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Original Article

# Formulation and in vitro evaluation of sustained release tablets of tapentadol hydrochloride

**Suhair Murtada[1]*, Ahmed Sami Abduljabbar[1], Ahmed Abdul Kareem AbdulAbbas Alsaad[1]**

[1]Department of Pharmaceutics, College of Pharmacy, University of Basra, Basra, Iraq.

**Correspondence:** Suhair Murtada, Department of Pharmaceutics, College of Pharmacy, University of Basra, Basra, Iraq. suhar.ashor@uobasrah.edu.iq

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## ABSTRACT

This work aims to develop a Tapentadol Hydrochloride (TPHCl) sustained-release tablet. TPHCl is an analgesic drug that can act centrally, so it has efficacy in different types of pain, such as inflammatory origin pain, neuropathic pain, as well as acute and chronic pain. Tapentadol has very low plasma protein binding, and its activity is independent of metabolic activity. The research showed that conventional therapy cannot obtain prolonged release of the drug from the dosage form. TP belongs to the BPCS class- I drug, and in order to reduce the frequency of its administration, Tapentadol is suggested to be prepared as a sustained-release dosage form through oral delivery. Sustained release tablets of TPHCI were prepared by using polymers such as Hydroxypropyl methylcellulose (HPMC K4M) and Eudragit RL100 by the wet granulation method, and then the physical and chemical characteristics were evaluated. The tablets with a hydrophilic-based matrix were unsuccessful in extending the release of the drug, whereas the tablets with a hydrophobic-based matrix had less drug release. Zero-order kinetics can be obtained from the tablets with a hydrophilic and hydrophobic polymer matrix, and the drug release mechanism was non-Fickian diffusion-controlled. Therefore, the latter tablets can be formulated as an alternative to conventional TPHCl tablets.

**Keywords:** TPHCl, HPMC K4M, Sustained release, Matrix tablet, Dissolution

## Introduction

Sustained release (SR) drug delivery is considered one of the most common modified drug release systems. The drug delivery has been established with an aim to provide drug therapeutic action for a prolonged time period. Generally, the main purposes of this SR dosage form are to reduce the daily dose, to reduce the frequency of dosage administration, and to exhibit the maximum therapeutic effect of the drug. All of the previous purposes can contribute to improving patient compliance. Apart from these dosage forms, modified release dosage forms, which include prolonged release, extended release, and controlled release. The SR dosage forms are better to improve drug release for a prolonged time period because the initial release of the drug is enough to provide a therapeutic dose in a short time after drug administration, and then the drug is gradually released over an extended period [1-6]. Tapentadol HCl is widely prescribed for musculoskeletal pain. Tapentadol is an analgesic that acts centrally and has a dual action mode; it can act as a μ-opioid receptor agonist as well as an inhibitor for norepinephrine reuptake. TPHCl has a (4hrs) half-life. It can be classified as BPCS- Class-I (drugs which have high permeability and high solubility). TPHCl shows extensive first-pass metabolism after oral administration. TPHCl can be used orally in the treatment of musculoskeletal pain with a maximum dose of 600 mg per day by controlled release. Otherwise, it may be administered as an immediate-release tablet (50, 75, and 100 mg) once every 4 to 6 hrs in order to control the pain [7-11]. The aim of this study is

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the production of a sustained-release TPHCl tablet in order to decrease the frequency of drug administration.

## Materials and Methods

### *Materials*

Tapentadol hydrochloride was collected from Sigma Aldrich, Avicel PH-101 (Loba Chemie Pvt. Ltd, Mumbai). HPMC -K4M (Signet Chemical Corporation, Mumbai). Ethylcellulose N-14 from Sigma Aldrich. Eudragit- RL 100 from (Degussa Germany, Mumbai), Talc, Magnesium Stearate & lactose (Qualikems Fine Chemicals Pvt. Ltd, New Delhi).

### *Methods*

#### *Formulation of sustained-release TPHCl tablet*

Sustained-release TPHCI tablets were prepared with different polymers such as HPMC-K4M, Eudragit RL- 100. Six formulations were prepared; among these six formulations, three were prepared with Eudragit RL-100, and the remaining three formulations were prepared with HPMC- K4M [12-15]. The total daily dose required to produce the therapeutic efficacy was calculated by using the Robinson-Eriksen equation with the help of available pharmacokinetic data. The tablet composition is given in **Table 1**.

