RESEARCH PAPER

Preformulation Evaluation of the Drug Substance for Sustained-Release Floating Microspheres

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ABSTRACT
The present study was undertaken to design, develop, and evaluate floating microspheres of Tolperisone Hydrochloride for sustained drug delivery with prolonged gastric residence time. Tolperisone Hydrochloride, a centrally acting muscle relaxant with a relatively short biological half-life, was selected as a suitable candidate for the development of a gastroretentive controlled-release system. Preformulation studies, including drug identification, Fourier Transform Infrared (FTIR) spectroscopy, solubility analysis, melting point determination, and drug–polymer compatibility studies, were performed to establish the physicochemical characteristics of the drug and its compatibility with selected polymers. The results indicate that floating microspheres of Tolperisone Hydrochloride can serve as a promising gastroretentive sustained-release delivery system capable of improving gastric residence time, enhancing drug availability, and reducing dosing frequency.

Keywords: Tolperisone Hydrochloride, Floating Microspheres, Gastroretentive Drug Delivery System, Sustained Release, Emulsion Solvent Evaporation, Eudragit RS100, Ethyl Cellulose, Drug Entrapment Efficiency, Buoyancy, Release Kinetics.
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INTRODUCTION

Controlled drug delivery technology represents a multidisciplinary field that integrates pharmaceutics, polymer science, and biomedical engineering (1,2,3). These systems are designed to overcome the inherent limitations of conventional dosage forms, such as frequent dosing, fluctuations in plasma drug concentrations, and poor patient compliance. Consequently, controlled drug delivery systems offer improved therapeutic efficacy, reduced toxicity, and enhanced patient convenience (4,5,6,).

Preformulation studies constitute the initial and most critical phase in the rational development of pharmaceutical dosage forms. Preformulation can be defined as the systematic investigation of the physical and chemical properties of a drug substance, bothalone and in combination with selected excipients. The primary objective of preformulation testing is to generate essential information that aids in the design of stable, safe, and bioavailable dosage forms suitable for large-scale manufacturing. (7,8,9)

A comprehensive understanding of the physicochemical characteristics of a drug substance provides a scientific basis for formulation development. Such knowledge may justify specific formulation strategies, indicate the necessity for molecular modification, or confirm the absence of significant formulation barriers during product development. (10,11)

The specific goals of a preformulation program include: (10-11)

- To determine the essential physicochemical properties of the drug substance.
- To evaluate the drug release characteristics from various formulations.
- To assess the compatibility of the drug with different pharmaceutical excipients.

Accordingly, preformulation studies conducted on the obtained drug sample involve a series of physical evaluations and

compatibility studies, which form the foundation for successful formulation development. (12)

Identification of Pure Drug (11-12)

The selected drug Tolperisone HCl was subjected for investigation of physical characterization parameters such as:

IR Spectroscopy

The Fourier Transform Infrared (FTIR) spectrum of the obtained drug sample was recorded and compared with the standard FTIR spectrum of pure Tolperisone hydrochloride. This comparison was carried out to confirm the identity and purity of the drug sample by matching characteristic functional group peaks (12, 13).

Solubility Analysis

Preformulation solubility studies were conducted to identify a suitable solvent system capable of dissolving the drug as well as the excipients used in the preparation of microspheres. These studies aided in the selection of appropriate solvents for formulation development and analytical procedures (12, 15).

Melting Point Determination

The melting point of the obtained Tolperisone hydrochloride sample was determined as an initial indicator of drug purity. Even small amounts of impurities can cause depression and broadening of the melting point range. The melting point was measured using the Thiele's tube method, and the observed value was compared with reported literature data (16, 17).

Compatibility Studies of Tolperisone Hydrochloride with Polymers

Preparation of Stock Solution

A stock solution of Tolperisone hydrochloride was prepared by accurately weighing 100 mg of the drug and dissolving it in 100 mL of simulated gastric fluid (SGF, pH 1.2) without enzymes, to obtain a concentration of 1000 µg/mL. The solution was mixed thoroughly to ensure complete dissolution of the drug.

