH: GP (1:3) | 400 |
| MG4 | TH: GP (1:4) | 500 |
| DC | TH: GP (1:2) | 300 |

Note: TH =tramadol hydrochloride; GP = glyceryl palmitostearate

Direct compression method

The drug (TH) and the glyceride (GP) were mixed together (see Table 1) in a mortar for 10 min, and compressed into flat-faced tablets by direct compression.

Evaluation of drug - glyceride interaction

The pure drug, wax and the matrix tablet formulation were subjected to IR spectroscopy using FT-IR spectrophotometer (IRAffinity-1, Shimadzu). Their spectra were obtained over the wave number range of 4000 – 400 cm⁻¹.

Determination of drug content of granules

Drug content was determined by dispersing a quantity of the pre-compression granules, equivalent to 100 mg of tramadol hydrochloride, in 70 ml of distilled water. It was shaken for 15 min, diluted to 100 ml with distilled water and then filtered through Whatman filter paper no. 41. One ml of this solution was transferred to a 10 ml volumetric flask, the final volume made 10 ml, and the absorbance of the resulting solution measured using a UV spectrophotometer (UV – 1800, Shimadzu corporation, Kyoto, Japan) at 271 nm. Drug content was determined from the absorbance data.

Evaluation of *in vitro* drug release

In vitro dissolution assessment of the tablets was carried out in a USP II dissolution apparatus (Electrolab, TDT-08L). Nine hundred millilitres of 0.1 M HCl was used as the dissolution medium for 2 h and then replaced with phosphate buffer (pH 6.8) as the dissolution medium for another 8 h. The medium change was effected by adding 4.32 g of sodium hydroxide and 6.08 g of potassium dihydrogen phosphate dissolved in 5 ml water to the acid [18]. Test temperature was 37±0.5° C while paddle rotation speed was kept at 100 rpm. At predetermined time intervals, 5 ml samples were withdrawn over a period of 12 h, filtered, suitably diluted and

assayed at 271 nm spectrophotometrically (Shimadzu 1800). Sink condition was maintained by replenishing the dissolution medium with 5 ml fresh dissolution fluid on each occasion. All tests were carried out in triplicate. The regression equation of the calibration curve was: $y = 0.0053x + 0.0133$ ($r^2=0.9996$, $n=9$) ($p < 0.05$).

Drug release kinetics

To determine the mechanism of drug release from the formulations, the data were subjected to zero-order (Eq 1), first order (Eq 2) and Higuchi (Eq 3) release kinetics [19,20]

$$M_t = M_0 + k_0t \dots\dots\dots (1)$$

$$\ln M_t = \ln M_0 + k_1t \dots\dots\dots (2)$$

$$M_t = M_0 + k_H t^{1/2} \dots\dots\dots (3)$$

where M_t is the cumulative amount of drug released at any time, t , and M_0 is the dose of the drug incorporated in the delivery system. k_0 , k_1 and k_H are rate constants for zero-order, first order and Higuchi models, respectively. The dissolution data were also fitted according to the well-known exponential equation of Peppas [21], as in Eq 4, which is often used to describe drug release behaviour from polymeric systems.

$$M_t/M_\infty = kt^n \dots\dots\dots (4)$$

where, M_t/M_∞ is the fraction of drug released at time, t , k is the kinetic constant, and n is the diffusional exponent for drug release. The diffusional exponent, n , is dependent on the geometry of the device as well as the physical mechanism of release. Zero order release describes a release rate independent of drug concentration while the Higuchi square root kinetic model describes a time-dependent release process. The value of n indicates the drug release mechanism; if $0.1 < n < 0.5$, Fickian diffusion is indicated while $0.5 < n < 1$ indicates non-Fickian diffusion.

