RESEARCH PAPER

DEVELOPMENT AND IN VIVO DRUG RELEASE OF GASTRO RETENTIVE FLOATING MICROBALLOONS OF TOLPERISONE HCl

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ABSTRACT

The present investigation deals with the development and evaluation of floating microballoons of Tolperisone HCl to extend the gastric residence time (GRT) and prolong the drug release. In the present work, floating microballoons of Tolperisone HCl were formulated using Eudragit RS 100, Eudragit S 100, and HPMC K4M and ethyl cellulose polymers by the solvent evaporation method. The prepared microballoons were evaluated for their physicochemical properties, in-vitro drug release, and in-vitro buoyancy. The in-vivo Radiographic study showed that the $BaSO_4$ loaded optimized formulation remained buoyant up to 5.5 h in the stomach. The in-vivo pharmacokinetic study was conducted in healthy albino rabbits revealed that the oral bioavailability of optimized formulation was increased significantly when compared to the marketed formulations. The increased bioavailability may be due to the floating mechanism of the dosage form in the stomach for longer duration.

Keywords: Eudragit S 100, Eudragit RS 100, Ethyl Cellulose, Floating Microballoons, Hydroxy Propyl Methyl Cellulose (HPMC), Tolperisone HCl.

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I. INTRODUCTION:

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs[1]. It improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment[2].

Microballoons (Hollow microsphere) are in the strict sense, empty particles of spherical shape without core. These Microballoons are characteristically free-flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometer[3]. The slow release of drug at desired rate and better-floating properties of floating Microballoons mainly depends on the type of polymer, plasticizer, the solvents employed for the preparation and the release of the drug can be modulated by optimizing polymer concentration and the polymer - plasticizer ratio[4].

Tolperisone, a centrally acting muscle relaxant agent, which has been in therapeutic use for more than three decades, has been widely used as spasmolytics of choice. It is recently launched drug in India for acute and chronic back pain and spasticity of neurological origin. It has also been used in treatment of condition which includes dysmenorrhoea, climacteric complaints, lockjaw, and neurolatyrism. Tolperisone hydrochloride is a “Class-I” drug according to Biopharmaceutics Classification System (BCS), possessing both high solubility and high permeability absorption characteristics. Tolperisone hydrochloride

is rapidly and completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 0.9-1.0 hours after oral dosing and its elimination half-life ranges from 1.5 to 2.5 hr. Tolperisone hydrochloride has a short elimination half- life and rapidly absorbed from gastrointestinal tract. If it is formulated by conventional tablets, it will require multiple daily administrations (2-3 times daily) which ultimately results into inconveniency to the patients and possibility of reduced compliance with prescribed therapy[5]. Tolperisone conventional tablets are unable to ensure a constant concentration of the active substance (tolperisone) in the blood. However, especially in cases of spastic muscle cramps, a constant efficacy throughout the night is very important to the quality of life of the patients. Known tablet formulations release the active substance tolperisone in the intestine at pH 4 to 7. In this pH range, tolperisone breaks down into 4-MMPPO and piperidine, this can be demonstrated in laboratory tests. Thus, the patient is exposed to an uncontrollable quantity of 4-MMPPO [2methyl-1-(4methylphenyl)-propanone]. Proposed are floating tolperisone microballoons with the controlled release of the active substance tolperisone in the stomach at pH 1 to 2. For tolperisone, a floating microballoons based on the non-effervescent approach having a lower density than the gastric juice was developed. By adding acid adjuvant, such as citric acid, it is possible to produce a GRDDS (Gastro Retentive Drug Delivery System) that is free from 4-MMPPO. The present investigation describes the formulation development of an floating drug delivery system for Tolperisone HCl. It will be evaluated for buoyancy property, content uniformity, and *In-vivo* drug release for 24 hours[6].

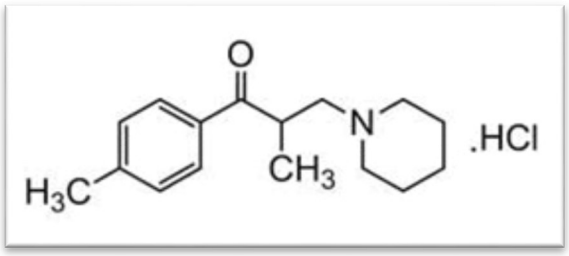

Figure 1: Structure of Tolperisone HCl

II. MATERIALS AND METHODS:

2.1. Materials: Tolperisone HCl was purchased from Yarrow chem. Products, Mumbai, India. Vitamin E TPGS, Eudragit RS 100, Eudragit S 100, HPMC K_4M, Ethyl cellulose, Ethanol, Dichloromethane chemicals of Laboratory-grade from SD Fine chemicals Pvt. Ltd., were used.

