Formulation and evaluation of controlled release floating microspheres of tolperisone hydrochloride

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Main aim of this study was to develop controlled release (CR) floating multiparticulate drug delivery system of tolperisone hydrochloride. Microspheres were prepared by nonaqueous solvent evaporation technique consisting of porous calcium silicate (Florite or FLR) as porous carrier, tolperisone hydrochloride (API), Ethyl cellulose (EC), and HPMC 15 cPs as rate controlling polymers. 2³ full factorial design was applied for optimization of formulation. The effect of various formulation and process variables on the particle morphology, micromeritic properties, in vitro floating behavior, entrapment efficiency, and in vitro drug release were studied. The size of microspheres was varied from 300 to 500 μm. The microspheres were found to be highly porous and regular in shape. All the formulations showed excellent flow properties. The percentage entrapment efficiency of all batches was greater than 80%. The percentage buoyancy varied from 85% to 98% at the end of 12 h. The release rate was determined in simulated gastric fluids. The formulation demonstrated favorable in vitro floating and release characteristics. Different kinetic models were applied to study the release mechanism. All formulations followed Higuchi model, which indicates the diffusion control release of water soluble drug from polymer matrix. Multiple regression analysis was applied for study of the effect of independent variables on the dependent variables.

Key words: Ethyl cellulose, floating multiparticulate, FLR, HPMC 15 cPs, tolperisone hydrochloride

INTRODUCTION

The novel drug delivery system (NDDS) is an advanced drug delivery system that improves drug efficacy, controls drug release to give a sustained therapeutic effect, provides greater safety, and improves the pharmacokinetic profiles of active pharmaceutical ingredients (APIs). Oral drug delivery has been known for decades as the most widely utilized route of administration of pharmaceutical products for the systemic delivery. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which resides in the stomach for a longer period of time than conventional dosage forms.[1,3] Controlled release (CR) implies the predictability and reproducibility to control the drug release.[4] Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation and require frequent dosing. To avoid this problem, the oral controlled release formulations have been developed.[1,4] Gastro retentive dosage forms have potential for use as controlled-release drug delivery systems. Various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract. FDDS have been the most commonly used approach.[1,3] Multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. Single unit oral dosage forms offer no control over drug delivery, leading to fluctuations in the plasma drug level while multiple unit systems release the drug more uniformly...
by avoiding the “all or none” gastric emptying nature of single-unit systems. Other benefits of the multiparticulate drug delivery system are increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation, predictable gastric emptying, better reproducible pharmacokinetic behavior, etc.

Tolperisone hydrochloride is an official drug in Japanese Pharmacopoeia. It is a centrally acting muscle relaxant having half life of 2 to 3 h, bioavailability of 20% and more stable in acidic than basic media with high solubility in water. So it is the mostly preferred candidate for preparing floating controlled release formulation. It is mostly used in the treatment of back pain, arthritis of large joints (degeneration of cartilage tissue in joints), spastic muscle cramps, paralysis, and muscle pain. Tolperisone conventional tablets are unable to ensure a constant concentration of the active substance in the blood. However, especially in cases of spastic muscle cramps, a constant efficacy, in particular throughout the night, is very important to the quality of life of the patients. Conventional tablet formulations release the active substance in the intestine at pH 4 to 7. In this pH range, tolperisone breaks down into 2-methyl-1-(4-methylphenyl)-propenone (4-MMPPPO) and piperidine. Thus, the patient is exposed to an uncontrollable quantity of 4-MMPPPO. A control release floating formulation with tolperisone as the active substance, which can also be prepared free from 4-MMPPPO (<1.5 ppm).

**MATERIALS AND METHODS**

**Materials**

Tolperisone hydrochloride was procured as a gift sample from Amanath pharmaceutical, Puducherry, India. Highly porous calcium silicate (Florite®) was received as gift sample from Tomita Pharmaceutical, Japan. Ethyl cellulose and Hydroxypropyl methylcellulose were obtained from astron chemicals Ahmedabad. Methanol, dichloromethane and other solvents were purchased from Astron chemicals Ahmedabad. Heavy liquid paraffin and Tween 80 were received from Loba chemicals, Mumbai and Samir Tech Chem Pvt Ltd, Vadodara respectively.

