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Original Article

# Formulation of Sustained-Release Tablets of Tolperisone HCl Using Different Blends of Hydrophilic and Hydrophobic Polymers

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## ABSTRACT

**Background:** Tolperisone Hydrochloride (HCl) is a muscle relaxant that relaxes muscles by acting on the Central Nervous System (CNS). It acts at the spinal cord level by blocking calcium and sodium channels. It primarily inhibits transmitter release from primary afferent terminals through pre-synaptic inhibition via simultaneous action on voltage-gated sodium and calcium channels. Its elimination half-life $t_{1/2}$ is 1.5 to 2.5 hr. To maintain a constant plasma concentration, conventional Tolperisone HCl tablets are administered multiple times in divided dosages, which results in patient noncompliance. This problem can be overcome by preparing Tolperisone HCl sustained-release tablets. **Materials and Methods:** Tolperisone HCl sustained release matrix tablet was prepared by utilizing the wet granulation method with Hydroxypropyl Methylcellulose (HPMC K100) and Ethyl Cellulose (EC) in combination at different ratios. Evaluation: The powdered blend was evaluated for adequate flow properties using Carr's compressibility index, tapped density, bulk density, angle of repose, and Hausner's ratio before compression. The compressed tablets were then further evaluated for diameter, friability, content uniformity, thickness, hardness, weight variation, and *in vitro* drug release. **Results:** The drug release study showed that HPMC K100 and EC in combination were able to sustain the drug release in acid buffer pH 1.2 for the first 2 hr, followed by phosphate buffer pH 6.8 for the next 12 hr. It is also suggested that if the amount of ethyl cellulose increases, drug release decreases because ethyl cellulose is a water-insoluble polymer. All the formulations show drug release for more than 12 hr.

**Keywords:** Tolperisone HCl, Muscle Relaxant, Sustained Release, HPMC K100, Ethyl Cellulose.

## INTRODUCTION

A muscle spasm is an involuntary muscular contraction that happens suddenly, generally with fast recovery and is usually painful. The contraction that occurs during a muscle spasm is involuntary, which means that the brain sends a signal to the muscle to contract in a way that the body does not want. We employ voluntary muscular contractions to accomplish work when we exercise. During a muscular spasm, the brain sends a jumbled signal to the muscle, causing it to contract against the person's will.[1] It can last from a few seconds to several minutes or even an hour. Deep breathing and relaxation exercises might aid in the progressive relaxing of the muscle. Muscular spasms can be caused by various factors, including muscle tension, dehydration, trauma, illness such as cerebral palsy or multiple sclerosis, as well as poisons like strychnine and nerve or spinal cord injury.[2] Another form of muscular spasm is angina, which is caused by a shortage of blood in the heart. Angina has been related to atherosclerosis or the hardening of the arteries.[3] Angina produced by muscular spasms usually manifests itself as severe cramping in the arms, as well as the back, shoulders, and jaw. In most cases, treatment includes addressing underlying heart disease issues as well as treating angina symptoms with medication.[4]

A muscle relaxant is a medication that affects the function of the skeletal muscle and reduces muscular tone. It is used to treat muscle spasms, discomfort, and hyperreflexia. The term "muscle relaxant" is used to describe two types of drugs: neuromuscular inhibitors and spasmolytics. Neuromuscular blockers inhibit transmission at the neuromuscular end plate while not affecting the central nervous system.[5] Patients are usually paralyzed during surgery, acute care, or emergency medicine. Spasmolytics, sometimes known as "centrally-acting" are used to treat musculoskeletal discomfort and spasms as well as spasticity in persons who have a range of neurological problems.[6]