#### *Dose calculation of TPHCl sustained release tablet* [12]

The total dose per day was calculated as…

The rate constant (k0) for zero-order drug release was determined by utilizing the following equation: $k_0$ = DI x ke

where DI is the initial extended-release tablet dose, which is about 50mg orally twice daily (100mg), and ke is a rate constant for first-order elimination.

ke = 0.693 / t1/2

where t1/2 = half-life of TPHCl = 4 h

Therefore, ke = 0.693 /4 = 0.17325 mg/h.

Availability rate R = ke x DI

R = 0.17325x 100= 17.32 mg/h.

DM = K0(T-t1/2)

DM= 17.32(24-4) = 346.5 mg

Loading dose = DL = DI – Rx tmax

Therefore DL = 100-(17.32 x 5) = 13.4 mg.

DM=R x H

Where DM = Maintenance dose, H = prolonged action hours number required after initial drug release

H = 346.5/ 17.32

H = 20 hrs

DM =346.25

Total dose required, DT = DL + DM

= 13.4+346.5 = 359.9 mg

The total dose was calculated as 359.9 mg. But for formulation convenience, the total dose was rounded to 360mg/tablet.

**Table 1. Composition of TPHCl Formulations**

| S/N | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|
| 1 | TPHCl | 360 | 360 | 360 | 360 | 360 | 360 |
| 2 | HPMC-K4M | 80 | 85 | 70 | - | - | - |
| 3 | Eudragit-RL100 | - | - | - | 80 | 85 | 70 |
| 4 | Avicel PH-101 | 43.5 | 38.2 | 52.5 | 40 | 34.7 | 50.4 |
| 5 | Ethyl cellulose N-14 | 8 | 7.5 | 8 | 7.5 | 7.8 | 8.3 |
| 6 | Lactose | 1.5 | 2.5 | 3 | 5.5 | 6 | 4.5 |
| 7 | Magnesium Stearate | 2 | 1.8 | 1.5 | 2 | 1.5 | 1.8 |
| 8 | Talc | 5 | 5 | 5 | 5 | 5 | 5 |
| 9 | Starch mucilage | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |

*All the ingredients were taken at the mg level, and the tablet weight from each batch of TPHCl is equivalent to 500 mg

#### *Preparation of TPHCl sustained release tablet*

The wet granulation method was used for the development of TPHCI sustained-release tablets. TPHCl and polymers were accurately weighed, and sieve #40 was used for sieving the drug and polymers; then, the latter materials were blended for 10 minutes. The granulating solution was prepared by using a quantity of purified water and starch in order to form a binder solution. The starch was dispersed in an aqueous medium with continuous stirring by using a magnetic stirrer until a clear solution was obtained. The solution of binder was incorporated into the mixture of drug and polymers. This whole blend was passed through sieve #20 after attaining granules with this blend, lactose, talc, and magnesium stearate were added. These three additives were already sieved using sieve#40, and the mixture of them was blended for 10min. The obtained granules were sieved by using sieves #22 and #40 simultaneously. The formed granules had some moisture content; hence, the moisture can be removed by using an oven that provides 160 °C hot air for 30 min. After removing the dried granules from the oven, a rotary tableting machine (16-station) with 7mm flat, round punches was used to compress these dried granules into the tablets [16, 17].

### *Evaluation of TPHCl SR tablets*

#### *Analytical method for the estimation of TPHCl*

A spectrophotometric method was used to measure TPHCl absorbance at 272nm, and the buffer medium was phosphate buffer with pH 7.4.

#### *Construction of calibration curve of TPHCl in phosphate buffer (pH 7.4).*

### Preparation of stock solution

Twenty-five milligrams of TPHCl were dissolved in 25 ml of phosphate buffer (pH 7.4) in a volumetric flask. From this solution, a volume of 10 ml was withdrawn and diluted up to 100 ml using phosphate buffer with pH 7.4. The yielded solution had a 100 µg/ml concentration, which was used as the stock solution [18, 19].

