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# DESIGN AND DEVELOPMENT OF DALFAMPRIDINE EXTENDED RELEASE TABLETS BY USING VARIOUS POLYMERS

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**Abstract:**

*Increased complications and costs of marketing of innovative drugs focused greater attention to the development of sustained release (SR) or controlled release (CR) drug delivery systems. Delivery systems extended release or controlled release rate can achieve predictable and reproducible, the extended duration of activity for the short time of life - drugs, reduced toxicity and dose reduction request, the optimized therapy and better patient compliance. It is controlled primarily by the type and the proportion of the polymers used in the preparation. The objective of present work was to develop and evaluated oral extended release tablet of Dalfampridine prepared by the method of direct compression, using Carbapol 934, HPMC K15 and Sodium CMC as matrix formation polymers. The FTIR spectra of the Dalfampridine and other excipients alone and in combination show the compatibility of the drug and excipients. Nine formulations of different polymer percentages were formulated (F1-F9). Pre-compression parameters were evaluated. The influence of matrix forming agents and binary mixtures of them on Dalfampridine release was investigated. The formulated tablets were characterized by thickness and diameter, drug content, hardness, friability, uniformity of weight, and dissolution rate studies. The formulated tablets had acceptable physicochemical characters. The data obtained from the in-vitro dissolution studies of optimized batch F7 were fitted in different models. The optimized formulation F7 showed 98.2% in-vitro drug release. Drug release mechanism was found to be Higuchi release kinetics.*

***Keywords:*** *Dalfampridine, Carbapol 934, HPMC K15, Sodium CMC and Extended release tablets.*

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## INTRODUCTION:

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes. A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimized.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time. The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.

Oral route still remains the most popular for drug administration by virtue of its convenience to the patient. A sizable portion of orally administered dosage forms, so called conventional, are designed to achieve maximal drug bioavailability by maximizing the rate and extent of absorption. While such dosage forms have been useful, frequent daily administration is necessary, particularly when the drug has a short biological half life. This may result in wide fluctuation in peak and trough steady-state drug levels, which is undesirable for drugs with marginal therapeutic indices. Moreover, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Fortunately, these short comings have been circumvented with the introduction of controlled release dosage forms. These dosage forms are capable of controlling the rate of drug delivery, leading to more sustained drug levels and hence therapeutic action.

Hydrophillic matrix systems are among the most commonly used means for oral controlled drug delivery as they can reproduce a desirable drug profile and are cost effective. The primary mechanism of drug release from hydrophilic matrices occurs when the polymer swells on contact with the aqueous medium to form a gel layer on the surface of the system. The drug then releases by dissolution, diffusion and/or erosion.

## TERMINOLOGY:

A list of important terms that describe different modified release dosage forms are defined below.

**Modified release dosage forms (MRDF):** Defined as those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

**Controlled release (CR):** The drug is released at a constant (zero order) rate and the drug concentration obtained after administration is invariant with time.

**Delayed release:** The drug is released at a time other than immediately after administration.

**Extended release (ER):** Slow release of the drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours).

**Prolonged release:** The drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

**Repeat action:** Indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

**Sustained release (SR):** The drug is released slowly at a rate governed by the delivery system.[1]

## ZERO ORDER DELIVERY:

Zero order, or constant rate release of drug is desirable in order to minimize swings in drug concentration in the blood. In conventional dosage forms rapid increase in concentration is followed by a rapid decrease, and little time is spent inside the so-called therapeutic range, which is bounded below by a minimum effective concentration (MEC) and above by a minimum toxic concentration (MTC). Frequent repetitive dosing is required to maintain concentration within these limits, and compliance and control are difficult [2].

Dosage forms that prolong release can maintain drug concentration within the therapeutic range for extended periods and minimize episodes of underexposure or toxicity. A well designed system displays a narrow, predictable residence time distribution in the gastrointestinal (GI) tract, and releases drug by a controlled mechanism. Zero order release leads, in principle, to the best control of plasma concentration. Such control leads to constant drug effect, provided the drug's pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion (ADME), and

its pharmacodynamic properties relating plasma concentration to drug effect, are stationary.

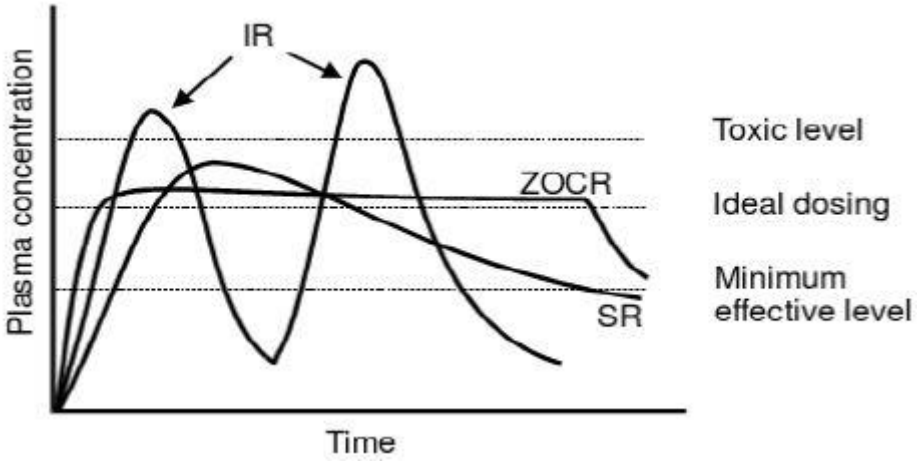


**Fig.1.1 Diagram shows characteristic representation of plasma concentrations of a conventional immediate relese dosage form (IR), a sustained release dosage form (SR) and an idealized zero-order controlled release (ZOCR) dosage form (in combination with a start-up dose).**

Zero order oral drug release can be achieved, in principle, by surrounding a core tablet with a membrane that is permeable to both drug and water, as illustrated in. After swallowing, the core becomes hydrated, and drug dissolves until it reaches its saturation concentration or solubility. The core serves as a saturated reservoir of drug. Drug release proceeds by partitioning from the reservoir into the membrane, followed by diffusion across the membrane into the gastrointestinal fluid. So long as saturation is maintained in the core, there will be a stationary concentration gradient across the membrane, and release will proceed at constant rate. Eventually, the dissolved drug's concentration in the core falls below saturation, reducing the concentration gradient and hence the release rate, which decays to zero. If the membrane consists of a water-soluble polymer of high molecular weight, then it will initially swell into a gel, through which drug diffuses. The thickness of the gel layer initially increases with time due to swelling, but ultimately it decreases due to disentanglement and dissolution of polymer chains. At intermediate times, the gel layer may be of approximately constant thickness, and release occurs at a relatively constant rate [2].