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Tolperisone HCl, a centrally acting muscle relaxant, is quickly and thoroughly absorbed from the whole Gastrointestinal Tract (GIT). Tolperisone works on the central nervous system to relax muscles. Moreover, it promotes membrane stability and has analgesic properties.[7] It acts at the spinal cord level by blocking calcium and sodium channels. Conventional Tolperisone HCl tablets are unable to maintain consistent plasma concentration; they require multiple administrations of divided doses, which causes patient noncompliance.[7] This problem can be overcome by prolonging the release of Tolperisone HCl in GIT for up to 12 hr. It primarily inhibits transmitter release from primary afferent terminals through pre-synaptic inhibition via simultaneous action on voltage-gated sodium and calcium channels.[8] Muscle relaxation is dose-dependent. The elimination half-life ($t_{1/2}$) of Tolperisone HCl is 1.5 to 2.5 hr.[7] Tablets with a prolonged-release hydrophilic matrix are prepared from Hydroxyl Propyl Methylcellulose (HPMC).[9] It is frequently and effectively used hydrophilic polymer for sustained release drug delivery. It has various properties, like non-toxicity, pH- independence, and high water swellability, which help to achieve a desired sustained release effect. In this study, sustained-release matrix tablets were created using HPMC as a release retardant carrier.[10] HPMC as gelling agents plays a vital role in the formulation because they create a diffusion- and erosion-resistant gel layer to develop through hydration, which helps in regulating drug release. Hydrophobic substances may also be used as matrix carriers for sustained-release solid dosage forms. Because of its hydrophobic substituents.[11] EC is considered a water-insoluble, hydrophobic, non-toxic, polymer that has been extensively used to formulate pharmaceutical dosages. It is frequently used as a tablet and granules coating material, in microcapsules and microspheres as a tablet binder, and as a film-forming material in dosage forms for sustained release.[12] To alter the release qualities by supplying hydrated channels for drug release, EC is used with HPMC.[13] The combination of HPMC and EC of various ratios alters the diffusivity of medication through the polymer barrier, and gives a broad variety of release rates.[14]

In the current work, Tolperisone HCl sustained-release tablets have been prepared and tested for controlled and prolonged drug delivery using hydrophilic and hydrophobic polymers. Ethyl cellulose in conjunction with matrix polymer HPMC K 100 gave sustained drug release and thus reduces the frequency of Tolperisone HCl dosage and subsequently its dose-related adverse effects. The formulation will maintain the therapeutic effectiveness of Tolperisone HCl for the required period, increase bioavailability with minimal side effects and thus increases patient compliance. Hence, Tolperisone HCl sustained release tablet is a great choice for prolonging the release of medication.

## MATERIALS AND METHODS

### Materials

Tolperisone HCl was collected as a gift sample from MSN Labs Hyderabad, India. HPMC K 100 (Polymer), Ethyl Cellulose (Polymer), and Talcum (Adsorbent) were obtained from the central drug house in New Delhi, India.

### Pre-Formulation Studies

Pre-formulation studies are used to identify the physical as well as chemical properties of a pharmaceutical material on its own and in combination with other substances.[15]

### Organoleptic Properties

By using suitable methods different organoleptic properties like colour, odor, taste, and physical form of the drug samples can be determined.

### Melting Point

For determining the drug's melting point, the capillary tube method was used.

### Solubility

The solubility of Tolperisone HCl was obtained in water, acetone, and di ethyl ether. Solubility was determined using magnetic stirrers. The samples were properly filtered and diluted before examination through Ultraviolet-visible (UV-visible) spectrophotometer.[16]

### Formulation of Tolperisone HCl Sustained-Release Tablets

Tolperisone HCl sustained-release tablets were manufactured by wet granulation method with different ratios (HPMC K100, Ethyl cellulose) as mentioned in Table 1. Drug and polymers were passed through sieve number 40; all the ingredients were combined and blended properly for 20 min for uniform distribution of the drug.[17] The mixture is granulated by using the required amount of distilled water for granulation. The granules obtained were sized via sieve number 20 and dried. The granules were blended with talcum, magnesium stearate, and aerosol for 5-10 min. The granules were compressed by Cadmach multi-station automatic compression machine.[18]

### Evaluation Parameters of Sustained Release Tablet

#### *Pre-compression Studies*

The powdered blend was evaluated for adequate flow properties using the bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's compressibility index, before compression.[19,32]

## Angle of Repose

Over the platform, a 10 mm diameter funnel was placed at a height of 2 cm. The sample was progressively moved down the funnel's wall until the tip of the pile formed touched the stem of the funnel. The radius of the powder cone was measured and a rough circle was formed around the base of the pile.