### Preparation of standard solutions

Volumes of 2.5, 5, 7.5, 10, 12.5, and 15 ml were withdrawn from the stock solution (100 µg/ml). Stock solutions with volumes of 2.5 ml, 5 ml, and 7.5 ml were diluted using phosphate buffer (pH 7.4) to 10 ml using 10 ml volumetric flasks. Stock solutions of volumes 10 ml, 12.5 ml, and 15 ml were taken directly (without dilution). The concentrations of solutions obtained were 25, 50, 75, 100, 125, and 150 µg /mL, respectively. The above dilutions' absorbance was determined at 272 nm using a UV spectrophotometer; the phosphate buffer solution with pH 7.4 was utilized as a blank. A calibration curve was constructed by plotting the absorbance of TPHCl against its concentration. A regression equation was derived from the plot, which was used for the estimation of drug release of TPHCl in a 7.4 pH phosphate buffer.

## Pre-formulation studies

The Preformulation studies are useful to understand the rationale in the development of dosage forms. It also gives information about whether a newly developed dosage form shows sufficient therapeutic effect or not, and also the physicochemical properties of the drug are suitable to make a dosage form that will affect the entire dosage form. The Preformulation parameters are useful to optimize the formulation in terms of acceptability, efficacy, safety, and stability [20-22].

## Angle of repose

The flow properties of powder/granules can be determined by the angle of repose. The angle of repose is studied using a fixed funnel and a standing cone method. The method can be summarized by weighing granules accurately, then pouring them into the funnel. The height of the funnel was adjusted in a better method in order to avoid touching the granule's apex and heap. After funnel adjusting, the granules were allowed to pass through the funnel and fall onto the horizontal surface. The diameter of the cone was determined, then the angle of repose was counted by using Eq. 1.

$$tan\theta = \frac{h}{r} \quad (1)$$

Where, h represents the heap height of the powder, r is the powder heap radius & $\theta$ is the angle of repose [23].

## Calculation of bulk density and tapped density

The bulk density and the Carr's index value of the powder can give information about milling and crystallinity of the material, and also to realize the correct powder density and porosity of packed powder beds [24, 25]. Granules/powders were accurately weighed and poured into the graduated cylinder, and then the powder volume in the cylinder was measured. This volume was considered as Vo. After that, the lid was used to close the graduated cylinder, and the tap density tester was set up for 100 taps. After 100 taps, the powder volume was measured. The latter volume was considered as Vf. The tapping procedure was continued until the differences between the Vo and Vf values were equal to or less than 2ml. The bulk density and tapped density were determined by Eqs. 2 & 3.

$$Bulk\ density = \frac{W}{Vo} \quad (2)$$

$$Tapped\ density = \frac{W}{Vf} \quad (3)$$

Where W is the power weight, Vo is the powder initial volume & Vf is the volume of powder after tapping.
The Carr's index was calculated using Eq. 4

$$Carr's\ index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100 \quad (4)$$

## Sieve analysis

The sieve analysis is used to determine the drug particles of the powder with various sizes. A series of sieves was vertically arranged, so the top sieve had large-sized pores while the bottom one had small-sized pores. The powder was accurately weighed and put on the top sieve. The serially arranged sieves were shaken for about 10 minutes. Then the powders that remained on each sieve were collected separately, and the percentage of weight for the retained powders was determined [26, 27].

## Quality control tests for TPHCl SR tablets

The prepared tablets were evaluated by using the following quality control tests [28-31].

### Weight Variation

The tablet weight variation test was conducted by randomly selecting 20 tablets from each prepared formula; these 20 tablets were weighed together by an electronic balance (Mettler Toledo, Switzerland). Subsequently, each tablet was separately weighed, and the weight of each tablet was noted down; then the average weight for 20 tablets of each formulation was calculated. Mean and standard deviation values were determined, and the results of the weight variation test are illustrated in **Table 3**.