2.2. Methods:

2.2.1. Drug Excipient Compatibility Study:

2.2.1.1. FTIR Spectroscopy: Drug-polymer compatibility studies were carried out using the FTIR spectrophotometer by KBr pellet technique. Pure drug and optimized formulation were subjected to FTIR study. Compatibility studies were carried out to know the possible interactions between Tolperisone HCl and excipients used in the formulation[7].

2.2.2. Formulation of Floating Microballoons:

The floating microballoons were formulated by solvent evaporation method. The polymer is dissolved in an organic solvent and the solid dispersion (10 mg) equivalent to 30 mg of drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing suitable additive (surfactants /polymer) to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure. Stirring was continued for 6 h under 3 blade propellers at 500 rpm, 40 °C until the smell disappears[8].

The solvent removal leads to polymer precipitation at the oil/water interface of droplets, forming cavity and thus making them hollow to impart the floating properties. Then microballoons are collected and washed with excess amount of distilled water to remove any remnants. Collected microballons were dried at room temperature and subjected for further evaluation[9].

Table 1: Composition of floating microballoons of Tolperisone HCl

Materials	TP1	TP2	TP3	TP4	TP5	TP6	TP7	TP8	TP9	TP10	TP11	T	TP13	TP14	TP15
Tolperisone HCl SD	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
Eudragit RS 100	10	10	10	20	20	20	10	10	20	20	NA	NA	NA	NA	NA
Eudragit S 100	10	20	30	10	20	30	30	30	20	20	NA	NA	NA	NA	NA
HPMC K4M	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	10	10	10	20	20
Ethyl cellul	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	10	20	30	10	20

ose																
Ethanol	15	15	15	15	15	15	20	10	20	10	15	15	15	15	15
Dichloromethane	15	15	15	15	15	15	10	20	10	20	15	15	15	15	15
Ratio of drug to polymer	1:01:01	1:01:02	1:01:03	1:02:01	1:02:02	1:02:03	1:01:03	1:01:03	1:02:02	1:02:02	1:01:01	1:01:02	1:01:03	1:02:01	1:02:02
Ratio of solvent	1:01	1:01	1:01	1:01	1:01	1:01	2:01	1:02	2:01	1:02	1:01	1:01	1:01	1:01	1:01

2.2.3. *In-vivo* Evaluation of Microballoons: The experimental protocol to carry out *in-vivo* studies were reviewed and approved by the Institutional Animal Ethical Committee. The *in-vivo* performance of the optimized formulations was evaluated on healthy albino rabbits[10].

2.2.4. *In-vivo* Radiographic Studies: *In-vivo* floating behavior of optimized floating microballoons formulation was studied in healthy albino rabbits, weighing 1.5 kg to 2 kg. The 3 healthy male albino rabbits were used for the study. Animals were maintained for one week in the animal house to acclimatize them and were fed a fixed standard diet, under standard laboratory conditions (Temperature 25 ± 2°C). To monitor the *in-vivo* transit behavior of the prepared floating microballoons. First X-ray was taken for all the rabbits to ensure the absence of radio-opaque material in the stomach. Radiopaque microballoons were prepared by incorporating 500 mg of barium sulfate into the polymeric solution, and a similar procedure by which optimized microballoons were prepared was followed. Optimized microballoons prepared with $BaSO_4$ equivalent to rabbit dose (3.5 mg/kg) were administered to rabbits with a sufficient amount of water. Gastric radiography is done at intervals of 0.5, 2.5, and 4. 5, 5.5 h in both fed and unfed state[11].

2.2.5. *In-vivo* Pharmacokinetic Evaluation of the Optimized Microballoons: Six healthy albino rabbits with body weight range of 1.5-2.5 Kg were selected through physical examination. An open-label, balanced, randomized, single-dose complete crossover study design in which six healthy albino rabbits received one treatment (product) each with a washout period of 7 days was designed and pharmacokinetic parameters are assessed. Healthy rabbits are divided into 2 groups (n=6 for each group). Group I animals are treated with optimized formulation (TP10) and group II animals are treated with marketed formulation. At the predetermined time intervals of 0, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 12.00, and 24.00 h, 0.5 ml of blood samples were withdrawn from marginal ear vein and analyzed using HPLC[12].