The angle of repose was measured using a formula.[20]

$$\emptyset = \tan - 1\,(h/r)$$

## Bulk Density

Bulk density was calculated by transferring the sample through a funnel into a 100 mL graduated cylinder. The volume covered by the sample was calculated.[21]

Bulk density was measured by the formula:

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume}}$$

## Tapped Density

Tapped density was calculated by transferring the sample through a funnel into a 100 mL graduated cylinder, then the cylinder was tapped from a height of 2.5 cm at an interval of 2 sec. After tapping, the sample's volume was recorded by using Electrolab's Tap Density Tester ETD-1020. Tapped density was measured using a formula.[22]

$$\text{Tapped density} = \text{Weight of powder}/\text{Tapped volume}$$

## Carr's Compressibility Index

The relative flow rate, cohesion, and particle size distribution of the powder are all indirectly related to compressibility. It is used to calculate a material's compressibility. It has been found that powders with compressibility values less than 20% have good flow properties.

The compressibility index was measured using formula.[23]

$$\text{Carr"s Compressibility Index}\,(\%) = 100x\,(1 - \text{Bulk Density}/\text{Tapped Density})$$

## Hausner's Ratio

It is the ratio of bulk volume to tapped volume or tapped density to bulk density. Hausner's ratio was measured using formula.[24]

$$\text{Hausner"s ratio} = \text{Tapped density}/\text{Bulk density}$$

## Post Compression Study

The prepared Tolperisone HCl tablets were assessed for post-compression studies like weight variation, hardness, thickness, friability, and *in vitro* dissolution.[25]

## Weight Variation Test (w)

The weight variation study is performed using a digital electronic balance, according to the official method described in Indian Pharmacopoeia (IP), to ensure uniformity in the weight of the tablets in a batch twenty tablets from each formulation batch were taken and the total weight was assessed. The average weight of all twenty tablets was calculated. The limit for weight variation for tablets more than 250 mg is ±5. The individual weight of each tablet is also measured, and the weight variation was determined as specified inIndian Pharmacopoeia (IP) by using the formula.[26]

$$\%\,\text{Weight variation} = (\text{weight of single tablet} - \text{Average weight of 20 tablets}) \times 100$$

## Hardness Test (h)

The force that is required to break a tablet is known as hardness (diametral crushing strength). Tablets must be resistant to mechanical stress while handling and transportation. The acceptable range for hardness is 4-7 kg/cm$^2$. A Monsanto hardness tester was used to determine the hardness of the tablets. The average hardness of five tablets was measured and reported.[27]

## Thickness (t) and Diameter of the Tablet

Tablet thickness and diameter were evaluated using Vernier Calipers. From each batch, three tablets were randomly selected and tested. The average of three readings was taken.[28]

**Table 1: Formulation table of Tolperisone HCl tablet.**

| Ingredients | TB1 (mg) | TB 2 (mg) | TB 3 (mg) | TB 4 (mg) | TB 5 (mg) |
|---|---|---|---|---|---|
| Tolperisone HCl | 500 mg | 500 mg | 500 mg | 500 mg | 500 mg |
| HPMC K-100 | 185 mg | 152 mg | 115.5 mg | 76 mg | 38 mg |
| Ethyl Cellulose | 37 mg | 76 mg | 115.5 mg | 152 mg | 190 mg |
| Talcum | q.s | q.s | q.s | q.s | q.s |
| Magnesium Stearate | q.s | q.s | q.s | q.s | q.s |
| Aerosil | q.s | q.s | q.s | q.s | q.s |
| Total weight | 870 mg | 880 mg | 885 mg | 880 mg | 880 mg |

