Formulation and evaluation of controlled porosity osmotic pump-based tablet of tramadol hydrochloride

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ABSTRACT

Introductions: Extended-release formulation of tramadol hydrochloride based on osmotic technology was developed and evaluated. The effect of different formulation variables, namely, level of swellable polymer in the core and membrane weight gain, was studied. Drug release was found to be affected by the level of swellable polymer in the core formulation. Tramadol release was inversely proportional to the level of swellable polymer and membrane weight. Drug release from the developed formulations was independent of pH and agitation intensity. Results: The manufacturing procedure was found to be reproducible, and formulations were stable after 3 months of accelerated stability studies.

Key words: Extended release, osmotic pressure, osmotic pump, stability, tramadol hydrochloride

INTRODUCTION

Osmotically controlled oral drug delivery systems utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastrointestinal tract to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system.[1-3] Tramadol hydrochloride, an oral opioid analgesic, is one of the most commonly prescribed drugs for the treatment of post-operative pain. It is highly water-soluble drug belonging to class 1 of the Biopharmaceutic Classification System.[4] Since tramadol hydrochloride is used for long-term treatment for low back pain and osteoarthritis thereby requiring 3–4 times daily dosing in large number of patients which often leads to patient non-compliance. Thus, there is a strong clinical need and market potential for a dosage form that will deliver tramadol hydrochloride in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance.

The present study was aimed toward the development of extended-release formulations of tramadol hydrochloride based on osmotic technology. Different formulation variables were studied and optimized to achieve the desired release profile.

The manufacturing procedure was standardized, and the stability of the formulations was evaluated after 3 months of storage at accelerated stability conditions.

MATERIALS AND METHODS

Materials
Tramadol hydrochloride (99.79% purity) a gift sample was purchased from Aar Ge Drugs Ltd., Parwanoo, India. Following chemicals and excipients were purchased from commercial sources and used as such. Cellulose acetate, mannitol, and microcrystalline cellulose (MCC) from Thomas Baker (Mumbai), polyvinylpyrrolidone (PVP) K 30, polyethylene glycol 400, methanol, and acetone (S.D. Fine Chem Ltd., Mumbai), and hydroxypropyl methylcellulose (HPMC), talc, and magnesium stearate (Central drug house (P) Ltd., New Delhi).

Formulation Development
Before initiating formulation development, compatibility of tramadol hydrochloride with different excipients was tested using the techniques of Fourier-transform infrared.[5]

Excipients used in the final formulation were found to be compatible with tramadol hydrochloride. Core tablets of tramadol hydrochloride were prepared by direct compression method, and batch size was kept as 100 tablets. Tramadol hydrochloride was mixed with HPMC for 10 min. After passing this mixture through #30 mesh sieves, osmotic agent (mannitol), MCC, and PVP were added and mixed continuously for additional 10 min. To this, talc and magnesium stearate were mixed and passed through #60 mesh sieve and mixing continued for additional 5 min. The blend was then compressed into tablets having an average weight of 300–320 mg using a tablet punching machine.

Coating of Core Tablet
Composition of coating solutions used for coating of core tablets is given in Table 1. Various components of coating solution were added to solvent mixture in sequential manner. The component added first was allowed to dissolve before next component was added. Coating process was done on a batch of 100 tablets. Coat weight and thickness were controlled by the volume of coating solution consumed in coating process. Coating was applied to the
tablets by dipping them into the coating liquid. The wet tablets are dried in a conventional manner in coating pan. Alternative dipping and drying steps are repeated several times to obtain the desired coating.

**Composition of Core Tablets**
Osmotic tablet of tramadol is optimized using a varying amount of excipients, which are used in the formulation. Optimized final amount of all excipients is tabulated in Table 2.

**Coating Composition of Core Tablet**
Composition of coating solution is given in Table 1.

### EVALUATION OF FORMULATION OF TRAMADOL HYDROCHLORIDE

#### Evaluation for Pre-compressive Parameters

**Bulk density**
Loose bulk density: An accurately weighed (2.5 g) quantity of powder was transferred to a 10 ml measuring cylinder and the volume occupied by the powder in terms of ml was recorded.

\[
\text{Loose bulk density} = \frac{\text{Weight of powder in g}}{\text{Volume of packing in ml}}.
\]

Tapped bulk density: The loosely packed powder in the measuring cylinder was tapped 100 times on a plane hard wooden surface and volume occupied in ml was noted.

\[
\text{Tapped bulk density} = \frac{\text{Weight of powder in g}}{\text{tapped volume in ml}}.
\]

**Hausner’s factor**
Hausner found that the ratio \(D_f/D_o\) was related to interparticle friction and, as such, could be used to predict powder flow properties.

\[
\text{Hausner's factor} = \frac{\text{Tapped bulk density}}{\text{Poured bulk density}}
\]

**Carr’s compressibility index**

\[
\text{Percent Carr’s index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100
\]

**Angle of repose**
It is measured to find frictional forces in loose powder or granules. It is the maximum angle possible between the surface of a pile of powder or granules and horizontal plane.

\[
\tan \theta = \frac{h}{r} \quad \text{or} \quad \theta = \tan^{-1}\left(\frac{h}{r}\right)
\]

The values ≤30 indicate the free flowing powder.