Pharmacokinetic parameters such as peak plasma concentration (C_{max}), time at which C_{max} occurred (t_{max}), area under the curve (AUC), biological half-life ($t_{½}$), were calculated in each case using the data by kinetica TM 2000 software (Inna phase corporation, U. S. A) Using the non-compartmental approach. Percent relative bioavailability of the optimized formulations with reference to the marketed preparation is studied[13].

III. RESULTS AND DISCUSSION:

3.1. Drug Excipient Compatibility Study:

3.1.1. FTIR Spectrum

The FTIR spectrum of the Tolperisone HCl pure drug was found to be similar to the standard spectrum of Tolperisone HCl. The spectrum of Tolperisone HCl showed the characteristic peaks at the wave number: 3850cm-1, 3741cm-1, 3617cm-1, 2360cm-1, 1746cm-1, 1699cm-1, 1646cm-1, 1517cm-1, 1460cm -1, 1394cm-1, 1171cm-1, 1068cm-1, 977cm-1, 876cm-1 and 685cm-1.

In comparison with pure drug, the absorption peak of the spectra for Tolperisone HCl in different formulations showed no significant shift and no disappearance of characteristic peaks suggesting that there was no interaction between drug and polymer matrices or no degradation in Tolperisone HCl molecule. The differences in transmittance may be due to concentration of drug present in formulations.

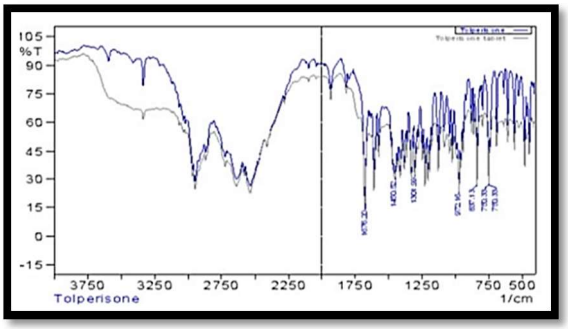

Figure 2: FTIR Spectrum of Tolperisone HCl pure drug

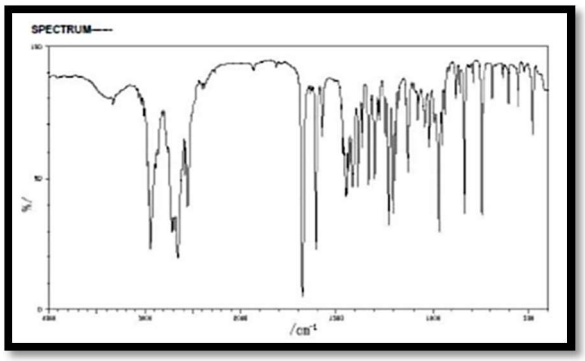

Figure 3: FTIR Spectrum of Optimised Formulation

There is no incompatibility of pure drug and excipients. There is no disappearance of peaks of pure drug and in optimized formulation.

3.2. *In vivo* floating behavior:

The optimized floating microballoons formulation prepared were tested for *in vivo* floating behavior in healthy albino rabbits. Radiographic images obtained at 0.5hrs, 2.5 hrs, 4.5 hrs & 5.5 hrs are shown in Figure 4 & 5. It was observed from the images that the formulation was remained buoyant for up to 5.5 hrs in the stomach indicating the uniform distribution of formulation in the stomach. But in unfed state the formulation remained buoyant in the stomach only up to 2.5 hrs this is because in fasting condition myoelectric migrating contractions forces the contents to duodenum from stomach. The forceful waves will remove all the contents of stomach including dosage form. This will not take place in fed state. Therefore from these studies it was clearly observed that the floating microballoons should be given to patients after a standard diet.