Statistical analysis

Statistical analysis was performed using GraphPad InStat 3 and GraphPad Prism 5 software. All tests were run 3 times ($n = 3$) except the pre-compression parameter. Experimental results were expressed as mean \pm SD, and Student's t-test and one-way analysis of variance (ANOVA) were applied to determine significant difference. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS

FT-IR Spectroscopy

The infrared spectra of the drug, glyceride and tablet formulation are shown in Fig 1. The major IR peaks observed in the spectra for tablet formulation were 1737 (C=O stretching, carbonyl group), 1625 (C=C stretching) which are characteristic of glyceryl palmitostearate, and also 2780 (C-H stretching), 3392 (N-H stretching vibration, tertiary amine), and 1295 (C-N stretching vibration) which are characteristic of tramadol hydrochloride. When this is compared to the spectra of the drug and glyceride, it would appear that there was no obvious interaction between drug and the glyceride.

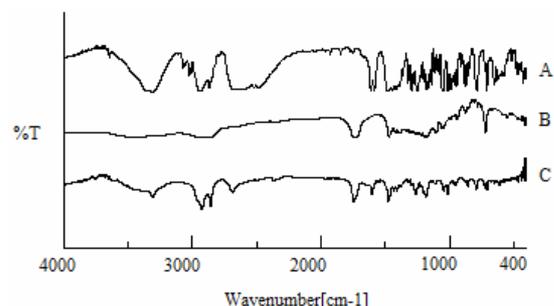


Fig 1: FTIR spectra of tramadol hydrochloride (A), glyceryl palmitostearate (B) and tablet formulation containing both the drug and glyceride (C)

Table 2: *In vitro* release kinetics of tramadol hydrochloride matrix tablets

| Tablet code | Cumulative release (%) after 12 h | Zero order (R ²)±SD | First order (R ²)±SD | Higuchi (R ²)±SD | Peppas | |
|-------------|-----------------------------------|---------------------------------|----------------------------------|------------------------------|--------|----------------------|
| | | | | | (n) | (R ²)±SD |
| MG1 | 93.34±0.89 | 0.996±0.005 | 0.924±0.022 | 0.977±0.004 | 0.3271 | 0.949±0.006 |
| MG2 | 81.58±1.29 | 0.996±0.003 | 0.963±0.001 | 0.968±0.005 | 0.2929 | 0.934±0.012 |
| MG3 | 69.66±1.02 | 0.994±0.006 | 0.987±0.003 | 0.975±0.007 | 0.2610 | 0.938±0.014 |
| MG4 | 58.36±1.09 | 0.993±0.004 | 0.995±0.004 | 0.981±0.007 | 0.2110 | 0.941±0.016 |
| DC | 98.18±0.20 | 0.997±0.006 | 0.854±0.009 | 0.984±0.007 | 0.3868 | 0.970±0.009 |

SD=Standard deviation (n=3). The difference between batch series 'MG' and 'DC' was significant ($p < 0.05$).

***In vitro* drug release**

The drug release data are shown in Table 2. Expectedly, drug release from the tablets prepared by melt granulation was 93.3 ± 0.9 , 81.6 ± 1.3 , 69.7 ± 1.0 and 58.4 ± 1.1 % after 12 h for formulations MG1, MG2, MG3 and MG4, respectively, thus indicating that drug release fell as the glyceride content of the tablets increased. The difference in release rate between the batches was statistically significant ($p < 0.05$). Furthermore, comparison of the two methods of formulation used indicate that cumulative release from the tablets prepared by direct compression (DC, 98.2 %) was significantly higher ($p < 0.05$) than from the equivalent formulation made by melt granulation (MG2, 81.6 %)

Drug release kinetics

Table 2 shows that the best-fit release kinetic data with the highest values of regression coefficient (R²) were shown by zero order and Higuchi models. The values of *n* were in the range of 0.2110 to 0.3868 (i.e., less than 0.5) indicating Fickian release (diffusion-controlled). R² data indicate that Higuchi and Peppas models also suitably described the release of tramadol hydrochloride from the matrix tablets.