### Drug Content (Assay)

The drug content of the TPHCl sustained-release tablets was measured. Ten tablets were weighed from each formulation, then the tablets were ground into a fine powder using a mortar and pestle. The powder amount equivalent to 100mg of tapentadol hydrochloride was weighed precisely and poured into a volumetric flask that contained 100 mL phosphate buffer (pH 7.4). The resulting solution was placed in a sonicator for around 30 minutes. The latter solution was filtered by using filter paper and diluted with phosphate buffer pH 7.4, and the absorbance of TPHCL was determined at a wavelength of 272 nm against a blank. The results are tabulated in **Table 3**.

### Hardness

Tablets` hardness can be determined by selecting 6 tablets from each formulation, and a hardness tester (Monsanto) was used for such determination. The mean and standard deviation values were measured, and tablets` hardness in terms of kg/cm² values are displayed in **Table 3**.

### Friability

Tablets` friability is measured to know the tendency of the tablets to powder, chip, and fragment during shipping, transportation, and packaging. From each formulation, 20 tablets were randomly selected and weighed together; after that, the tablets were placed in a friabilator (Roche friabilator). The machine allowed to rotate 100 rotations per 4 minutes (i.e., 25 rpm). The tablets were ejected and weighed after the friability test. The results are shown in **Table 3**. The friability of tablets was determined using Eq. 5

$$F = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100 \qquad (5)$$

Where F is friability, initial weight represents the weight of prepared tablets before testing & final weight means the tablet's weight after the friability test. Generally, an F value less than 1 is acceptable.

### Drug release of TPHCl (In vitro studies)

*In vitro* drug release of sustained-release TPHCl tablets was carried out. The release of the drug was determined by using a dissolution apparatus type USP-I. This apparatus consists of six dissolution baskets. 900ml of hydrochloric acid with a pH of 1.2 was placed in each jar as a medium of dissolution. For the initial two hours, the drug release was carried out using HCl with a pH of 1.2 in order to mimic the stomach fluids. After two hours, the dissolution medium was replaced with 900 mL of phosphate buffer, pH 7.2. This experiment was conducted at 37°C ± 0.5°C, and the setting for the dissolution apparatus was 100 rpm. 5 mL of the sample was withdrawn based on the time intervals through a 0.45µm filtrated syringe and then replaced with fresh phosphate buffer solution in order to maintain sink conditions. The test was conducted for 24 hours. For each time interval, the amount of the drug that was released was determined by using UV-spectroscopy at a 272 nm wavelength. The results are shown in **Table 4** and **Figure1**.

### Kinetic data analysis

The data of *in vitro* release of the drug is fitted to different models of kinetics, which were utilized to illustrate the mechanism and kinetics of drug release. In order to establish drug release kinetics, the data are fitted to a zero-order kinetic model (cumulative % drug release vs. time) and a first-order kinetic model (log cumulative % drug remaining vs. time). In order to realize the drug release mechanism, the data is fitted into the Higuchi model (cumulative % drug release vs. square root of time) and the Korsmeyer model (log cumulative % drug release vs. Log time) [28-30, 32]. The kinetic mathematical expression is shown in **Table 2**.

**Table 2. Mathematical models for dissolution profiles comparison**

| Model | Equation | |
|---|---|---|
| | Kinetic | Mechanism |
| **Zero order** | $Qt=Q_0+K_0 t$ | - |
| **First order** | $\ln Q0 = \ln Q0 - K1t$ | - |
| **Higuchi** | - | $Q_t=K_H \sqrt{t}$ |
| **Korsmeyer-Peppas** | - | $Qt/ Q_\infty = K_K t^n$ |

### FTIR Studies

The FTIR technique was used for the analysis of IR spectra. Samples` IR spectra were recorded on a Bruker FTIR spectrophotometer, which was equipped with OPUS software. FTIR was used to test the samples. Adequate amounts of TPHCl and the TPHCl physical mixture of the formulation were investigated for their interaction studies. The IR spectra of the drug and physical mixture of samples were recorded in the range of 400 to 4000 $cm^{-1}$. The resultant IR spectra are shown in **Figure 2**.

## Results and Discussion

The TPHCl SR tablets were prepared and evaluated. The tablets are preferably used in the treatment of inflammation. The tapentadol sustained-release tablets may reduce the side effects produced by other opioids. At a 25- 150 µg/mL concentration range, the TPHCl analytical estimation method obeyed Beer's law, and it is appropriate for the TPHCl estimation from various solutions of the sample. The correlation coefficient "r" value was found to be 0.9974, which indicates a direct relationship between the concentration of TPHCl and its absorbance.