**A 2^3 full factorial design**

A 2^3 factorial design was utilized in this study. In this design, three factors were evaluated, each at two levels and experimental trials were carried for all eight possible combinations. The factors were selected based on preliminary study. The amount of FLR (A), amount of EC (B) and amount of HPMC 15 cPs (C) were selected as independent variables [Table 1]. The percentage buoyancy, time for 30% drug release \(t_{30}\) and time for 90% drug release \(t_{90}\) were selected as dependent variables.

\[
Y_i = b_0 + b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC + b_{123}ABC
\]

Where, \(Y_i\) was the dependent variable,

\(b_0\) was the arithmetic mean response of the eight runs

\(b_1, b_2\) and \(b_3\) were the estimated coefficient for the factor A, B and C respectively

\(b_{12}, b_{23}, b_{13}\) and \(b_{123}\) were coefficients corresponding interaction

**Method of preparation of floating microspheres**

**Preparation of drug adsorbed FLR**

FLR was dispersed in 10 mL methanolic solution of tolperisone hydrochloride to prepare slurry. The slurry was ultrasonicated for 30 min in an ice bath using a bath sonicator to entrap the drug solution inside the pores of porous carrier. The excess methanolic solution was removed by filtration and then dried at room temperature for 1 h, which resulted in Tolperisone hydrochloride absorbed FLR powder.

**Preparation of floating microspheres**

Microspheres were prepared using emulsion solvent diffusion technique. Eight batches of microspheres were prepared by taking different amount of FLR with different EC: HPMC 15 cPs ratio. The drug absorbed FLR was added into the polymer solution of ethylcellulose and HPMC 15 cPs in methanol and dichloromethane (1:1) and sonicated using probe sonicator. The resulting suspension was slowly poured into the dispersion medium consisting of heavy liquid paraffin (50 mL) containing 1.5% span 80. The system was stirred using propeller type agitator at a speed of 900 rpm at 40°C over a period of 2–3 h, to ensure complete evaporation of the solvent. The microspheres were separated by filtration through a Whatman filter paper, washed twice with petroleum ether (40–60°C) and air dried for 6–8 h.

**Drug–polymer interaction studies**

**Infrared spectroscopy**

Interaction between drug–polymer was studied by infrared spectroscopy using FTIR spectrometer (Nicolet IS10, Thermoscientific Janki inpex, Ahmedabad). Sample preparation involved potassium bromide (KBr) pallet technique. The spectrum was scanned over a frequency range 4000–400 cm\(^{-1}\).

**Differential scanning colorimetry**

DSC thermogram of drug and polymer were recorded using Differential Scanning Calorimeter (DSC-60 Shimadzu Corporation, Japan). Thermogram was obtained at a scanning...
rate of 10°C/min conducted over a temperature range of 50–300°C in the environment of air.

**Percentage yield of microspheres**
The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all nonvolatile components that were used for the preparation of the microspheres.

\[
\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipient and drug}} \times 100
\]  
(1)

**Particle size and morphology of microspheres**
The microsphere size was determined by using the optical microscopic method with the help of the ocular and stage micrometer. The sizes of around 100 particles were measured and their average particle size was determined. The morphology of the microspheres and was studied by scanning electron microscopy (SEM) [Figure 1]. The samples for SEM were prepared by lightly sprinkling the powder on a double-sided adhesive tape stuck to an aluminum stub. The stubs were then coated with gold to a thickness of ∼300 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken.

**Micromeritic properties**
The prepared microspheres are characterized by their micromeritic properties such as bulk density, tapped density, Carr’s index, Hausner’s ratio and Angle of repose.