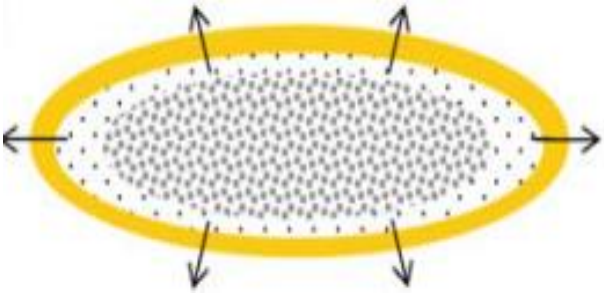

**Fig.1.2 Membrane diffusion controlled release. Drug in core (granulated pattern) dissolves to form saturated solution (dilute dots). Drug then diffuses across membrane (thin tipped arrows). Zero order release persists as long as there is sufficient drug in core to form saturated solution.[2]**

**Drawbacks of Conventional Dosage Forms [3,4]**

- Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

**Advantages of Extended Release Delivery System** [5,6]

- Extended release products have many advantages.
- The extended release formulations reduce dosing frequency of drugs.
- The extended release formulations may maintain therapeutic concentrations.
- Reduce the toxicity by slowing drug absorption.
- The use of these formulations avoids the high blood concentration.
- Extended release formulations have the potential to improve the patient compliance and convenience.
- Minimize the local and systemic side effects.
- Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improve the bioavailability of some drugs.
- Usage of less total drug.
- Improve the ability to provide special effects. For example, Morning relief of arthritis through bed time dosing.

**Disadvantages of Extended Release Delivery System** [5,6]

- Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
- The larger size of extended release products may cause difficulties in ingestion or transit through gut.
- The release rates are affected by various factors such as food and the rate of transit through the gut.
- Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
- High cost of preparation.
- Sometimes the target tissue will be exposed to constant amount of drug over

**Factors Affecting Extended Release Formulation** [7-8]

**I. Physicochemical Properties of Drug**

**a) Aqueous Solubility**

Generally drugs are weak acids or weak bases, since the unchanged form of a drug preferentially permeates across lipid membranes, drugs aqueous solubility will be decreased by conversion to an unchanged form. Drugs with low water solubility will be difficult to incorporate into extended release mechanism. The lower limit on solubility for such product has been reported 0.1 gm/ml. Drugs with extreme water solubility are equally difficult to incorporate in extended release system because it is difficult to control release of drug from dosage form. pH dependent solubility, particularly in the physiological pH range, would be another problem because of the varied pH of gastro intestinal tract, which ultimately gives variation in dissolution profile. e.g.: Aspirin, which is less soluble in stomach, but more soluble in intestine.

## METHODOLOGY:

**Characterization of Dalfampridine**

**Organoleptic properties:**

Take a small quantity of sample and spread it on the white paper and examine it visually for color, odour and texture.

**Determination of Dalfampridine Melting point**

The melting point of Dalfampridine was determined by capillary tube method according to the USP. A sufficient quantity of Dalfampridine powder was introduced into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Dalfampridine in the tube passed into liquid phase**.**

**Determination of Dalfampridine Solubility**

Determination of solubility of drug by visual observation. An excess quantity of Dalfampridine was taken separately and adds in 10 ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed and observations are shown in the Table.

**9.2. Analytical method development:**

**9.2.1 Determination of Wavelength:**

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

**9.2.2 Determination of Calibration Curve:**

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 10.1 and 10.2) and those concentrations absorbance were found out at required wavelength.

**9.3. Preformulation parameters**

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

**9.4. Formulation development of Tablets:**

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 9.3. The tablets were prepared as per the procedure given below and aim is to prolong the release of Dalfampridine. Total weight of the tablet was considered as 120mg.

**Procedure:**

1) Dalfampridine and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

**Table 9.3: Formulation composition for tablets**

| INGREDIENTS | FORMULATION CHART | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Dalfampridine | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Carbapol 934 | 10 | 20 | 30 | - | - | - | - | - | - |
| HPMC K15 | - | - | - | 10 | 20 | 30 | - | - | - |
| Sodium CMC | - | - | - | - | - | - | 10 | 20 | 30 |
| MCC | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| Magnesium stearate | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Aerosil | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Total Weight | 120 | 120 | 120 | 120 | 120 | 120 | 120 | 120 | 120 |

All the quantities were in mg

## RESULTS AND DISCUSSION:

**Organoleptic properties**

**Table 10.1: Organoleptic properties**

| S NO. | Properties | Results |
|---|---|---|
| 1 | State | Solid |
| 2 | Colour | White |
| 3 | Odour | Odourless |
| 4 | Melting point | 160 °C |

**Solubility studies**

**Table 10.2: Solubility studies of drug in different solvents**

| S NO. | Solvents | Solubility of Dalfampridine |
|---|---|---|
| 1 | Methanol | Soluble |
| 2 | Acetonitrile | Sparingly soluble |
| 3 | Water | Soluble |
| 4 | Dimethylsulfoxide | Soluble |

The present study was aimed to develop Extended release tablets of Dalfampridine using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

**10.1. Analytical Method**

Graphs of Dalfampridine were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 263 nm and 265 nm respectively.