The prepared TPHCl granules from various batches were subjected to micromeritic studies, such as angle of repose, bulk density, tapped density, and Carr's index, to determine the flow properties of the granules.

The angle of repose of TPHCl was found to be 38.3°. This value indicates that the API has fair or passable flow properties. From

the prepared granule, the values of the angle of repose were found in the range of 21.0 to 32.6°. Only the F3 granules batch showed excellent flow property; F1, F2, and F6 batches showed passable or poor flow properties, and F4 and F5 showed good flow properties. Thus, to improve the flow property of granules, in composition 1.0 to 1.2 % of talc was added.

The tapentadol hydrochloride and all the prepared batches of granules are subjected to bulk density and tapped density. The API shows that the car's index value is 20.11. This value indicated that the API powder had a fair flow property. The Carr's index values of all the prepared batches were shown in the range of 6.41 to 28.70. The Carr's index value of F4 batch granules was excellent, F3 and F5 batch granules are termed as good flow properties, and all the remaining batch granules were shown as fair and passable flow properties. Therefore, it was decided to add 1.0 to 1.2 % of talc in all prepared granule batches to improve the flow property.

The sieve analysis of API powder was used to determine the milling capability of the powder and also the forces present in it. The sieve analysis was performed, and the percentage weight of TPHCl retained in the microns was reported in the range of 75 to 200µ approximately. Thus, the particles in this size range were not able to develop any charge on the power particles, and the available TPHCl consists of a high amount of fine powder particles. In order to decrease the cohesive forces, there is no need to process any milling mechanism to get a fine powder. Hence, the TPHCl is directly used to prepare formulations without milling.

**Table 3. Physico-chemical properties of tablets**

| S/N | Batch | Drug content (%) | Avg. uniformity of weight (mg) | Friability (%) | Hardness (Kg/cm2) |
|---|---|---|---|---|---|
| 1. | F1 | 98±0.1 | 750±2.1 | 0.24 | 7.5±0.3 |
| 2. | F2 | 100±0.3 | 680±1.0 | 0.12 | 5.6±0.1 |
| 3. | F3 | 101±0.5 | 760±1.8 | 0.11 | 6.0±0.8 |
| 4. | F4 | 99.6±0.6 | 650±2.5 | 0.19 | 7.3±0.9 |
| 5. | F5 | 98±0.4 | 630±2.4 | 0.18 | 8.6±0.1 |
| 6. | F6 | 99±0.8 | 710±2.1 | 0.24 | 4.5±0.5 |

Each value represents mean ± s.d. (n=3)

Initially, F1, F2 & F3 were formulated using HPMC-K4M polymer, and later F4, F5, and F6 batches were formulated with Eudragit RL-100 polymer. All the prepared formulations were evaluated using quality control tests, including drug content, average weight uniformity, friability, and hardness. The average uniformity of weight was found in the range of 630±2.4 to 760±1.8mg. These values indicated that more than 5% of the weight variation percentage of tablets as are found in the USP. So, the prepared sustained-release tablets showed very little average weight deviation. The drug content studies were conducted, and the report stated that the drug was uniformly distributed throughout its dosage. The values of drug content were found between 98±0.1 and 101±0.5. The hardness test was conducted for all the prepared tablet batches. The hardness values were found in the range between 4.5±0.5 and 8.6±0.1kg/ $cm^2$. These values indicated that the prepared tablets are neither too hard nor too fragile, and this test was important in the packaging of tablets. Thus, all the batches showed the values within the limits. The friability was studied to indicate the tablet weight loss during packaging and transportation. The calculated friability values of the evaluated tablets were found in the range between 0.11 and 0.24%. These friability values indicated that there is very less loss of tablets weight was observed and this percentage difference is acceptable during packaging and transportation.