#### Evaluation for Post-compressive Parameters

**Weight variation test**
A total of 20 tablets were randomly selected from each batch and weighed on an electronic balance individually, and the average weight calculated was compared.

**Hardness test**
Six tablets were randomly selected from each batch, and hardness of each tablet was determined using a hardness tester.

**Friability test**
It is the ability of tablets to withstand mechanical shocks during handling and transportations. Six tablets were randomly picked from each batch and weighed and placed in the friability test apparatus and operated at a rate of 25 RPM for 4 min (or up to 100 revolutions); tablets were dedusted and weighed again. The loss of tablet weight due to abrasion and fracture was measured in terms of percentage friability (a value of <1% F is acceptable).

\[
F = \frac{W_{\text{Initial}} - W_{\text{Final}}}{W_{\text{Initial}}} \times 100
\]

**Drug content estimation**
The tablets were tested for their drug content. Five tablets were finely powdered and transferred to a 100 ml of volumetric flask. The flask was filled with phosphate buffer (pH 7.4) solution and mixed thoroughly. The solution was made up to volume and filtered. Dilute 10 ml of the resulting solution to 200 ml with phosphate buffer (pH 7.4) and measure the absorbance of the resulting solution at the maximum of 271 nm using a UV/Vis double beam spectrophotometer.

**In vitro dissolution studies**
In vitro drug release studies of the prepared tablets were conducted for 12 h using an USP type 2 dissolution apparatus at 37.50°C, and the paddle speed was 100 ± 1 rpm. The dissolution medium used in each flask was 900 ml of buffer media (pH-7.4). At different intervals, 10 ml of samples was withdrawn and filtered through a Whatman filter paper. The equivalent volume of the medium was added to the dissolution vessel. After filtration and appropriate dilution, the sample solutions were analyzed at 271 nm using UV/VIS spectrophotometer and dissolution medium as blank. Experiments were performed in triplicates.

### Table 1: Composition of coating solution

| Ingredients           | Quantity  |
|-----------------------|-----------|
| Cellulose Acetate     | 4 g       |
| PEG                   | 400 mg    |
| Acetone               | 90 ml     |
| Methanol              | 10 ml     |

PEG: Polyethylene glycol

### Table 2: Composition of core tablets

| Ingredients used (mg/tab.) | Batch |
|---------------------------|-------|
|                          | I     | II    | III   | IV    |
| Tramadol HCL             | 100   | 100   | 100   | 100   |
| Mannitol                 | 136   | 136   | 136   | 136   |
| HPMC                     | -     | 30    | 50    | 70    |
| MCC                      | 50    | 20    | -     | -     |
| PVP                      | 10    | 10    | 10    | 10    |
| Talc                     | 2     | 2     | 2     | 2     |
| Magnesium stearate       | 2     | 2     | 2     | 2     |

MCC: Microcrystalline cellulose, HPMC: Hydroxypropyl methyl cellulose, PVP: Polyvinylpyrrolidone

### Formulation Aspects
Various formulation aspects that may affect the release rate are studied here.
Effect of pH
To study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were conducted according to pH change method. The release media were simulated gastric fluid (pH 7.4), acetate buffer (pH 6.8), and 0.1 N HCl. The samples (10 ml) were withdrawn at predetermined intervals and analyzed after filtration through 0.45 mm nylon membrane filters.

Effect of agitational intensity
To study the effect of agitational intensity of the release media, release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP-I (rotating basket) at 50 and 100 rev/min. Samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45 mm nylon membrane filters.\[15\]

RESULTS AND DISCUSSIONS

Drug-excipient Compatibility Studies
The individual IR spectra of the pure drug and the combination spectra of the drug and polymer are shown in Figures 1-3 which indicate no interaction between tramadol and polymers when compared with infrared spectrum of pure drug, as all functional group frequencies were present. Peaks obtained for drug, excipients, and combination of drug and polymers are shown in Table 3.

EVALUATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS OF TRAMADOL HYDROCHLORIDE

Evaluation for Pre-compressive Parameters
The powdered blend of tramadol hydrochloride prepared for compression was evaluated for their flow properties [Table 4].