**Table 10.3: Observations for graph of Dalfampridine in 0.1N HCl (263 nm)**

| Conc. [µg/ml] | Absorbance |
|---|---|
| 0 | 0 |
| 5 | 0.114 |
| 10 | 0.234 |
| 15 | 0.354 |
| 20 | 0.471 |
| 25 | 0.587 |

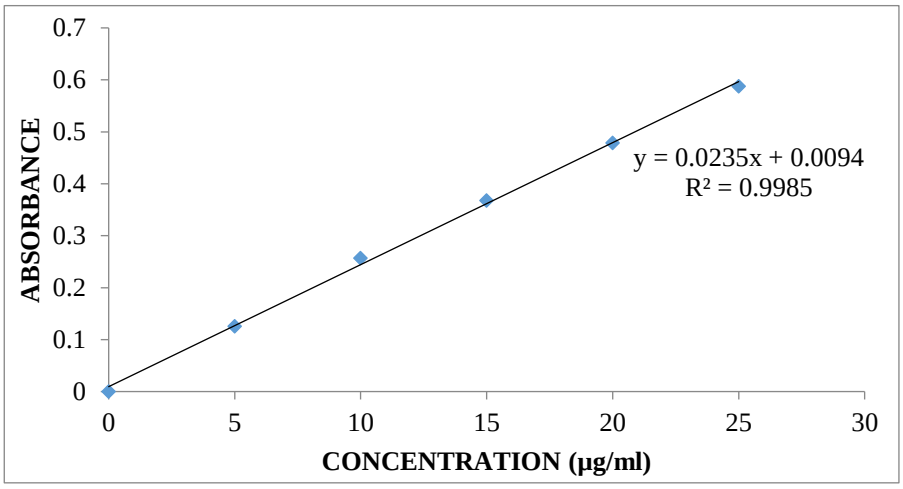


**Figure 10.1: Standard graph of Dalfampridine in 0.1N HCl**

**Table 10.4: Observations for graph of Dalfampridine in pH 6.8 phosphate buffer (265nm)**

| Concentration [µg/ml] | Absorbance |
|---|---|
| 0 | 0 |
| 5 | 0.126 |
| 10 | 0.257 |
| 15 | 0.368 |
| 20 | 0.479 |
| 25 | 0.588 |

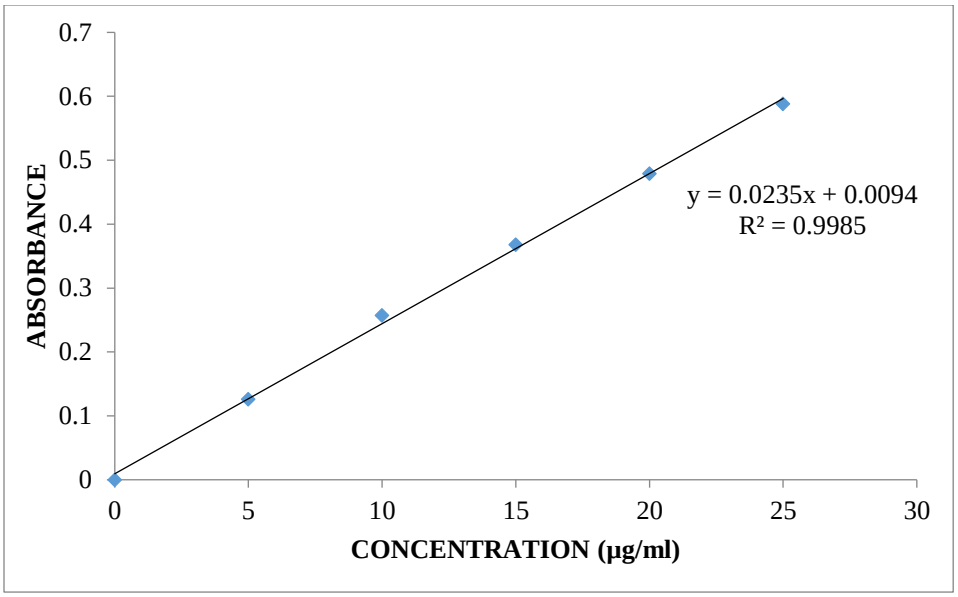


**Figure 10.2: Standard graph of Dalfampridine pH 6.8 phosphate buffer (265 nm)**

**10.3. Preformulation parameters of powder blend**

**Table 10.5: Pre-formulation parameters of Core blend**

| Formulation Code | Angle of Repose | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index (%) | Hausner's Ratio |
|---|---|---|---|---|---|
| F1 | 27.22±1.31 | 0.410±0.069 | 0.496±0.020 | 17.33±0.320 | 1.20±0.013 |
| F1 | 28.35±1.64 | 0.382±0.032 | 0.462±0.015 | 17.31±0.208 | 1.20±0.015 |
| F3 | 28.23±1.6 | 0.405±0.05 | 0.470±0.032 | 13.82±0.198 | 1.16±0.016 |
| F4 | 29°76′±0.02 | 0.536±0.05 | 0.593±0.03 | 15.96±0.01 | 1.18±0.02 |
| F5 | 26°49′±0.01 | 0.492±0.06 | 0.542±0.04 | 9.22±0.06 | 1.1±0.02 |
| F6 | 28°63′±0.02 | 0.521±0.03 | 0.596±0.02 | 12.5±0.03 | 1.14±0.03 |
| F7 | 27°09′±0.03 | 0.528±0.02 | 0.586±0.06 | 9.89±0.04 | 1.1±0.02 |
| F8 | 27°01′±0.02 | 0.498±0.03 | 0.549±0.02 | 9.22±0.02 | 1.1±0.06 |
| F9 | 26°14′±0.03 | 0.477±0.04 | 0.542±0.02 | 11.99±0.01 | 1.13±0.02 |

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.382±0.032 to 0.536±0.05 (gm/cm3) showing that the powder has

good flow properties. The tapped density of all the formulations was found to be in the range of 0.462±0.015 to 0.596±0.02 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 17 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.20 indicating the powder has good flow properties.