**Table 4. Dissolution profiles of all the prepared tablets**

| Time (hrs) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 22±0.8 | 18±0.1 | 20±0.5 | 15±0.1 | 25±0.2 | 16±0.1 |
| 2 | 29±0.5 | 26±0.1 | 31±0.1 | 26±0.4 | 36±0.2 | 29±0.1 |
| 4 | 35±0.1 | 40±0.5 | 48±0.3 | 38±0.7 | 48±1.1 | 38±0.3 |
| 6 | 42±0.3 | 49±1.2 | 64±0.4 | 51±0.5 | 57±0.2 | 58±0.3 |
| 8 | 44±1.2 | 59±1.1 | 81±0.5 | 65±0.1 | 71±1.2 | 69±0.1 |
| 12 | 47±0.1 | 64±0.2 | 89±0.2 | 74±0.1 | 78±0.1 | 75±0.2 |
| 24 | 51±0.4 | 69±0.5 | **96±0.1** | 81±0.2 | 80±0.2 | 78±0.4 |

Each value represents mean ± s.d. (n=3)

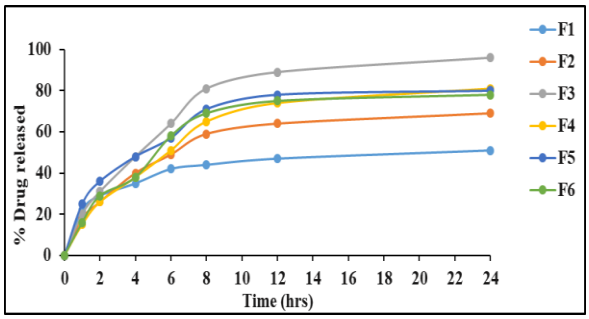


**Figure 1.** Percentage drug release profiles for prepared SR tablets

Dissolution studies of TPHCl sustained-release tablets were conducted using a USP-I dissolution apparatus. A total of six formulations were prepared. For the initial three formulations, a highly water-soluble cellulose derivative (HPMC-K4M) was used as a sustained-release polymer, and for the last three formulations, an insoluble, quaternary ammonium group-containing Eudragit RL-100 polymer was used. From the three HPMC-K4M polymer batches, the F3 formulation showed maximum drug release among other prepared sustained release tablets, which is (96±0.1) within 24 hrs., because of its high solubility and the presence of cellulose derivative, they may form gelation with the aqueous environment (medium used for dissolution). In addition, the drug particles are also suspended in the aqueous medium due to their thickening and suspending actions. This phenomenon was useful to predict the sustained release manner of the dosage form up to a prolonged period of

time (24 hours). Regarding F4, F5 & F6 formulations, the composition was made with Eudragit RL-100 sustained release polymer. The drug release of the tablet was found to be (81±0.2, 80±0.2, and 78±0.4), respectively. As compared with F3, these formulations showed less drug release. Although Eudragit RL-100 exhibits greater permeability and pH-dependent drug release profiles, it shows lower drug release due to its insolubility in aqueous media. The drug release kinetics values for all the prepared tablets are shown in **Table 5**.

**Table 5.** ***In vitro*** **drug release kinetics of TPHCl SR tablets**

| Batch Codes | Zero order (M/s or M/min or M/hr) | | First order ($s^{-1}$ or $min^{-1}$ or $hr^{-1}$) | | Higuchi | Korsmeyer-Peppas | |
|---|---|---|---|---|---|---|---|
| | $K_O$ | R | $K_1$ | r | r | R | N |
| **F1** | 0.8537 | 0.9239 | 0.9801 | 0.9606 | 0.9889 | 0.9891 | 0.364 |
| **F2** | 0.9637 | 0.9288 | 0.9934 | 0.9869 | 0.9935 | 0.9986 | 0.553 |
| **F3** | **0.9796** | **0.9716** | **0.9966** | **0.9933** | **0.9988** | **0.9985** | **0.677** |
| **F4** | 0.9858 | 0.9517 | 0.9926 | 0.9833 | 0.9913 | 0.9985 | 0.648 |
| **F5** | 0.9512 | 0.9047 | 0.9912 | 0.9825 | 0.9972 | 0.9972 | 0.478 |
| **F6** | 0.9683 | 0.9377 | 0.9935 | 0.9870 | 0.9904 | 0.9918 | 0.647 |

Based on the zero and first order 'r' values, all the formulations following first order drug release and 'n' value 0.677 exhibited non-Fickian diffusion of the drug, and the drug release mechanism was explained by the 'r' value of higuchi plot (0.9988).