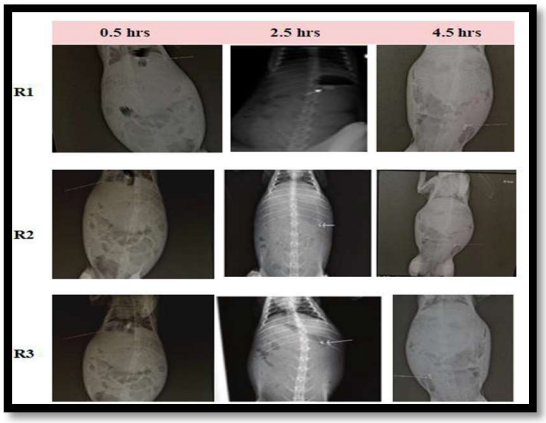

Figure 4: X-ray images of optimized microballoons of Tolperisone HCl in the gastric region of rabbit during unfed state at 0.5 hrs, 2.5 hrs, and 4.5hrs.

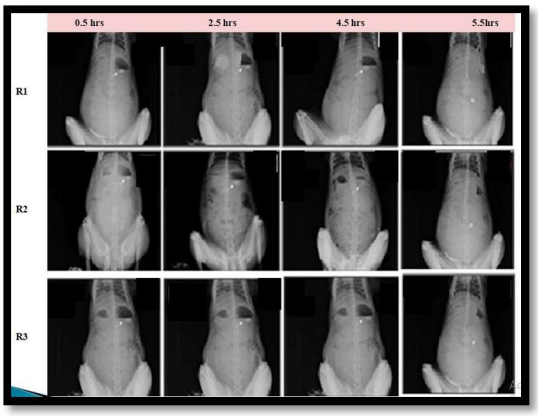

Figure 5: X-ray images of optimized microballoons of Tolperisone HCl in the gastric region of rabbit during fed state at 0.5 hrs, 2.5 hrs, 4.5hrs, and 5.5hrs.

Table 3: Plasma concentration of Tolperisone HCl conventional tablets in rabbits (n=6) at different time intervals (Reference formulation)

Time (hrs)	Plasma Concentration (ng/mL)							
	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Animal 6	Average	SD
0	0	0	0	0	0	0	**0**	0
0.5	4.5	4.6	4.8	5.2	4.9	4.7	**4.78**	0.

5								25
1	5.5	5.7	6.2	5.8	5.9	6.2	**5.88**	0.28
1.5	7.2	7.4	7.5	7.1	6.9	7.5	**7.27**	0.24
2	10.5	10.6	11.2	10.9	11.6	10.8	**10.93**	0.41
2.5	12.5	13.2	13.9	14.2	12.8	13.2	**13.30**	0.64
3	15.2	15.5	16.2	15.5	16.3	15.8	**15.75**	0.43
4	12.5	13.2	13.8	14.5	15.2	15.6	**14.13**	1.19
6	10.5	11.2	10.8	10.9	11.3	12.5	**11.20**	0.70
8	8.5	8.8	8.9	9.2	9.5	8.8	**8.95**	0.35
12	6.5	6.6	6.8	7.1	6.2	6.4	**6.60**	0.32
24	4.2	4.5	4.4	4.8	5.2	5.3	**4.73**	0.45

Table 4: Plasma concentration of Tolperisone HCl floating microballoons (TP10) in rabbits (n=6) at different time intervals (Test Formulation)

Time (hrs)	**Plasma Concentration (ng/mL)**							
	Animal 1	**Animal 2**	**Animal 3**	**Animal 4**	**Animal 5**	**Animal 6**	**Average**	**SD**
0	0	0	0	0	0	0	**0**	0
0.5	3.2	3.5	3.8	3.9	3.3	3.3	**3.50**	0.29
1	4.5	4.9	5.1	4.2	4.8	5.1	**4.77**	0.36
1.5	6.8	7.2	6.9	6.5	6.6	7.5	**6.92**	0.38
2	8.9	9.1	8.8	9.3	9.4	9.6	**9.18**	0.31
2.5	11.5	12.5	13.5	10.2	11.5	11.9	**11.85**	1.11
3	14.8	15.2	16.5	14.5	13.5	13.8	**14.72**	1.08
4	16.9	17.5	18.2	16.2	14.9	15.5	**16.53**	1.24
6	18.5	21.2	23.2	21.2	19.2	21.2	**20.75**	1.