**10.4. Quality Control Parameters For tablets:**
Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

**10.6. *In vitro* quality control parameters for tablets**

| Formulation codes | Weight variation (mg) | Hardness (kg/cm$^2$) | Friability (%loss) | Thickness (mm) | Drug content (%) |
|---|---|---|---|---|---|
| I1 | 120.25 | 4.9 | 0.56 | 3.14 | 98.34 |
| I2 | 117.52 | 4.4 | 0.43 | 3.69 | 99.60 |
| I3 | 119.10 | 4.6 | 0.31 | 3.41 | 97.82 |
| I4 | 120.01 | 4.0 | 0.50 | 3.97 | 99.24 |
| I5 | 117.96 | 4.7 | 0.41 | 3.52 | 96.12 |
| I6 | 118.58 | 5.1 | 0.35 | 3.47 | 99.05 |
| I7 | 119.72 | 4.8 | 0.43 | 3.66 | 98.76 |
| I8 | 119.18 | 4.3 | 0.34 | 3.87 | 97.64 |
| I9 | 118.34 | 5.0 | 0.30 | 3.21 | 99.31 |

**Weight variation test:**
Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 10.4. The average weight of the tablet is approximately in range of 117.52 to 120.25 mg, so the permissible limit is ±7.5% (>120 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

**Hardness test:**
Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 10.4. The results showed that the hardness of the tablets is in range of 4.0 to 5.1 kg/cm$^2$, which was within IP limits.

**Thickness:**
Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-10.4. The result showed that thickness of the tablet is raging from 3.14 to 3.97 mm.

**Friability:**
Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 10.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

**Drug content:**
Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 96.12 - 99.60 %.
All the parameters such as Weight Variation, Friability, Hardness, Thickness and Drug Content were found to be within limits.

***10.5. In Vitro* Drug Release Studies**

**Table 10.7: Dissolution Data of Dalfampridine Tablets**

| Time (HRS) | % of Drug release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | 11.4 | 8.1 | 6.9 | 7.2 | 10.4 | 14.3 | 20.1 | 18.8 | 16.9 |
| 1 | 18.8 | 15.6 | 13.0 | 12.9 | 14.9 | 18.9 | 24.3 | 22.1 | 20.4 |
| 2 | 25.4 | 20.7 | 18.6 | 17.3 | 20.1 | 26.4 | 29.7 | 27.2 | 23.8 |
| 3 | 36.1 | 31.2 | 22.4 | 24.3 | 29.6 | 34.2 | 40.5 | 32.8 | 30.7 |
| 4 | 41.5 | 39.9 | 25.8 | 30.1 | 33.5 | 40.9 | 48.9 | 42.7 | 38.1 |
| 5 | 50.2 | 46.6 | 30.5 | 38.6 | 40.8 | 47.1 | 55.8 | 45.6 | 41.5 |
| 6 | 59.9 | 52.1 | 35.8 | 44.8 | 49.1 | 55.7 | 63.9 | 57.1 | 55.2 |
| 7 | 66.7 | 56.3 | 38.4 | 49.4 | 60.8 | 63.8 | 70.8 | 61.0 | 58.7 |
| 8 | 73.2 | 61.8 | 44.3 | 53.2 | 68.9 | 70.3 | 79.4 | 72.8 | 62.1 |
| 9 | 79.9 | 67.9 | 50.1 | 57.4 | 74.3 | 78.9 | 82.1 | 77.3 | 73.5 |
| 10 | 87.2 | 74.2 | 53.5 | 61.5 | 77.6 | 83.4 | 90.5 | 85.9 | 80.4 |
| 11 | 92.4 | 79.6 | 68.2 | 68.1 | 81.0 | 89.1 | 93.2 | 88.3 | 83.2 |
| 12 | 97.5 | 86.7 | 78.1 | 72.4 | 89.8 | 94.7 | 98.2 | 91.5 | 87.0 |