**Bulk density and tapped density**
Bulk density and tapped density were measured by using 10 mL graduated cylinder. The pre weighed sample of microspheres was placed in a cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted and then tapped volume was recorded. Bulk density and tapped density were calculated from the following formula.

\[
\text{Bulk density} = \frac{\text{Mass of microspheres}}{\text{Bulk volume}}
\]  
(2)

\[
\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Tapped volume}}
\]  
(3)

**Carr’s index**
Carr’s index or compressibility index (CI) value of microcapsules was computed according to the following equation:

\[
\text{Carr’s Index (CI)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100
\]  
(4)

**Hausner’s ratio**
Hausner’s ratio of microcapsules was determined by comparing the tapped density to the bulk density using the equation:

\[
\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]  
(5)

**Angle of repose**
The angle of repose of microspheres was determined by the glass funnel method. Microspheres were weighed accurately and passed freely through the funnel so as to form a heap. The height of the funnel was so adjusted that the tip of the funnel just touched the apex of the heap. The diameter of the powder cone so formed was measured and the angle of repose was calculated using the following equation.

\[
\tan \theta = \frac{h}{r}
\]  
(6)

Where,
\( \theta \): Angle of repose,
\( h \): Height of the pile,
\( r \): Radius of the powder cone.

**Drug loading and entrapment efficiency**
Microspheres weighing 50 mg were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting the drug using 50 mL SGF (pH 1.2). The solution was filtered and take one mL extract in to 50 mL volumetric flask, dilute up to 50 mL using SGF (pH 1.2). The absorbance was measured at 260 nm against SGF (pH 1.2) as blank.

\[
\% \text{ Drug loading} = \frac{\text{Actual drug content}}{\text{Weight of microspheres}} \times 100
\]  
(7)

\[
\% \text{ Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100
\]  
(8)

**In vitro buoyancy**
Microspheres (100 mg) were spread over the surface of a USP XXV dissolution apparatus type II filled with 900 mL of hydrochloric acid buffer pH 1.2 containing 0.02% tween 80.
The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

\[
\% \text{ Buoyancy} = \frac{W_f}{W_f + W_s} \times 100 \quad (9)
\]

Where, \(W_f\) and \(W_s\) are the weight of the floating and settled microspheres respectively.

**In vitro release studies**

The release rate of tolperisone hydrochloride from floating microspheres was determined in a United States Pharmacopoeia (USP) XXV basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 150 mg drug was filled into a hard gelatin capsule (size 0) and placed in the basket of dissolution rate apparatus. Nine hundred milliliters of the SGF (pH 1.2) containing 0.02% w/v of tween 20 was used as the dissolution medium. The dissolution fluid was maintained at 37°C ± 1°C at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. Five milliliter samples were withdrawn at specific time interval, passed through filter paper dilute 10 times with SGF (pH 1.2) and analyzed using UV spectrophotometer at 260 nm to determine the concentration of tolperisone hydrochloride present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 mL of fresh dissolution fluid after each withdrawal.

**Drug release kinetic modeling**

Several theories and kinetic models describe the dissolution of drug from modified release dosage forms. There are several models such as zero order, first order, Higuchi, and Korsmeyer–Peppas used to represent the drug dissolution profiles where it is a function of time related to the amount of drug dissolved from the pharmaceutical dosage form:\(^{[18]}\)

\[
\begin{align*}
Q_t &= Q_0 + K_0 t \\
\log Q_t &= \log Q_0 + K_1 t/2.303 \\
Q_t/Q_\infty &= K_{kp} t^n
\end{align*}
\]

Where, \(Q_t\) is the amount of drug dissolved in time \(t\)  
\(Q_0\) is the initial amount of drug in the solution  
\(K_0\) is the zero-order release constant  
\(K_1\) is the first-order release constant  
\(K_h\) is the Higuchi release constant  
\(Q_\infty\) is the amount of drug dissolved in infinite time  
\(n\) is the release exponent indicative of drug release mechanism  
\(K_{kp}\) is the Korsmeyer–Peppas kinetic constant

**RESULTS AND DISCUSSION**

**Compatibility study**

**FT-IR spectroscopy**

The results from Figures 2 and 3 revealed no considerable changes in the FT-IR peaks of functional group available in tolperisone hydrochloride in the physical mixture when compared to pure drug, indicating the absence of any interaction.