### Friability Test (% F)

Twenty tablets from each batch were weighed, and loaded intoRoche friability tester. The test was performed at a speed of 25 rpm for 4 min. The tablets were then weighed again (FRV 100i). The % weight loss can be measured using formula.[29]

$$\% \, Friability = \frac{[W1 - W2] \times 100}{W1}$$

### *In vitro* Drug Dissolution Studies

*In vitro* drug dissolution rate studies were carried out using a USP paddle type II Dissolution apparatus (Electrolab) India Pvt. Ltd., Mumbai) at a speed of 50 rpm in 900 mL of acid buffer (pH 1.2) for the first 2 hr, followed by phosphate buffer (pH 6.8) for the next 12 hr. The dissolving medium's temperature was kept constant at 37°C. Samples were taken at definite intervals, filtered through a membrane filter and analyzed through UV-Visible spectroscopy at 261 nm. A volume of dissolving media equal to the volume of the samples taken was added to the vessel after each sampling to maintain the sink condition.[30]

### Kinetic Release Data

For the optimized formulations, the drug release kinetics was analyzed by using a DD solver. The data obtained from the study was fitted into several models, including the zero-order, first-order, Higuchi, Korsmeyer Peppas, and Hixon-Crowell to choose the best-fit model.[31]

### Similarity Factor

The Tolperisone HCl tablet *in vitro* drug release profile was carried out under similar conditions as the test formulation for the release of Tolperisone HCl.[24] Information obtained from the drug release profile was used to evaluate the similarity factor between the two formulations. The DD solver software 26 was used to analyze the similarity factor.[25]

## RESULTS AND DISCUSSION

### Pre-Formulation Studies

Tolperisone HCl was tested for a few pre-formulation studies, including organoleptic characteristics, solubility, melting point, and compatibility with excipients. The drug was identified as crystalline white or nearly white powder with a characteristic odour. The drug's melting point was reported to be between 181-183°C. The drug readily dissolves in water, slightly in acetone, and does not soluble in diethyl ether. The observed solubility of Tolperisone HCl in water was found to be 0.167 mg/mL

### Evaluation of Sustained-Release Tablets

#### *Pre and Post Compression Data*

Tolperisone HCl sustained-release tablets were formulated by using the wet granulation method. The tablets were then evaluated for pre and post-compression studies. The formulation showed good satisfactory results which were within the desired limits and ranges as mentioned in Table 2. The weight variation of all prepared batches was within the limit of ±5%. The % friability of all tablets was <1. The average hardness and thickness of tablets were in the range of 4.3-5.9 kg/cm$^2$ and 5.7-6.3 mm respectively.

### *In vitro* Drug Release Studies

The *in vitro* release data for all prepared formulations were tabulated in Table 3 and shown in Figure 1. All five batches of sustained-release tablets had an initial impact after being released *in vitro*. TB1, TB 2, TB 3, TB 4, and TB 5 had 33.88, 31.61, 29.39, 23.86, and 24.32% drug released in the 1$^{st}$ hr, respectively. According to the *in vitro* dissolution results, TB 1 releases 99% of the drug in 12 hr, this is because the quantity of ethyl cellulose (water insoluble in nature) used in the formulation was less. In TB 5 ethyl cellulose was added in the highest amount therefore, the formulation gave sustained drug release more than0000 24 hr.

The kinetic analysis of *in vitro* drug release data of optimized preparation (TB 5) was carried out using a DD solver as shown in Figure 2. The correlation coefficient (R2) and the Sum of Square Residues (SSR) value for each model was calculated and given in Table 4. The optimized preparation followed the Higuchi model because it has the lowest SSR value of 33.7614, the highest R2 equal of 0.9986 and adjusted R2 equal of 0.9979. Amongst all the models evaluated the model selection criteria of 4.1748 was found to be the highest, mentioning that the characteristics of drug release are best described by the Higuchi model.