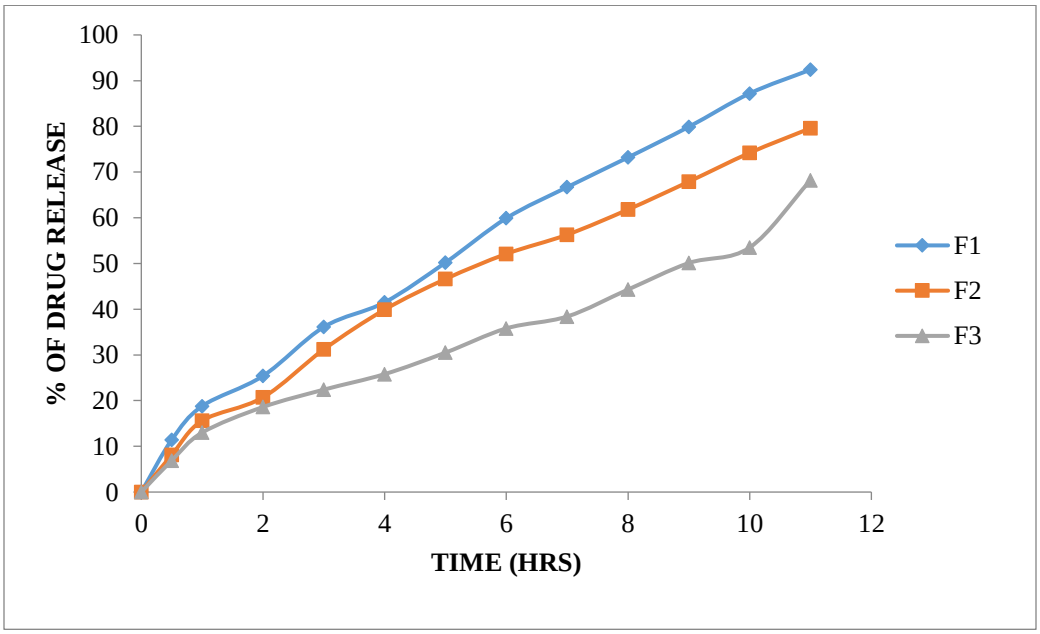


**Fig 10.3: Dissolution profile of Dalfampridine (F1, F2, F3 formulations)**

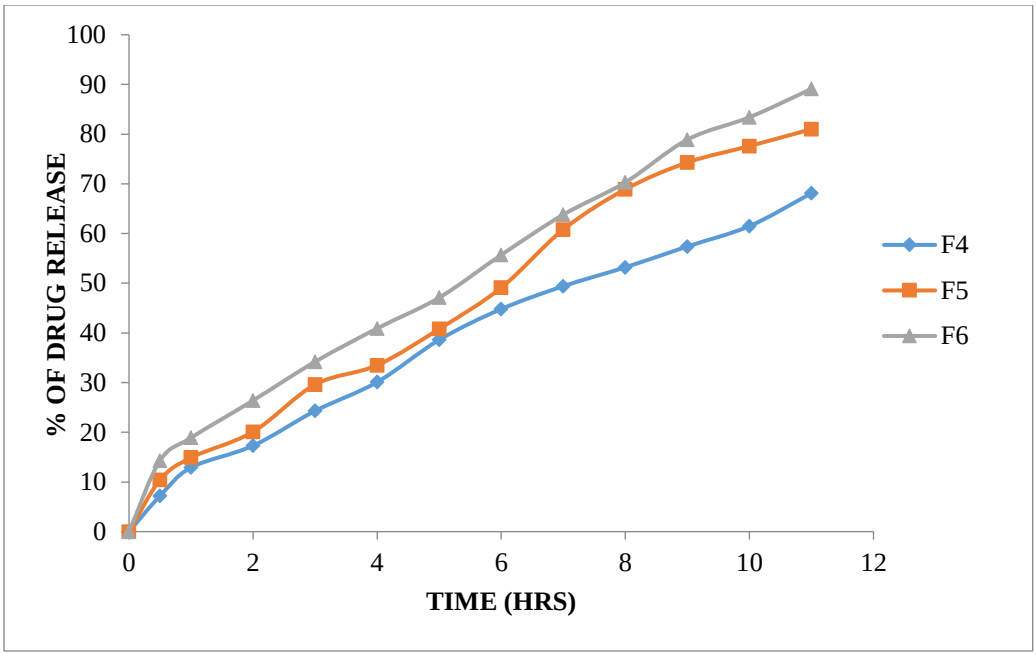


**Fig 10.4: Dissolution profile of Dalfampridine (F4, F5, F6 formulations)**

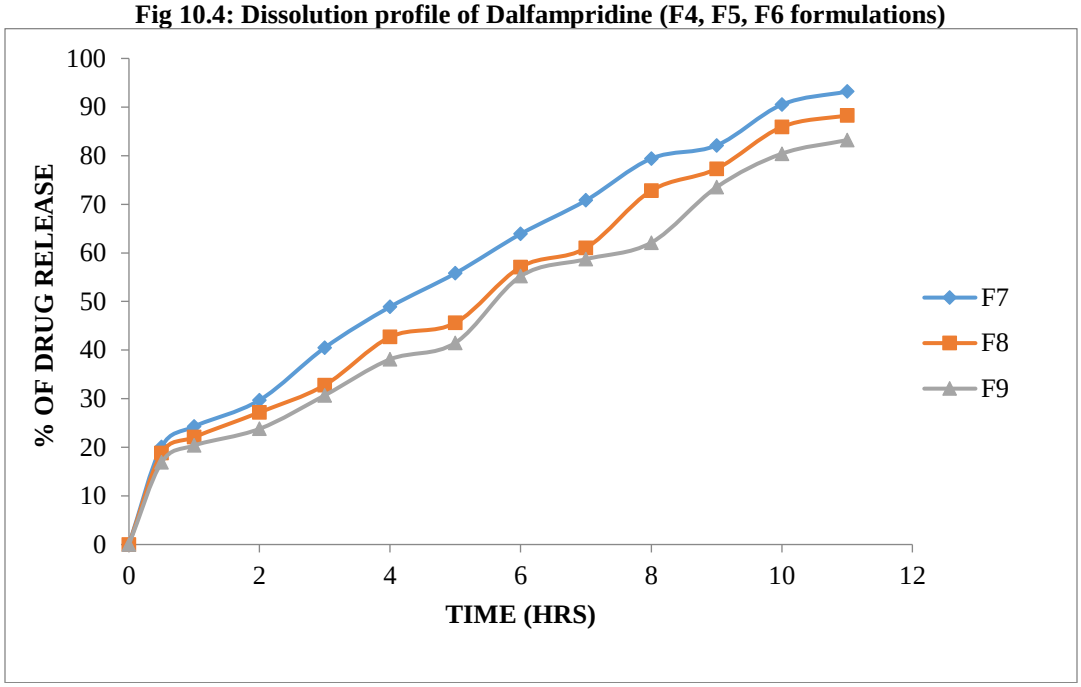


**Fig 10.5: Dissolution profile of Dalfampridine (F7, F8, F9 formulations)**

From the dissolution data it was evident that the formulations prepared with Carbapol 934 as polymer were retard the drug release up to desired time period i.e., 12 hours.

Formulations prepared with HPMC K15 retarded the drug release in the concentration of 30 mg (F6 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.7 % in 12 hours with good drug release.

The Formulation Containing Sodium CMC in 10 mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.2 %.

From the above results it was evident that the formulation F7 is best formulation with desired drug release pattern extended up to 12 hours.