Preparation of Standard Dilutions

From the prepared stock solution, a series of standard solutions containing 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 µg/mL of Tolperisone hydrochloride were prepared by appropriate dilution with SGF (pH 1.2) without enzymes. The absorbance of each solution was measured at 260 nm using a UV–visible double-beam spectrophotometer (Thermo Scientific, India).

The recorded absorbance values corresponding to each concentration were tabulated (Table 1). A calibration curve was constructed by plotting drug concentration (µg/mL) on the X-axis against absorbance on the Y-axis (Figure 1). The standard curve was utilized for the quantitative estimation of Tolperisone hydrochloride in dissolution samples.

Table 1
Standard Curve of Tolperisone Hydrochloride in Simulated Gastric Fluid (pH 1.2)

Conc.(µg/ml)	Absorbance at 260 nm
0	0
2	0.153
4	0.267
6	0.357
8	0.493
10	0.617
12	0.795
14	0.901
16	1.022
18	1.166
20	1.352

The linear relationship between the concentrations of Tolperisone Hydrochloride and the corresponding absorbance values confirmed that they followed Beer's law. The regression equation was obtained using Microsoft Excel® software:

$$Y = 0.0.066\ X + 0.014$$

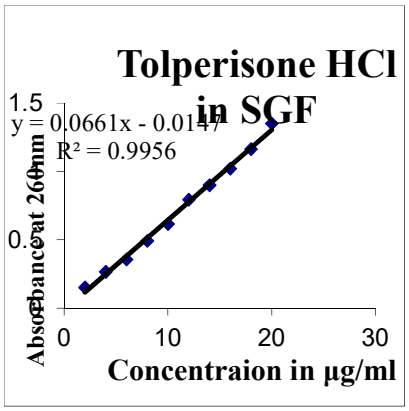
Where Y = Absorbance (nm)

X = Concentration of Tolperisone Hydrochloride (µg/ml)

A positive correlation between the concentration of Tolperisone Hydrochloride and the corresponding absorbance value was observed (correlation coefficient, R^2=0.995). The amount of Tolperisone Hydrochloride in tablet formulations and in the dissolution fluids was calculated using the linear relationship as given above with the help of Microsoft Excel® software.

Fig. 1

Standard Curve of Tolperisone HCl



Preparation Of Microspheres Of Tolperisone Hcl

Floating microspheres of **Tolperisone hydrochloride** were prepared using the **emulsion solvent evaporation technique**. Accurately weighed quantities of the selected polymers were dissolved in a solvent system consisting of **dichloromethane and ethanol (7:3 v/v)**, in which the calculated amount of Tolperisone hydrochloride was previously dissolved to obtain a uniform polymer–drug solution.

This viscous organic phase was then **added dropwise** into a **50 mL beaker containing liquid paraffin** incorporating **0.4% Tween 80** as an emulsifying agent. The dispersion was continuously stirred at **200–300 rpm** and maintained at a temperature of approximately **40°C** for **3–4 hours** to facilitate solvent evaporation.

Following complete removal of the solvent, the formed microspheres were **collected by filtration**, washed repeatedly with **n-hexane** to remove residual liquid paraffin, and subsequently **dried in a hot air oven at 50°C** until a constant weight was achieved.

Table No.2

COMPOSITION OF FORMULATION

Formulations	**Tolperisone HCl (mg)**	**Eudragit RS100 (mg)**	**Ethyl Cellulose (mg)**	**Eudragit S100 (mg)**
F 1	500	500	-	-
F 2	500	1000	-	-
F 3	500	1500	-	-
F 4	500	750	750	-
F 5	500	1000	500	-
F 6	500	500	1000	-
F 7	500	750	-	750
F 8	500	1000	-	500
F 9	500	500	-	1000

Evaluation Of Microspheres

Micromeritic Studies

The prepared microspheres were evaluated for their **micromeritic properties** to assess flow behavior and packing characteristics. Parameters such as **particle size, bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose** were determined.