**Table 2: Flow characteristics and physical parameters of all formulations.**

| Formulations | Angle of Repose | Bulk Density(g/mL) | Tapped Density (g/mL) | Carr's Index (%) | Hausner Ratio | Average wt. (mg) | Friability (%) | Hardness (kg/) | Thickness (mm) |
|---|---|---|---|---|---|---|---|---|---|
| TB1 | 26.1 | 0.4838 | 0.7142 | 20.11 | 1.21 | 870 | 1.0 | 4.3 | 5.7 |
| TB2 | 25.4 | 0.4285 | 0.5882 | 18.21 | 1.20 | 880 | 0.8 | 4.8 | 5.8 |
| TB3 | 28.4 | 0.3333 | 0.4166 | 20.01 | 1.16 | 885 | 1.0 | 5.1 | 6.3 |
| TB4 | 26.5 | 0.3488 | 0.4225 | 17.44 | 1.12 | 880 | 1.0 | 5.6 | 6.2 |
| TB5 | 25 | 0.3488 | 0.4120 | 15.5 | 1.18 | 880 | 0.9 | 5.9 | 6.0 |

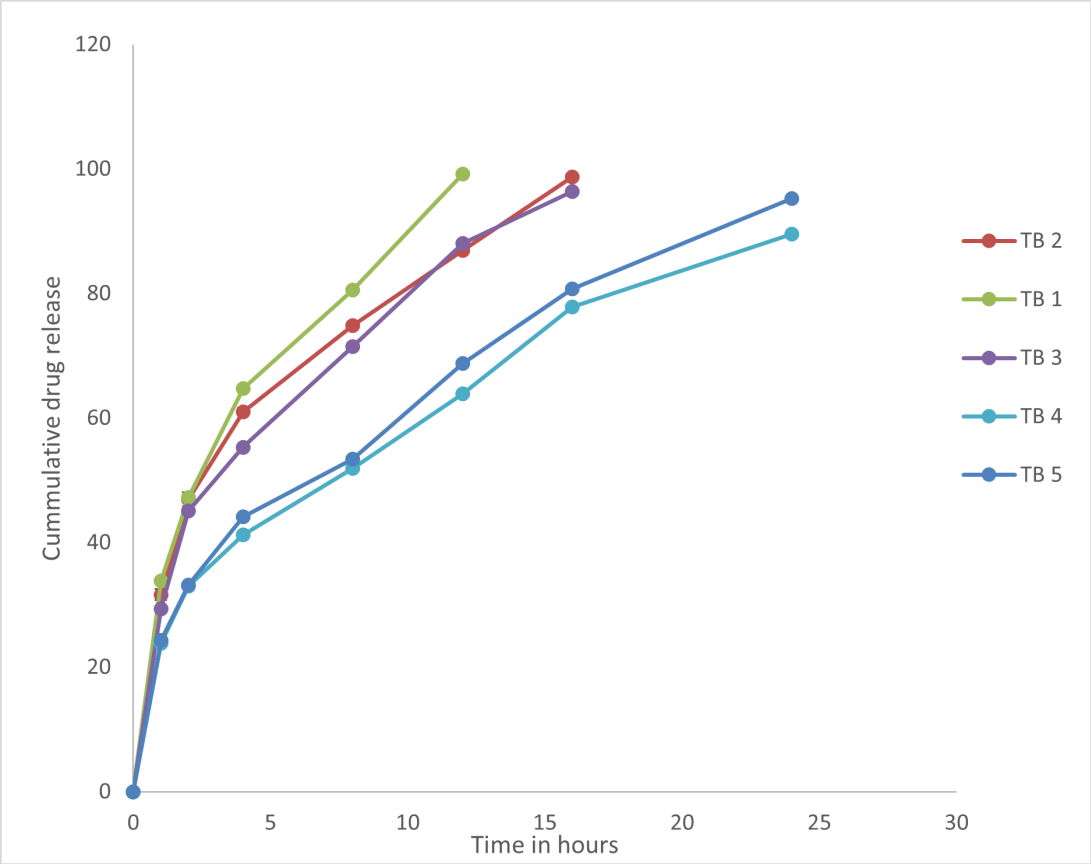


**Figure 1:** *In vitro* Dissolution study for All Batches of Tolperisone HCl Sustained release tablets .Kinetic analysis of release data.