**Application of Release Rate Kinetics to Dissolution Data:**

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

**Table 10.8: Release kinetics data for optimised formulation**

| CUMULATIVE (%) RELEASE Q | TIME ( T ) | ROOT (T) | LOG( %) RELEASE | LOG ( T ) | LOG (%) REMAIN | RELEASE RATE (CUMULATIVE % RELEASE / t) | 1/CUM% RELEASE | PEPPAS log Q/100 | % Drug Remaining | Q01/3 | Qt1/3 | Q01/3-Qt1/3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | | | 2.000 | | | | 100 | 4.642 | 4.642 | 0.000 |
| 20.1 | 0.5 | 0.707 | 1.303 | -0.301 | 1.903 | 40.200 | 0.0498 | -0.697 | 79.9 | 4.642 | 4.307 | 0.335 |
| 24.3 | 1 | 1.000 | 1.386 | 0.000 | 1.879 | 24.300 | 0.0412 | -0.614 | 75.7 | 4.642 | 4.230 | 0.411 |
| 29.7 | 2 | 1.414 | 1.473 | 0.301 | 1.847 | 14.850 | 0.0337 | -0.527 | 70.3 | 4.642 | 4.127 | 0.514 |
| 40.5 | 3 | 1.732 | 1.607 | 0.477 | 1.775 | 13.500 | 0.0247 | -0.393 | 59.5 | 4.642 | 3.904 | 0.738 |
| 48.9 | 4 | 2.000 | 1.689 | 0.602 | 1.708 | 12.225 | 0.0204 | -0.311 | 51.1 | 4.642 | 3.711 | 0.931 |
| 55.8 | 5 | 2.236 | 1.747 | 0.699 | 1.645 | 11.160 | 0.0179 | -0.253 | 44.2 | 4.642 | 3.536 | 1.106 |
| 63.9 | 6 | 2.449 | 1.806 | 0.778 | 1.558 | 10.650 | 0.0156 | -0.194 | 36.1 | 4.642 | 3.305 | 1.337 |
| 70.8 | 7 | 2.646 | 1.850 | 0.845 | 1.465 | 10.114 | 0.0141 | -0.150 | 29.2 | 4.642 | 3.079 | 1.562 |
| 79.4 | 8 | 2.828 | 1.900 | 0.903 | 1.314 | 9.925 | 0.0126 | -0.100 | 20.6 | 4.642 | 2.741 | 1.900 |
| 82.1 | 9 | 3.000 | 1.914 | 0.954 | 1.253 | 9.122 | 0.0122 | -0.086 | 17.9 | 4.642 | 2.616 | 2.026 |
| 90.5 | 10 | 3.162 | 1.957 | 1.000 | 0.978 | 9.050 | 0.0110 | -0.043 | 9.5 | 4.642 | 2.118 | 2.524 |
| 93.2 | 11 | 3.317 | 1.969 | 1.041 | 0.833 | 8.473 | 0.0107 | -0.031 | 6.8 | 4.642 | 1.895 | 2.747 |
| 98.2 | 12 | 3.464 | 1.992 | 1.079 | 0.255 | 8.183 | 0.0102 | -0.008 | 1.8 | 4.642 | 1.216 | 3.425 |