Bulk Density:

Bulk density is defined as the ratio of the mass of a powder to the volume it occupies before tapping. A known quantity of microspheres was carefully poured into a graduated measuring cylinder, and the initial volume was noted. Bulk density was calculated using the following equation:

Bulk density = Mass of microspheres/Volume of microspheres before tapping

Tapped Density:

Tapped density represents the density of powder after it has been compacted by mechanical tapping. A weighed amount of microspheres was transferred into a graduated measuring cylinder and tapped mechanically for approximately **1 minute** using a **tapped density apparatus** until a constant volume was obtained. The tapped density was calculated using the equation:

Tapped density = Mass of microspheres/ Volume of microspheres after tapping

Carr's Compressibility Index:

This is an important property in maintaining uniform weight. It is calculated using following equation**,**

% Compressibility Index = [(Tapped density-Bulk Density)/ (Tapped Density)] X 100

Lower the compressibility values indicate better flow.

Table No.3

Relationship between % Compressibility and Flow ability

% Compressibility	**Flow ability**
5-15	Excellent

12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor
> 40	Extremely poor

Hausner ratio:

Hausner's ratio is a parameter closely related to the percentage compressibility index and is used to evaluate the **flow properties of powders and microspheres**. It represents the relationship between tapped density and bulk density. A **Hausner's ratio value less than 1.25** indicates **good flowability**, whereas values **greater than 1.25** suggest **poor flow characteristics**. The addition of **glidants** generally enhances the flow properties of the material under investigation.(15)

Hausner's ratio is calculated using the following equation:

Hausner's ratio = (Tapped density/ Bulk density)

Angle of Repose (θ)

Good flow properties are essential for the successful development of **pharmaceutical tablets, capsules, and powder-based formulations**. Accurate evaluation of powder flow behavior at an early stage of formulation development aids in the rapid identification of an optimized formulation. The **angle of repose** is a widely used parameter for assessing **interparticulate forces and flow characteristics** of powders and microspheres. The angle of repose is defined as the **maximum angle formed between the surface of a powder heap and the horizontal plane**. It reflects the frictional forces between particles; lower angle values generally indicate better flowability.

The angle of repose of each powder blend was determined using the **glass funnel method**. Accurately weighed quantities of the powder were allowed to flow freely through a funnel to form a conical heap on a flat surface. The height of the funnel was adjusted so that the funnel tip just touched the apex of the formed heap. The **height (h)** and **radius (r)** of the powder cone were measured, and the angle of repose was calculated using the following equation:

$$\tan \Theta = h/r$$

$$\Theta = \tan^{-1} (h/r)$$

Where,

θ = Angle of repose

h = Height of the pile

r = Radius of the powder cone

The **angle of repose** is influenced by **particle size distribution**, as larger particles generally exhibit better flowability, while smaller particles tend to show increased cohesion and reduced flow. It serves as an important parameter for assessing the **flow behavior and quality** of powdered or granular pharmaceutical formulations. Materials demonstrating an angle of repose **below 30°** are typically considered to possess **good flow characteristics**, making them suitable for further processing in solid dosage form development.

Table No.2
Relationship between Angle of Repose and Flow ability

Angle of Repose	Flow ability
<30	Excellent
30-35	Good
35-40	Passable
>45	Very Poor

Particle Size & Surface Morphology

. Particle Size Determination:

The mean particle size of the prepared microspheres was determined using an **optical microscope** under normal polarized light. An **ocular micrometer**, previously calibrated with a stage micrometer, was used to measure the diameter of **100 randomly selected microspheres**. The average particle size was calculated and reported as the mean microsphere diameter.