**Table 3: Cumulative % Drug Release of All Five Batches(TB1-TB5).**

| Time (Hr) | % Cumulative Drug Release | | | | |
|---|---|---|---|---|---|
| | TB 1 | TB 2 | TB 3 | TB 4 | TB 5 |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 33.88±0.54 | 31.61±0.89 | 29.39±0.67 | 23.86±0.48 | 24.32±0.35 |
| 2 | 47.19±0.43 | 46.96±1.13 | 45.03±0.55 | 33±0.94 | 33.22±0.74 |
| 4 | 64.77±0.51 | 60.95±0.65 | 55.32±0.43 | 41.2±0.39 | 44.12±0.79 |
| 8 | 80.55±0.67 | 74.84±0.22 | 71.43±0.78 | 51.88±0.44 | 53.42±0.82 |
| 12 | 99.15±0.78 | 86.88±0.32 | 88.04±0.49 | 63.88±0.59 | 68.77±0.75 |
| 16 | - | 98.67±0.31 | 96.34±0.21 | 77.81±0.11 | 80.74±0.33 |
| 24 | - | - | - | 89.54±0.23 | 95.24±0.47 |

**Table 4: Kinetic release data.**

| Release model | $R^2$ | $R^2$ adjusted SSR | MSC |
|---|---|---|---|
| Zero-order | 0.3080 | 0.3080 | 0.0824 |
| First order | 0.8761 | 0.8761 | 1.8023 |
| Higuchi | 0.9986 | 0.9986 | 4.1748 |
| Korsmeyer-peppas | 0.9918 | 0.9901 | 4.2263 |
| Hixon Crowell | 0.8098 | 0.8098 | 1.3738 |

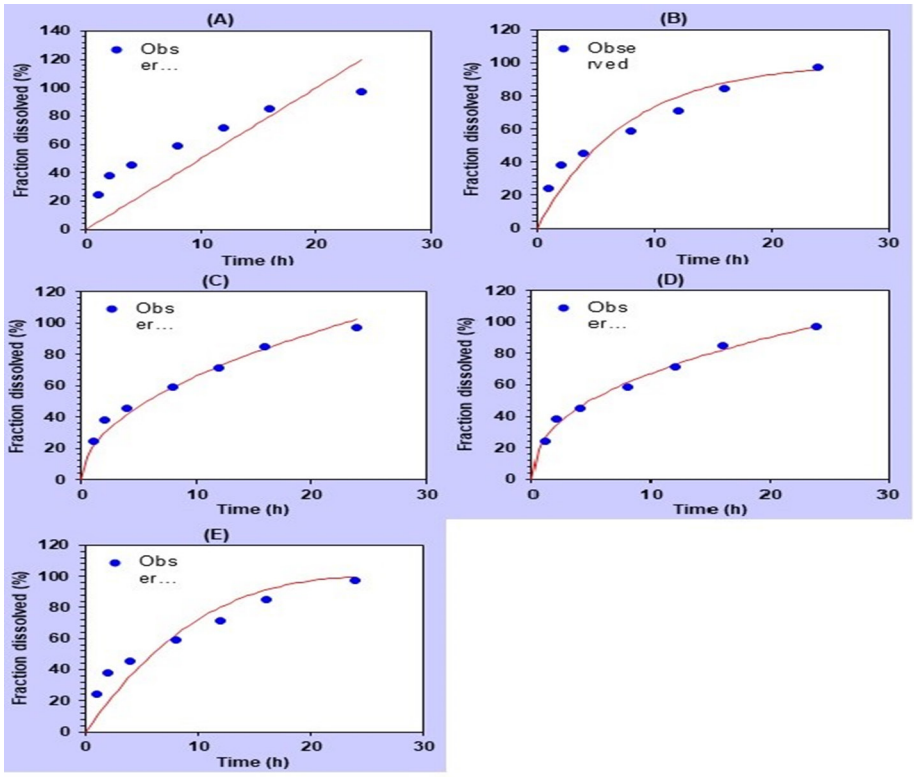


**Figure 2:** Kinetic Modeling study (A) zero order Kinetic (B) First order Kinetic (C) Higuchi Kinetic (D) Korsmeyer Peppas Kinetic (E) Hixon Crowell Kinetic.