According to USP limits, values of the angle of repose of all formulation were <30° indicating free-flowing material. Hausner ratio values of all formulation were <1.25 indicating excellent flow as per USP limits. Carr’s index values of all formulation were within limits (5–15) indicating excellent flow as per USP limits.

Evaluation for Post-compressive Parameters
The weights and thicknesses were found to be ranging from 310.17 to 324.31 mg and 3.10 to -3.14 mm, respectively, and were considered to be uniform as per USP standard deviation values. The drug content was ranging from 96.89 ± 0.15 to 98.44 ± 0.18%.

Table 3: Interpretation of FTIR spectra

| Drug peak | Excipients peak | Drug+Excipients peak | Conclusion |
|-----------|-----------------|----------------------|------------|
| 4347.16, 4258.53, 4060.64, 3307.16, 2862.28, 2931.11, 1922.59, 1655.37, 1670.23, 1580.32, 1462.62 | 3305.62, 3067.46, 2916.32, 2629.06, 2351.59, 1960.89, 1530.07, 1358.84, 1088.45, 777.47, 670.10, 456.29 | 4335.62, 4013.06, 3896.15, 3402.28, 2838.32, 2888.30, 1961.86, 1659.01, 1529.87, 1511.42, 1468.05 | No interaction |

FTIR: Fourier-transform infrared

Table 4: Pre-compressive parameters of tramadol hydrochloride blend

| Formulation code | Angle of repose (°) | Bulk density (g/cc) | Tapped density (g/cc) | Hausner ratio | Carr’s index (%) |
|------------------|---------------------|---------------------|-----------------------|--------------|------------------|
| F1               | 26.5±0.25           | 0.50±0.01           | 0.55±0.02             | 1.10±0.01    | 9.09±0.05        |
| F2               | 27.9±0.30           | 0.51±0.02           | 0.54±0.01             | 1.05±0.02    | 5.55±0.05        |
| F3               | 26.7±0.40           | 0.51±0.01           | 0.55±0.01             | 1.07±0.02    | 7.27±0.10        |
| F4               | 28.9±0.35           | 0.49±0.02           | 0.54±0.01             | 1.12±0.01    | 9.25±0.05        |

Figure 1: Fourier-transform infrared spectrum of tramadol hydrochloride (pure drug)
indicating uniformity of drug content as per IP limits (85–115%). The hardness was ranging from 6 to 8 kg cm². The friability was found to be <1 which complies with IP limits [Table 5].

In Vitro Dissolution Study of Tramadol Osmotic Tablet
Cumulative percentage release profile of tramadol hydrochloride is given in Table 6.

Table 5: Post-compressive parameter of tramadol hydrochloride osmotic pump tablets

| Formulation code | Hardness (kg/cm²) | Friablity (%) | Diameter (mm) | Thickness (mm) | Weight variation (mg) | Drug content (%) |
|------------------|-------------------|---------------|---------------|----------------|-----------------------|-----------------|
| F1               | 7.5±0.5           | 0.8±0.01      | 9.4±0.01      | 3.1±0.01       | 310.17±5.2           | 97.68±0.12      |
| F2               | 6.5±0.5           | 0.8±0.01      | 9.5±0.01      | 3.14±0.02      | 312.28±5.8           | 98.44±0.17      |
| F3               | 6.5±0.5           | 0.8±0.02      | 9.6±0.01      | 3.10±0.01      | 311.45±5.1           | 96.89±0.21      |
| F4               | 7.5±0.5           | 0.88±0.02     | 9.5±0.01      | 3.10±0.01      | 324.31±6.5           | 97.96±0.16      |

In vitro release study of all batches was performed. Since the amount of release of drug of batch (F4) was best controlled, therefore batch (F4) was selected as optimized formulation of osmotic pump-based tablet [Figure 4].

Release and Kinetic Study of Formulation (F1-F4)
From Table 7, all the values of release rate exponent (n) of Korsmeyer–Peppas release model were within the range of
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1.265–1.565 in phosphate buffered saline (PBS) (pH 7.4) (>1.0, Sajid et al., 2010). Therefore, it can be concluded that drug release in PBS (pH 7.4) were mainly following super case II transport.

FORMULATION ASPECTS

Effect of pH on Drug Release
To study the effect of pH, best formulation (F-4) found after in vitro dissolution study was further studied for in vitro dissolution study in pH 6.8 buffer and 0.1 N HCL [Table 8].

In vitro release study shows that there is no effect of pH change on in vitro release of drug [Figure 5].

Effect of Agitation on Drug Release
To study the effect of agitation, best formulation (F-4) found after in vitro dissolution study was further studied for in vitro dissolution study at 50 rpm in pH 7.4 buffer [Table 9].

In vitro release of drug shows that there is no effect of agitation on in vitro release of drug [Figure 6].