**Figure 2:** FT-IR spectra of tolperisone hydrochloride

**Figure 3:** FT-IR spectra of physical mixture of drug and polymers

**Figure 4:** DSC analysis of Tolperisone hydrochloride

**Figure 5:** DSC analysis of physical mixture
Differential scanning colorimetry
DSC curves obtained for pure Tolperisone hydrochloride as shown in Figure 4 and physical powder mixture containing drug and polymers as shown in Figure 5. Pure powdered Tolperisone hydrochloride showed a melting endotherm at 185.18°C. DSC thermo grams of physical powder mixture showed the melting peak of the drug at 189.64°C. From the above DSC analysis, no significant drug excipient interaction was observed. So it was concluded that drug and other excipients were compatible with each other.

Formulations of microspheres by applying factorial design are given in Table 2. The percentage yield of all the formulation was found to be more than 85% as shown in Table 3. It can be due to minimum involvement of process parameters and smaller amount of drug and polymer loss during manufacturing. The size of microspheres was in ranged 325.45 ± 11.34 to 463.69 ± 3.86 μm. The size of microspheres formed may be a function of many factors such as stirring speed, viscosity of the dispersed phase and dispersion medium, temperature, concentration of polymer, and amount and size of porous carrier. Scanning electron microphotographs of tolperisone-hydrochloride-loaded microsphere shows that microspheres obtained were discrete and spherical. The surface of microsphere was found to be rough in SEM images shown in Figure 6, which was due to presence of highly porous FLR.

In all batches, the bulk density values ranged 0.336 ± 0.0073 to 0.467 ± 0.009 gm/cm³, while their tapped density ranged between 0.378 ± 0.0092 and 0.508 ± 0.0052 gm/cm³ as shown in Table 4. Small difference in the bulk density and tapped density may be caused due to presence of low-density FLR particles in the microspheres. Angle of repose varied from 25.05 ± 1.35 to 30.84 ± 1.41. The Carr’s index ranged between 7.692 ± 0.851 and 11.111 ± 3.328, while Hausner’s ratio ranged 1.083 ± 0.010 to 1.125 ± 0.042. All the formulations showed excellent flowability. Flow properties were improved by increasing the FLR concentration in formula. The better flow property of microspheres indicates that the floating microspheres produced were nonaggregated.

The floating test was carried out to investigate the floatability of the prepared microspheres. In vitro % buoyancy of the microspheres were in the range of 87.81 ± 1.02 to 98.23 ± 1.22 at the end of 12 h. This characteristic may be attributed to the low tapped density of the microspheres as a result of the entrapment of low density FLR within the system. Microsphere formulation T8 showed the best floating ability 98.23 ± 1.22%
in SGF (pH 1.2) as compared with other formulations because it contained highest amount of FLR, EC and HPMC. The drug loading was found to be in the range of 30.48 ± 0.15 to 41.92 ± 0.16. The percentage entrapment efficiency of Tolperisone hydrochloride microspheres in all the batches was between 84.43 ± 0.38 and 95.47 ± 0.46. It was found that entrapment of drug increases with increase in the concentration of total amount of polymer. Drug entrapment was attributed to the permeation characteristics of polymers used, that could facilitate the diffusion of part of entrapped drug to the surrounding medium. The drug loading was found to decrease with increase in the polymer concentration due to its higher viscosity which affects the diffusion coefficient of drug.

It was found that with increase in concentration of FLR, EC and HPMC the drug release decreased, so increased t_{30} and t_{90} as shown in Figure 7. The increased density of the polymer matrix at higher concentration results in an increased diffusion path length. This may decrease the drug release from the polymer matrix. All the formulation did not show initial burst effect. Release pattern of Tolperisone hydrochloride in SGF from all floating microspheres of formulation T1 to T8 followed Higuchi matrix model as shown in Table 5. Non effervescent floating systems obeyed the Higuchi model indicating drug release via a diffusion mechanism. All the values of release rate exponent (n) of Korsmeyer–Peppas release model were 0.5 < n < 1.0. Therefore, it can be concluded that drug release were mainly following Anomalous Transport that corresponds to diffusion, erosion and swelling mechanism or mixed-order kinetics.