								6 8
8	14. 5	15. 5	14. 3	12. 9	13. 5	16. 8	**13. 92**	1 . 0 4
1 2	12. 5	13. 2	13. 5	10. 5	12. 6	15. 5	**13. 80**	1 . 0 5
2 4	3.5	3.5	3.5	3.8	3.8	3.5	**3.6 0**	0 . 1 5

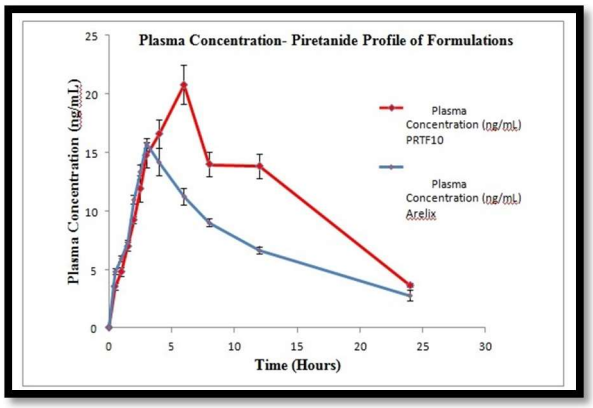

Figure 6: Mean plasma concentration time profile of Tolperisone HCl test (TP10) and Reference formulations

3.3. *In vivo* pharmacokinetic study

Table 5: Mean Pharmacokinetic Parameters of Tolperisone HCl as Reference and Test Tablets in Rabbits (N=6)

Pharmacokinetics parameters	Unit	Reference	Test
C_{max}	ng/ml	15.75	20.75
t_{max}	h	3	6
AUC_{0-t}	ng/mlX h	184.54	269.19
$AUC_{0-\alpha}$	ng/mlX h	302.4	327.9
$t_{1/2}$	h	7.45	18.72

The *in vivo* pharmacokinetic study was conducted in healthy albino rabbits. In this study, the pharmacokinetics parameters of Tolperisone HCl floating microballoons were compared with IR Tablets. The mean plasma concentration – time profile obtained from the study is shown in **Figure 6**. Various pharmacokinetic parameters were estimated such as C_{max}, t_{max}, AUC and relative bioavailability are given in **Table 5**. The significance of the difference between the treatments was evaluated by using Graph pad Prism by student paired t- test. The results showed that the difference between all pharmacokinetic parameters of IR and Floating microballoons were statistically significant ($p<0.050$).

The mean t_{max} of reference formulation was 3 hrs. This indicates that the drug release from the reference formulation was rapid while in the test formulation the mean t_{max} was 6 hrs. This indicates that the test formulation was effective in delaying the peak plasma concentration, thus showing prolonged plasma concentration of Tolperisone HCl from the floating microballoons. The mean biological half-life ($t_{1/2}$) of Tolperisone HCl from test and reference formulations was 18.72h and 7.45h respectively. The difference observed here is due to prolonged absorption of test formulation there is prolonged continuous release of drug into blood stream. Therefore, the test formulation shows to have longer half-life i.e., the drug stays in the plasma for a longer time than the reference formulation. The lower half-life of reference preparation indicates rapid removal of drug from plasma where as higher half –life of test formulation indicates prolonged release.The mean area under plasma time curve AUC_{0-t} and $AUC_{0-total}$ of reference formulation was 184.5458 ng/ml×h and 302.4ng/ml×h and while AUC_{0-t} and $AUC_{0-total}$ of test formulation was 269.19583 ng/ml×h and 327.9 ng/ml×h,

This indicates that the overall absorption of Tolperisone HCl was more in the test formulation with respect to the reference product at the same dose. It was observed from the results that the oral bioavailability of optimized formulation **(TP10)** was increased significantly when compared to marketed formulation. Relative bioavailability with respect to marketed formulation was found to be 108.4 which are due to prolonged gastric residence time of Tolperisone HCl floating microballoons.

IV. CONCLUSION:

Gastro-retentive drug delivery system for Tolperisone HCl was successfully prepared and evaluated by the solvent evaporation technique using Eudragit RS 100, Eudragit S 100, HPMC K4M, ethyl cellulose polymers. From the drug-excipient compatibility studies, it was observed that, there was no interaction between drug and excipients used in the formulations. Prepared floating microballoons showed significant floating ability, good buoyancy, and sustained drug release. *In vitro* drug release of microballoons was influenced by polymers concentration. *In-vivo* bioavailability study was conducted in rabbits optimized formulation (TP10) showed increased

bioavailability when compared to the reference marketed tablets due to controlled floating technology. Microballoons prepared in this study provide a promising gastro retentive drug delivery system to deliver Tolperisone HCl with sustained-release in order to improve oral drug bioavailability.

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