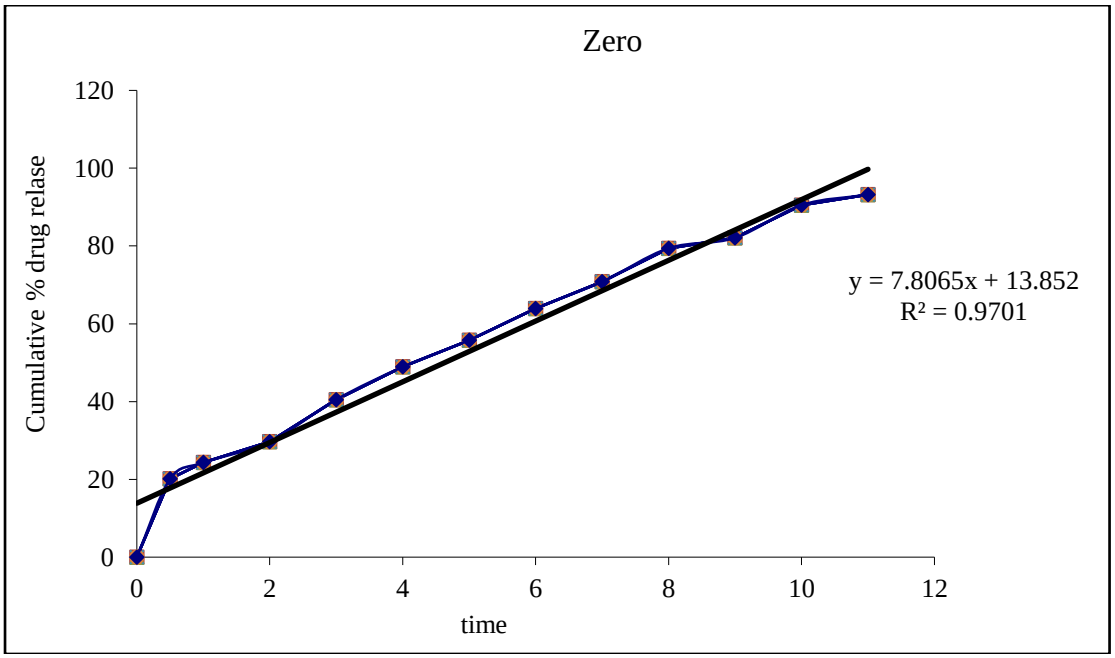


**Fig 10.6 : Zero order release kinetics graph**

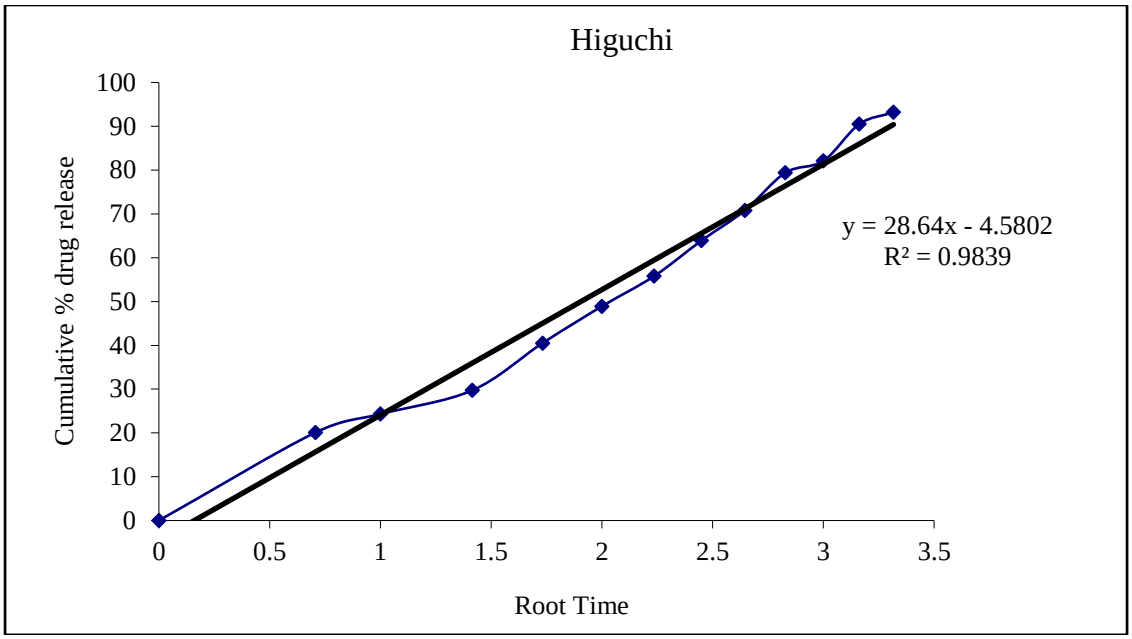


**Fig 10.7 : Higuchi release kinetics graph**

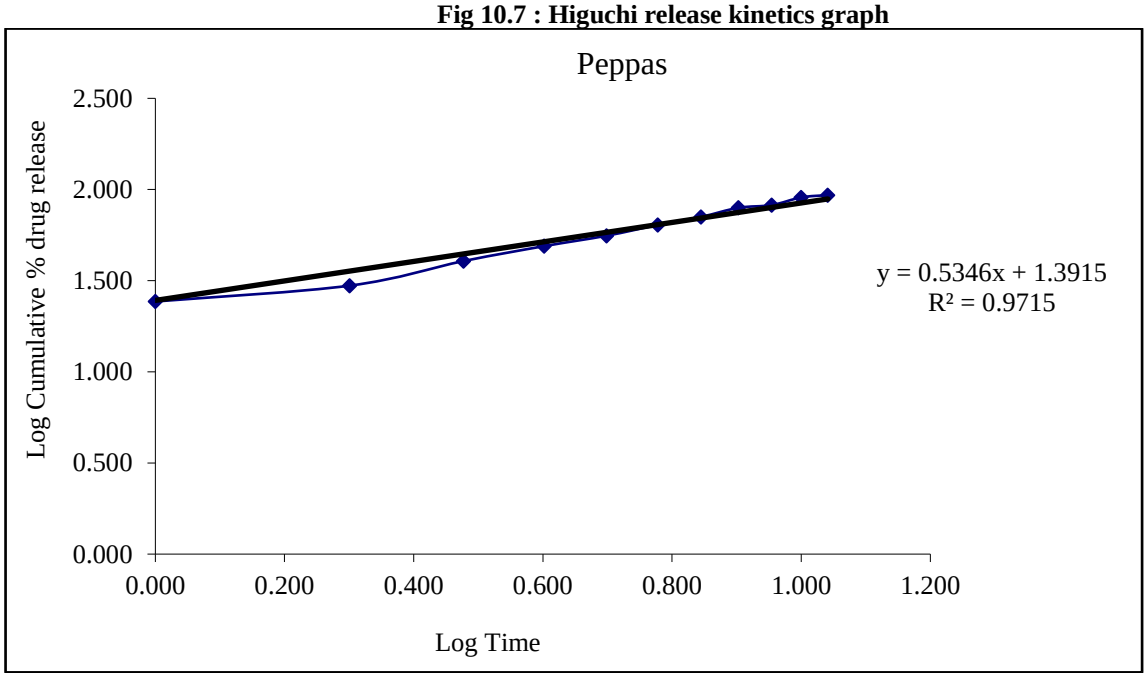


**Fig 10.8: Kars mayer peppas graph**

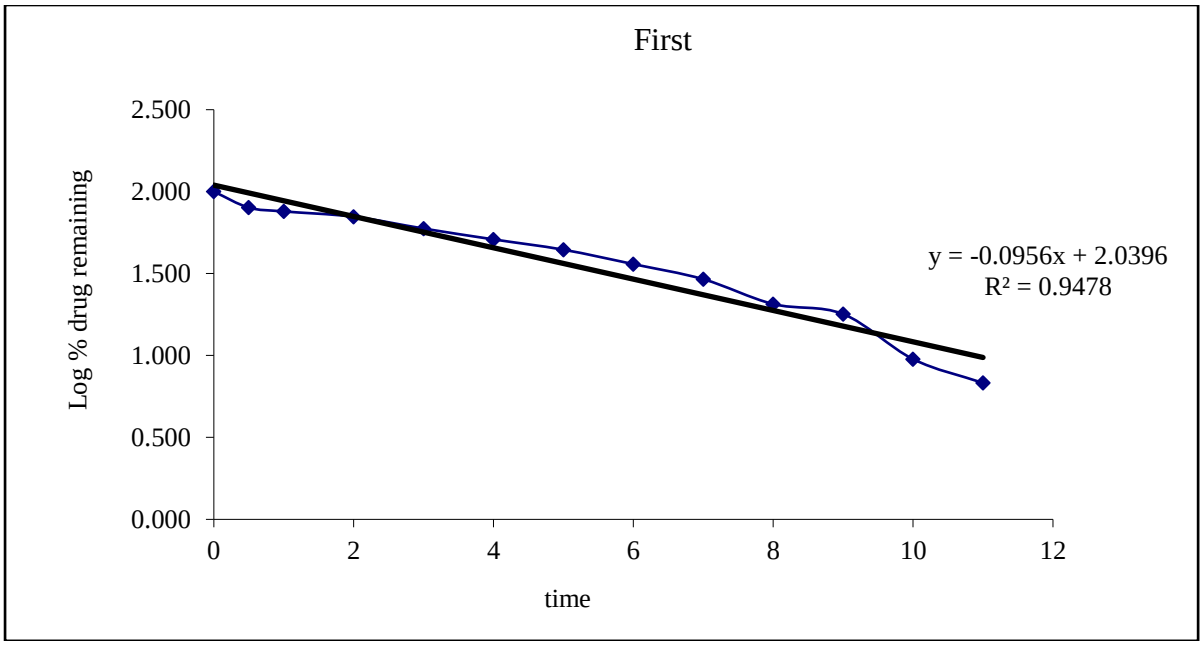


**Fig 10.9: First order release kinetics graph**

From the above graphs it was evident that the formulation F7 was followed Higuchi release kinetics.