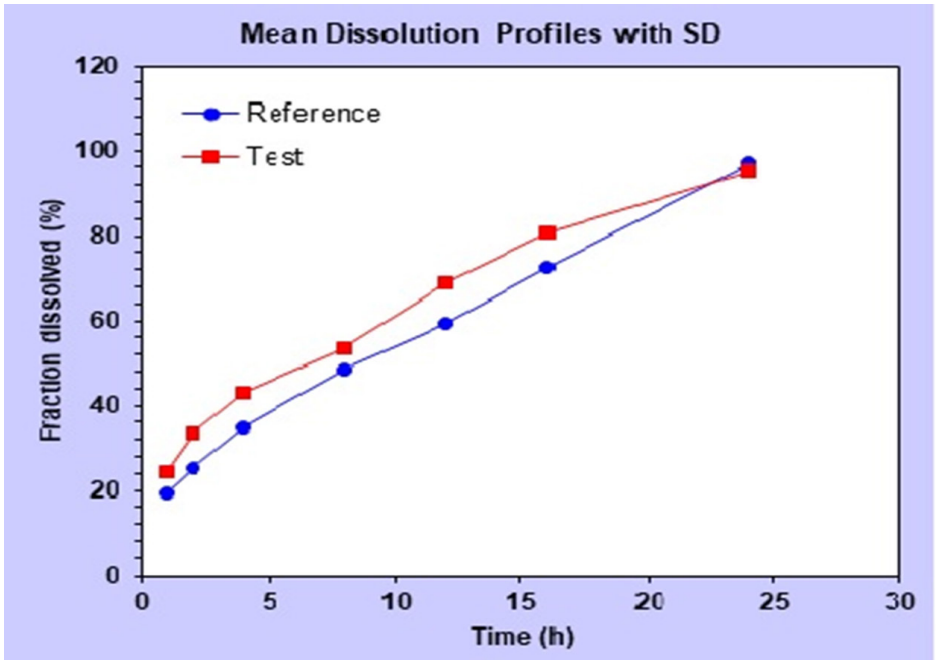


**Figure 3:** Graph of Similarity factor of test formulation (TB5) and reference formulation (Tolperitas).

## Similarity Factor

Dissolution studies are performed to ensure product uniformity from batch to batch, to predict bioavailability for formulation and development, and to determine what modifications should be made to an existing formulation. The dissolution profiles of formulated tablet (TB5) and marketed tablet of Tolperitas SR tablet (INTAS) was compared using the similarity

**Table 5: Similarity Factor data.**

| Time | % Drug release of Reference | % Drug release of optimized formulation (TB5) | f2 |
|---|---|---|---|
| 1 | 19.23 | 24.32 | 64.25 |
| 2 | 25.17 | 33.22 | 54.54 |
| 4 | 34.87 | 43.12 | 54.02 |
| 8 | 48.24 | 53.42 | 63.89 |
| 12 | 59.37 | 68.77 | 51.22 |
| 16 | 72.74 | 80.74 | 54.68 |
| 24 | 97.27 | 95.24 | 82.27 |

The average value of f2= 57.55.

factor (f2). The similarity factor f2 factor (f2=57.55) was found to be greater than 50 as shown in Table 5, Figure 3 confirms that the release of Tolperisone HCl from prepared formulations was similar to the marketed formulations (Tolperitas SR) (INTAS).

## CONCLUSION

In the current investigation, it is concluded that the release of Tolperisone HCl can be prolonged for duration of more than 12 hr by using a blend of hydrophilic and hydrophobic polymers. The process of drug release from both hydrophilic as well as hydrophobic polymer-based matrix tablets may first involve erosion and then diffusion. An improved formulation of HPMC and EC has been successfully able to extend the drug release for more than 12 hr. Hence it is proved that the Sustained Release tablet of Tolperisone HCl is a great choice for delaying the release of medication. This formulation will certainly improve patient compliance, enhanced bioavailability, low side effects and prolonged therapeutic action for the required duration of time after single-dose administration.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**DM:** Diabetes Mellitus; **HPMC:** Hydroxypropyl methylcellulose; **SR:** Sustained Release; **MSC:** Model Selection Criteria; **SSR:** Sum of Square Residual; **EC:** Ethyl Cellulose; **CNS:** Central Nervous System.

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