**Table 6. FTIR of Test Products**

| S/N | Tested products | FT-IR (Wave number and Characteristic Group frequencies) |
|---|---|---|
| **1.** | TPHCl | 3233.34 –OH stretch<br>1451.69 ring C=C stretch<br>1216.66 C-O stretch (Phenolic C-OH)<br>1177.84-N Stretch |
| **2.** | Physical Mixture | 3390.46 OH stretch as in TPHCl<br>1460.50 ring C=C stretch as in TPHCl<br>1249.67 C-O stretch (Phenolic C-OH) as in TPHCl,<br>1099.91 C-N Stretch as in TPHCl |

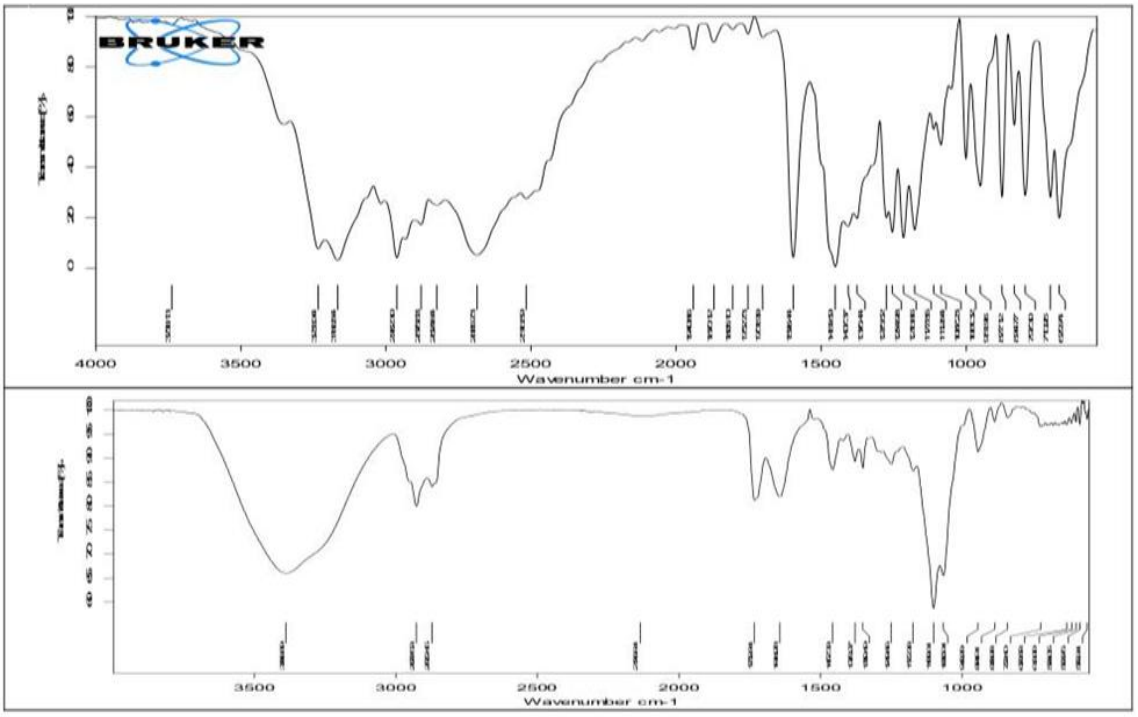


**Figure 2.** FTIR analysis of TPHCl and its physical mixture

The FTIR images of TPHCl and the physical mixture of the drug with excipients show characteristic peaks that are given in **Table 6**. The IR scan shows prominent peaks for the active groups present in TPHCl. These studies suggest that there is no physical interaction between the utilized excipients and the drug.

## Conclusion

TPHCl sustained-release tablets were prepared and evaluated. The optimized sustained-release tablet (F3) dose was within the therapeutic range of TPHCl. The physico-chemical characterizations of the prepared granules were within the limits, and the drug release profile showed that TPHCL formulated with HPMCK4M polymer exhibited sustained release among all the prepared formulations. Thus, sustained-release formulations can efficiently reduce the frequency of dosing.

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