Effect of Weight Gain due to Coating on Drug Release
In vitro drug release of final formulation at 6%, 10%, and 12% weight gain due to coating at 100 rpm in pH 7.4 buffer is shown in Table 10.

In vitro release of drug shows that release of drug decreased on increasing the weight due to coating [Figure 7].

RESULTS OF STABILITY STUDY

The results of stability study are shown in Table 11.
Hardness, weight variation, and drug content were found stable after 3 months’ storage [Table 12].

Selected formulation F4 was found stable after 3 months of period, as weight variation, hardness, drug content, and percentage cumulative drug release showed no significant changes and was within limits.

CONCLUSION

Sustained release formulations of tramadol hydrochloride were developed based on osmotic technology. The effect of different formulation variables was studied to optimize release profile. Drug release was inversely proportional to the level of swellable polymer and membrane weight. The release from the developed formulations was independent of pH and agitational intensity of the release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the body. Developed formulations were found to be stable after 3 months of storage at accelerated stability conditions. The system was found to deliver pseudoephedrine at a

| Table 8: In vitro dissolution study of tramadol in 6.8 buffer and 0.1 N HCL |
| Time (h) | F4 (7.4 buffer) | F4 (6.8 buffer) | F4 (0.1 N HCL) |
| 1 | 21.12±1.44 | 21.52±1.34 | 20.88±1.76 |
| 2 | 24.60±1.94 | 23.70±1.74 | 24.80±1.64 |
| 3 | 27.96±1.76 | 27.16±1.66 | 29.16±1.76 |
| 4 | 33.35±1.48 | 33.45±1.8 | 32.35±1.08 |
| 5 | 36.21±0.74 | 35.31±0.84 | 36.11±0.84 |
| 6 | 41.40±0.79 | 42.70±0.89 | 41.70±0.79 |
| 7 | 43.75±1.73 | 44.75±1.3 | 45.65±1.03 |
| 8 | 47.90±1.54 | 47.80±1.14 | 48.80±1.04 |
| 9 | 51.75±1.34 | 50.75±1.03 | 51.65±1.34 |
| 10 | 54.64±0.98 | 53.64±0.88 | 54.64±0.67 |
| 11 | 60.76±0.67 | 61.56±0.77 | 62.76±0.87 |
| 12 | 63.17±0.450 | 64.37±0.450 | 66.67±0.40 |

| Table 9: In vitro dissolution study of tramadol at 50 rpm |
| Time (h) | F4 (7.4 buffer) at 100 rpm | F4 (7.4 buffer) at 50 rpm |
| 1 | 21.12±1.44 | 21.22±0.44 |
| 2 | 24.60±1.94 | 24.70±1.94 |
| 3 | 27.96±1.76 | 26.96±1.91 |
| 4 | 33.35±1.48 | 34.65±1.8 |
| 5 | 36.21±0.74 | 35.89±0.74 |
| 6 | 41.40±0.79 | 41.80±0.89 |
| 7 | 43.75±1.73 | 44.85±1.03 |
| 8 | 47.90±1.54 | 47.60±1.24 |
| 9 | 51.75±1.34 | 50.65±1.24 |
| 10 | 54.64±0.98 | 55.74±0.88 |
| 11 | 60.76±0.67 | 61.86±0.77 |
| 12 | 63.17±0.450 | 63.57±0.350 |

| Table 10: Drug release at 6%, 10%, and 12% weight gain |
| Time (h) | F4 (6% weight gain) | F4 (10% weight gain) | F4 (12% weight gain) |
| 1 | 21.12±1.44 | 19.22±0.54 | 16.12±0.64 |
| 2 | 24.60±1.94 | 21.50±1.74 | 19.50±1.94 |
| 3 | 27.96±1.76 | 24.91±1.01 | 21.81±1.1 |
| 4 | 33.35±1.48 | 27.65±1.10 | 24.65±1.29 |
| 5 | 36.21±0.74 | 31.89±0.74 | 29.09±0.64 |
| 6 | 41.40±0.79 | 37.80±0.69 | 32.80±0.59 |
| 7 | 43.75±1.73 | 41.55±1.03 | 37.55±1.13 |
| 8 | 47.90±1.54 | 47.60±1.24 | 40.65±1.84 |
| 9 | 51.75±1.34 | 50.65±1.24 | 44.95±1.04 |
| 10 | 54.64±0.98 | 55.74±0.88 | 48.74±0.88 |
| 11 | 60.76±0.67 | 61.86±0.77 | 51.96±0.17 |
| 12 | 63.17±0.450 | 63.57±0.350 | 55.57±0.80 |
zero-order rate for 12 h independent of the environmental pH. This system is simple to prepare with no drilling required, and hence, it can be used in the field of controlled delivery of drugs.

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