Coefficients with one factor were representing the effect of that particular factor, while the coefficients with more than one factor represent the interaction between those factors. Positive sign in front of the terms indicates a positive effect and negative sign in front of the factor indicates a negative effect of the factors as shown in Table 6. The response surface diagrams were known to facilitate an understanding of the contribution of variables and their interactions. The plots were drawn using DOEPRO trial version. Figures 8-10 showed the response surface plots of % buoyancy, t_{30} and t_{90} respectively.

The selection of optimized formulation was done by following way. The criteria for selection of suitable feasible region were % buoyancy ranged of 94–98%, t_{30} ranged of 2 - 2.4 h and t_{90} ranged of 11.8 - 12.2 h. By considering the desired criteria the overlay plot was obtained [Figure 11].

### Table 6: Multiple regression analysis for measured responses

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% buoyancy</td>
</tr>
<tr>
<td>b_0</td>
<td>93.325</td>
</tr>
<tr>
<td>b_1</td>
<td>1.49</td>
</tr>
<tr>
<td>b_2</td>
<td>1.815</td>
</tr>
<tr>
<td>b_3</td>
<td>2.11</td>
</tr>
<tr>
<td>b_{12}</td>
<td>0.325</td>
</tr>
<tr>
<td>b_{13}</td>
<td>−0.885</td>
</tr>
<tr>
<td>b_{23}</td>
<td>0.255</td>
</tr>
<tr>
<td>b_{123}</td>
<td>−0.205</td>
</tr>
</tbody>
</table>

### Table 5: Regression coefficients and rate constants for kinetic models

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order</th>
<th>First order</th>
<th>Korsmeyer</th>
<th>Higuchi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r^2</td>
<td>k</td>
<td>r^2</td>
<td>k</td>
</tr>
<tr>
<td>T1</td>
<td>0.985</td>
<td>8.025</td>
<td>0.835</td>
<td>0.260</td>
</tr>
<tr>
<td>T2</td>
<td>0.974</td>
<td>7.517</td>
<td>0.943</td>
<td>0.203</td>
</tr>
<tr>
<td>T3</td>
<td>0.970</td>
<td>7.802</td>
<td>0.934</td>
<td>0.219</td>
</tr>
<tr>
<td>T4</td>
<td>0.966</td>
<td>6.991</td>
<td>0.978</td>
<td>0.177</td>
</tr>
<tr>
<td>T5</td>
<td>0.985</td>
<td>7.118</td>
<td>0.898</td>
<td>0.193</td>
</tr>
<tr>
<td>T6</td>
<td>0.983</td>
<td>6.979</td>
<td>0.924</td>
<td>0.177</td>
</tr>
<tr>
<td>T7</td>
<td>0.985</td>
<td>6.959</td>
<td>0.916</td>
<td>0.187</td>
</tr>
<tr>
<td>T8</td>
<td>0.961</td>
<td>6.411</td>
<td>0.960</td>
<td>0.164</td>
</tr>
</tbody>
</table>

Figure 6: (a) SEM image of microspheres (Mag 136×), (b) SEM image of microspheres (Mag 315×)
It indicated desirability region by overlaying the plots of all responses. It shows that any point in this region gives desired responses. Formulation T7 fulfilled all above criteria, so it was selected as a most satisfactory formulation in this study.

Short-term stability test was performed as per ICH guideline. The formulation T7 was analyzed for the drug physical appearance, entrapment efficiency, floating ability, and in vitro release study. No major changes were found in physical appearance, percentage entrapment efficiency, percentage buoyancy, and in vitro drug release. So it was concluded that final formulation passed the stability test.

**CONCLUSION**

It was satisfactory attempt to prepare a floating and controlled release preparation using FLR as the floating carrier by covering the pores of the FLR particles with adsorbed drug by a polymer solution containing both of HPMC and EC in suitable proportions. Incorporation of FLR in the microspheres proved to be an effective method to achieve the desired release behavior and buoyancy. It concluded that the check point batch was the optimized batch with the fulfillment of all the desirabilities. Thus, the prepared microspheres proved to be a potential candidate as a floating microparticulate controlled release drug delivery system.

**REFERENCES**


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