



CODEN [USA]: IAJ PBB

ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

Available online at: <http://www.iajps.com>

Research Article

**ANALYZING DALFAMPRIDINE'S POTENTIAL FOR
PROLONGED RELEASE AS A MATRIX TABLET USING
VARIOUS GRADES OF HPMC AND EUDRAGIT****M Ameer Khan¹, Niranjan Panda^{1*}, Sameera Fatima², Ayesha Farhath Fathima³**
^{1, 2, 3}PG Department of Pharmaceutics, Anwarul Uloom College of Pharmacy, Hyderabad**Abstract:**

Present studies aimed to formulate a once-daily sustained-release matrix tablet of Dalfampridine to reduce the frequency of administration and improve patient compliance. Multiple sclerosis patients who have trouble walking can benefit from dalfampridine. Dalfampridine is taken orally twice daily in doses of 10 mg, with a plasma half-life of 5.2 to 6.5 hours. A once-daily sustained-release version of dalfampridine is preferred to lessen administration frequency and boost patient compliance. BCS Class I chemical with high solubility, high permeability, and pH-independent solubility. Using hydrophilic synthetic polymers like hydroxyl propyl methyl cellulose (HPMC K4M & HPMC K15M) and hydrophobic synthetic polymers like Eudragit RSPO and RLPO, the current work sought to evaluate and improve sustained released Dalfampridine matrix tablets. To improve the release rate for a once-daily drug, a matrix tablet containing dalfampridine was created using the wet granulation process at various ratios of HPMC and Eudragit. Utilizing a USP type-II paddle type eight station dissolving device, an in vitro release investigation was carried out. To confirm the drug's compatibility with polymers, FTIR and DSC studies were conducted. Different pre- and post-compression characterizations of the tablet were conducted, and the results complied with pharmacopeia requirements. Accelerated stability experiments were done to confirm the stability of the dosage formulations.

Key Words: Sustained release tablet, Dalfampridine, Matrix tablets, HPMC, Eudragit.**Corresponding author:**

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Please cite this article in press Niranjan Panda et al **Analyzing Dalfampridine's Potential For Prolonged Release As A Matrix Tablet Using Various Grades Of HPMC And Eudragit**, Indo Am. J. P. Sci, 2024; 11 (01).

1. INTRODUCTION

Among all drug delivery methods, oral drug administration is the most preferred and beneficial choice since it increases the medication's residence time for absorption by providing the largest dynamic surface area. Conventional dose forms typically result in broad variations in the drug's concentration in the tissues and circulation, which causes unfavorable, toxicity and ineffectiveness [1]. The notion of regulated drug delivery systems was inspired by these circumstances, which included uncertain absorption and recurrent dosage. By localizing the medicine at the site of action, lowering the dosage needed, or ensuring consistent drug administration, sustained or controlled delivery systems aim to either decrease the frequency of dosing or boost the drug's efficacy [2]. Better pharmacological effects and longer therapeutic action are displayed by these dose formulations. Because they release the medication in a regulated way, matrix tablets are among the most widely utilized controlled-release dosage forms [3, 4]. Chronic conditions including asthma, migraines, diabetes, hypertension, and inflammation that need constant plasma levels for maintenance therapy can benefit from such a wide range of medications [5].

A potassium channel blocker called Dalfampridine is used to help multiple sclerosis patients walk more easily. Dalfampridine is expressed chemically as 4-aminopyridine. A illness called multiple sclerosis causes malfunctioning nerves, which can lead to weakness, numbness, loss of muscular coordination, and issues with speech, vision, and bladder control. Dalfampridine is an oral drug that the gastrointestinal (GI) system absorbs fully and swiftly. It takes three to four hours after injection to reach its maximal concentration (C_{max}), and its relative bioavailability is 96%. 2.6 L/kg is the apparent volume of distribution. Most of the time (97–99%), Dalfampridine is not attached to plasma proteins. A dosage of dalfampridine is excreted in the urine in around 95.9% of cases, and the feces in 0.5% of cases. Dalfampridine has a plasma half-life of 5.2 to 6.5 hours. Dalfampridine is prescribed at a dose of one 10 mg tablet twice a day.[6]

The goal of this study was to create sustained-release Dalfampridine tablets by employing polymeric retardant materials such as Eudragit (Eudragit RSPO and RLPO) and hydroxyl propyl methylcellulose (HPMC K4M & K15M) to decrease the frequency of dose and increase therapeutic effectiveness. Different formulations of sustained release tablets were created by combining various amounts of HPMC and Eudragit to enhance the drug release profile of the medicine under research. Because the current

formulation lowers dosage frequency and helps with improved treatment of chronic migraine, it is anticipated to increase patient compliance.[7]

2. MATERIALS AND METHODS:

Materials

Dalfampridine was obtained from Sunshine Laboratories in Mumbai, India, as a gift sample. Gift samples of HPMC K4M and HPMC K15M polymers were obtained from Glenmark Pharma, located in Nasik, India. Dr. Reddy's Laboratories in Hyderabad, India provided gift samples of the Eudragit RSPO and RLPO. We bought lactose monohydrate, magnesium stearate, talc, and insoluble starch from S.D. Fine Chemicals Pvt. Ltd. in Mumbai, India. Every component was of laboratory quality. In the laboratory, a double distillation procedure was performed to prepare the distilled water used in the study process.