Morphological Study using SEM:

Surface morphology and structural characteristics of the microspheres were examined using a **Scanning Electron Microscope (HITACHI SU-1500, Japan)**. The microsphere samples were mounted on a **copper sample holder** using double-sided adhesive tape and sputter-coated with a thin layer of **carbon followed by gold** to render the surface electrically conductive. The coated samples were then observed under suitable magnification to assess shape, surface texture, and porosity.(13-18)

Percentage Yield (19,20)

The percentage yield of microspheres was determined by accurately weighing the dried microspheres obtained from each batch. The

actual weight of the recovered microspheres was compared with the total weight of drug and excipients used in the formulation. The percentage yield was calculated using the following equation:

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipients and drug}} \times 100$$

Drug Loading and Drug Entrapment (16,17)

Microspheres equivalent to **50 mg of Tolperisone hydrochloride** were selected for evaluation. The microspheres were crushed and the drug was extracted by repeatedly washing with aliquots of **0.1 M HCl (pH 1.2)**. The extracts were pooled and transferred to a **100 mL volumetric flask**, and the volume was adjusted with the same medium. The solution was filtered, suitably diluted, and analyzed using a **UV–visible spectrophotometer (UV-2700, Shimadzu, Japan)** at **260 nm** against an appropriate blank.

The **percentage drug loading** and **drug entrapment efficiency** were calculated using the following formulas:

$$\% \text{ Drug Loading} = \frac{\text{Weight of the drug loaded in the microspheres}}{\text{Total weight of microspheres}} \times 100$$

$$\% \text{ Drug entrapment Efficiency} = \frac{\text{Amount of drug actual present}}{\text{Theoretical drug load expected}} \times 100$$

Floating behaviour (buoyancy %)

The floating capacity of microspheres was evaluated by dispersing **50 mg of microspheres** in **100 mL of simulated gastric fluid (pH 1.2)**. The dispersion was agitated at **100 rpm** using a magnetic stirrer. After a predetermined time interval, the floating and settled microspheres were separated by filtration. Both fractions were dried in a desiccator and weighed separately.(20,21,22)

The buoyancy percentage was calculated using the following equation:

$$\text{Buoyancy (\%)} = \frac{\text{Weight of floating microspheres after time t}}{\text{Initial weight of microspheres}} \times 100$$

***In-vitro* Release Study (12,13)**

In-vitro drug release studies were conducted using microspheres containing drug equivalent to **100 mg of Tolperisone hydrochloride**, employing a **USP Type-II dissolution apparatus (USP TDT-08L)**. The dissolution medium consisted of **900 mL of 0.1 M HCl (pH 1.2)** maintained at **37 ± 0.1°C**, with the paddle speed set at **50 rpm**. At predetermined time intervals for **1 hour**, **5 mL samples** were withdrawn and replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The samples were filtered, suitably diluted, and analyzed spectrophotometrically at **260 nm**. A comparative dissolution study was also performed using the **pure drug**. The cumulative percentage drug release was calculated using the previously constructed calibration curve.

Details of dissolution testing

- Apparatus: USP TDT 08L
- Dissolution media: 0.1 M HCl
- Speed: 50 rpm
- Volume of medium: 900 ml
- Temperature: 37±0.1°C
- Wavelength: 260 nm**.**

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Conclusion

The present study successfully demonstrated the design, development, and evaluation of floating microspheres of Tolperisone Hydrochloride as a gastroretentive sustained-release drug delivery system. Preformulation studies confirmed the identity, purity, and suitability of the drug for formulation development. FTIR compatibility studies indicated the absence of significant interactions between Tolperisone Hydrochloride and the selected polymers, confirming their compatibility.

Floating microspheres were successfully prepared using the emulsion solvent evaporation technique with Eudragit RS100, Ethyl Cellulose, and Eudragit S100 as release-retarding polymers. The prepared formulations exhibited satisfactory micromeritic properties, good flow characteristics, acceptable percentage yield, efficient drug entrapment, and excellent floating behavior in simulated gastric fluid. Surface morphology studies revealed the formation of discrete and spherical microspheres suitable for controlled drug delivery.

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