**Table 10.9: kinetics Correlation coefficient values**

| Release Kinetics | Correlation coefficient values |
|---|---|
| Zero order release kinetics | $R^2 = 0.970$ |
| Higuchi release kinetics | $R^2 = 0.983$ |
| Peppas release kinetics | $R^2 = 0.971$ |
| First order release kinetics | $R^2 = 0.947$ |

**10.2. Drug – Excipient compatibility studies**

**Fourier Transform-Infrared Spectroscopy:**

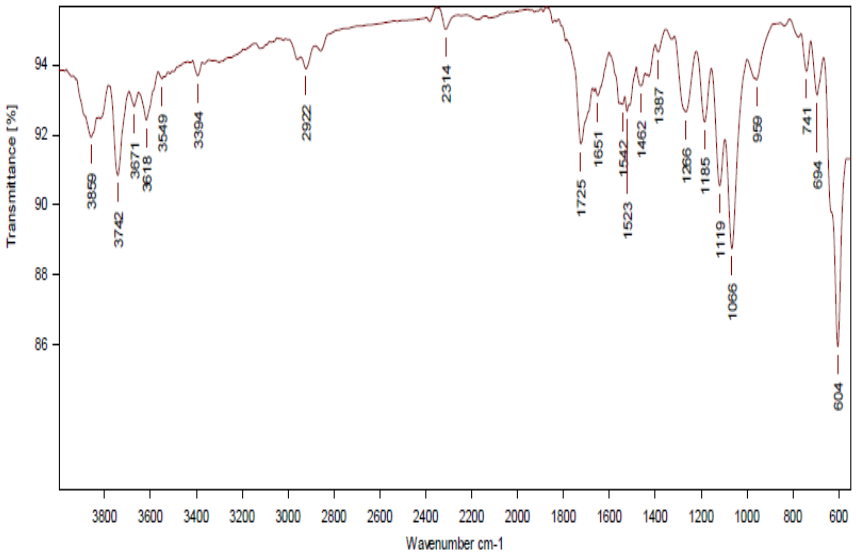


**Figure 10.10: FT-TR Spectrum of Dalfampridine pure drug**

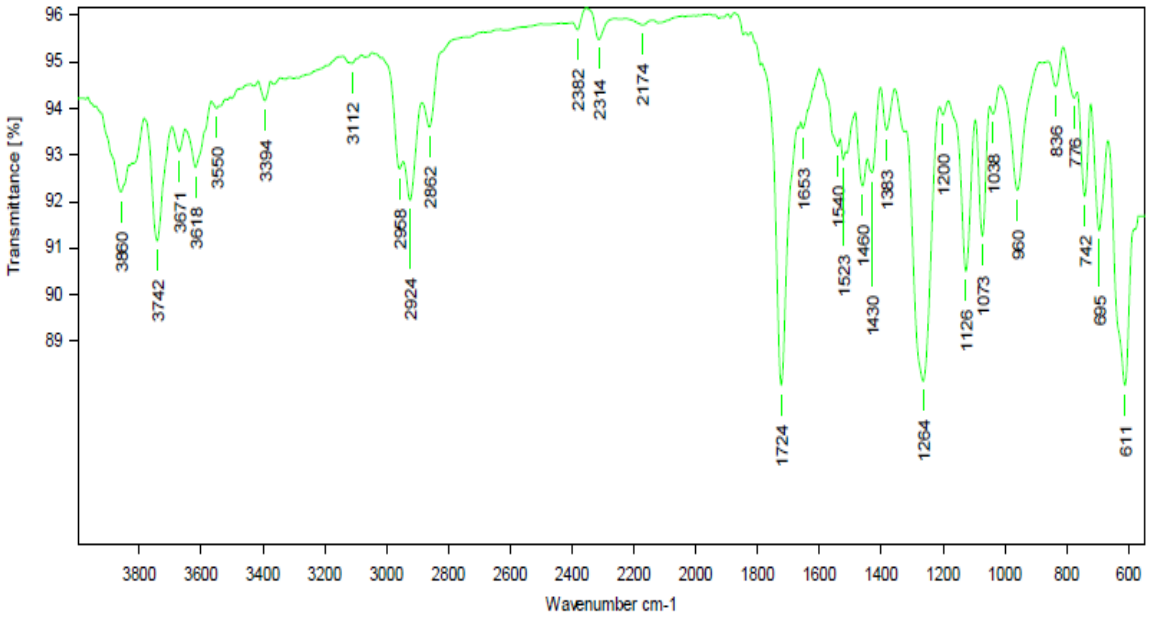


**Figure 10.11: FT-IR Spectrum of Optimised Formulation**

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Dalfampridine and excipients used in the preparation of different Dalfampridine extended release tablets formulations. Therefore the drug and excipients are compatible to form stable.

Formulations under study The FTIR spectra of extended release tablets and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

## CONCLUSION:

The present research work was successful in improving the efficacy of Dalfampridine oral therapy as the drug release was extended for 12 hours thus reducing dosing frequency thereby improving patient compliance.

The extended release matrix tablets of Dalfampridine were prepared by direct compression method. FTIR spectra indicated the absence of probable chemical interaction between the drug and polymers.

Dalfampridine tablets were formulated with Carbapol 934, HPMC K15 and Sodium CMC.

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose, bulk density, tapped density, compressibility index and hausner ratio powder has good flow properties.

Post compression studies like Weight variation, Hardness, thickness, friability, drug content was determined within IP limits.

Among 9 formulations, F7 is optimized based on the cumulative % drug release is 98.2 in 12 hrs. The *in vitro* drug release data was plotted for various kinetic models. The $R^2$ value for optimized formulation F7 for first order was found to be 0.983. It is evident from the results that a matrix tablet of Dalfampridine is a better system sustained release dosage regimen. Furthermore the *in-vivo* and pharmacokinetic study have to carry out.

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