DISCUSSION

Effect of concentration of the glyceride matrix on drug release

During preliminary studies (not reported here), it was observed that at low concentrations of the glyceride, the matrices of the tablets readily disintegrated during dissolution test. This was not, however, the case when the content of the matrix former was increased, thus indicating that a minimum of level of the glyceride is required to form a proper matrix that would not readily disintegrate. This study revealed that as the concentration of lipophilic matrix material (i.e., the glyceride) increased, drug release from matrices of the met-granulated tablets decreased (see Fig 2). This may be due to slower penetration of the dissolution medium into the waxy matrices. Formulation MG4 (TH:GP ratio, 1:4) which exhibited the highest drug release retardation, also had the highest matrix concentration. As stated earlier, based on kinetic analysis of release data, tramadol hydrochloride release occurred by a non-Fickian diffusion mechanism. The initial drug release (i.e., in the 1st hour) of 42.9, 40.0, 37.4 and 35.5 % for MG1, MG2, MG3 and MG4, respectively, may be attributed to 'burst' release of the drug on the tablet surface. Reza et al [22], has stated that the drug particles present on the surface of a matrix system were initially released into the surrounding media generating many pores and cracks which facilitate further release of drug and also formation of channels within the matrix in the case of a water soluble drug.

Effect of method of tablet preparation on drug release

Fig 3 compares the release profiles of tablets (TH:GP ratio, 1:2) prepared by melt-granulation and direct compression methods, respectively. Both cumulative drug release and drug release rates were higher for the matrix tablets made by direct compression of physical mixtures than for the tablets obtained by the compression of granules made by melt granulation. This can be attributed to the formation of a more uniform and, therefore, more effective coating of the glyceride matrix around the drug particles in the tablets prepared by melt granulation technique than in those made by direct compression. Thus the tablets made by the former technique are likely to show greater integrity. Consequently, while the probable mechanism of drug release from the direct compressed-matrix tablets is erosion control, drug release from melt granulated tablets would likely be diffusion-controlled as confirmed by the kinetic data in Table 2.

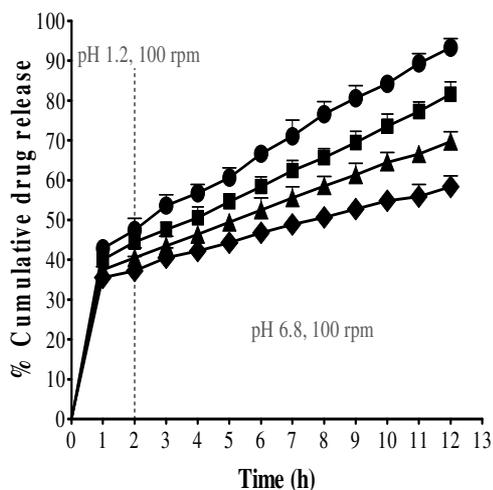


Fig 2: Effect of different concentration of Precirol ATO 5 on in vitro release of formulation MG1 (●), MG2 (■), MG3 (▲) and MG4 (◆) of tramadol hydrochloride matrix tablets.

CONCLUSION

The study showed that glyceryl palmitostearate (Precirol ATO 5) is an appropriate waxy matrix former for sustained release of a water-soluble drug such as tramadol hydrochloride. In this regard, matrix tablets prepared by melt granulation technique were far superior to those prepared by direct compression of the physical mixture. Drug release was diffusion-controlled in the formulations obtained by melt granulation. Furthermore, Higuchi and zero order release kinetics were achieved, thus holding out prospects for a low-cost oral solid dosage form of tramadol hydrochloride with prolonged drug release characteristics.

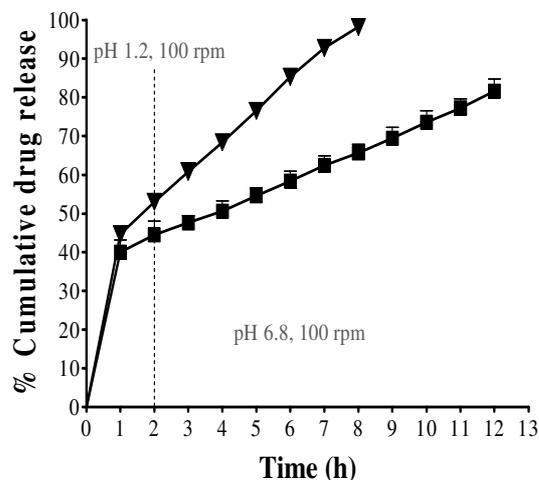


Fig 3: Release profiles of sustained release matrix tablet made by direct compression (DC ▼), and melt granulation (MG ■) in the ratio of 1:2

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