Methods

Formulation of sustained-release matrix tablets of Dalfampridine

Wet granulation techniques were employed to manufacture Dalfampridine sustained release matrix tablets, and twelve alternative formulations were chosen based on the various polymer concentrations. Before being used in formulations, precise amounts of each constituent were weighed and run through sieve number 80. Precise amounts of powder such as lactose monohydrate, HPMC, Dalfampridine, Eudragit RSPO, and RLPO, and insoluble starch were mixed and filtered through #20 for every formulation. While starch (insoluble) was utilized as a binder, lactose monohydrate was employed as a diluent. By adding the necessary amount of distilled water as a granulating agent, a wet lump mass was created. To lower the moisture content and avoid the aggregates adhering to the sieve while being sieved, they were first dried for ten minutes. To get granules, the aggregates were run through filter #20. To decrease the moisture content to 3–5%, the granules are dried in a hot air oven set at 40°C for about 20 minutes. The formulations were assessed for angle of repose, bulk density, and compressibility before compression after being lubricated with talc and magnesium stearate. The assessed granules were crushed using 8 mm concave punches on a 10-station rotary tablet punching machine to create sustained-release matrix tablets. Dalfampridine comes in a sustained-release matrix format with 20 milligrams each tablet. The same procedure was used for each formulation, and the compositions for the various formulations are listed in Tables 1 & 2. Next, several post-

compression characteristics, including average thickness, weight variation, hardness, friability, swelling tests, drug content, and in vitro dissolution

experiments, were evaluated for the generated tablet formulations.[9]

Table 1: Various excipients used in formulations and their compositions (DF₁ to DF₆)

Ingredients (mg)	DF ₁	DF ₂	DF ₃	DF ₄	DF ₅	DF ₆
Dalfampridine	20	20	20	20	20	20
HPMC K4M	20	30	40	-	-	-
HPMC K15M	-	-	-	20	30	40
Eudragit RSPO	30	20	10	-	-	-
Eudragit RLPO	-	-	-	30	20	10
Lactose monohydrate	135	135	135	135	135	135
Starch (Insoluble)	20	20	20	20	20	20
Mg. stearate	3	3	3	3	3	3
Talc	2	2	2	2	2	2
Total weight	200	200	200	200	200	200

Table 2: Various excipients used in formulations and their compositions (DF₇ to DF₁₂)

Ingredients (mg)	DF ₇	DF ₈	DF ₉	DF ₁₀	DF ₁₁	DF ₁₂
Dalfampridine	20	20	20	20	20	20
HPMC K4M	20	30	40	-	-	-
HPMC K15M	-	-	-	20	30	40
Eudragit RSPO	-	-	-	30	20	10
Eudragit RLPO	30	20	10	-	-	-
Lactose monohydrate	135	135	135	135	135	135
Starch (Insoluble)	20	20	20	20	20	20
Mg. stearate	3	3	3	3	3	3
Talc	2	2	2	2	2	2
Total weight	200	200	200	200	200	200

3. EVALUATION

Drug excipients compatibility studies

Drug excipients compatibility studies were done by Fourier Transform Infrared (FTIR) and Differential Scanning Calorimetric (DSC) analysis.

Fourier Transform Infrared (FTIR) spectroscopy:

A Fourier transform infrared (FTIR) study was carried out to verify any physical or chemical interaction between the drug and the excipients used in the formulation. It was performed by the potassium bromide (KBr) pellet method. The samples were

trituated with KBr and the pellet was prepared by setting the pressure to 100 kg/cm² for 2 min. The obtained pellet was analyzed in FTIR 8400S, Shimadzu, Japan. KBr background was obtained initially before the analysis of test samples. The same procedures were repeated for the analysis of drug and excipients.[10] The FTIR studies of pure drug Dalfampridine, HPMC, Eudragit, and optimized formulation (DF₁₁) were carried out and the presence of functional groups was compared through obtained spectra.

Differential Scanning Calorimetric (DSC) analysis:

Differential scanning calorimetry, or DSC, is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Exactly weighed 5 to 6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10 °C/min over a temperature range of 40 to 300 °C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.[11] The DSC analysis of Dalfampridine, HPMC, Eudragit, and a physical mixture of drugs with excipients used for formulations was carried out using a Shimadzu DSC 60, Japan; to evaluate any possible polymer-drug thermal interaction.

Evaluation of precompression parameters Angle of Repose (θ)

The angle of repose is a method used to determine the flow properties of powder and granules from the hopper to the die cavity during the tablet compression process. The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules. Funnel used was a stainless-steel funnel and the size of the orifice was 10 mm and the height from the beginning of the funnel to end of the orifice was 111 mm. The funnel was fixed in place, 4 cm above the bench surface. After the cone from 5 g of sample was built, the height of the granules forming the cone (*h*) and the radius (*r*) of the base were measured.

$$\theta = \tan^{-1} \frac{h}{r}$$

Where θ was called as angle of repose that indicates flow properties of granules, *h*, and *r* were height and radius of the granule heap respectively. According to the specifications, an angle of repose value less than 25° indicates excellent flow whereas an angle greater than 40° indicates poor flow.[12]

Bulk density and tapped density

Bulk density and tapped density is usually measured for powder and granules for determination of compressibility index and Hausner's ratio. Bulk and tapped densities were determined using the methods outlined in the USP. Samples (9–13 g) of the sample were passed through a no. 18 sieve into a pre-weighed 25 ml graduated cylinder with 0.5 ml markings. The bulk volume was measured after

manually tapping the cylinder two times on a flat tabletop surface. The tapped volume was measured with the Electrolab ETD-1020 Tap Density Tester after tapping in increments of 500, 750, and 1250 taps with 250 drops per minute. For the determination of both the bulk density (BD) and tapped density (TD) of prepared Dalfampridine sustained release granules of all the formulations, the following formulas were adopted.[13]

$$BD = \frac{\text{weight of the granule taken}}{\text{volume of the packing}}$$

$$TD = \frac{\text{weight of the granule taken}}{\text{tapped volume of the packing}}$$

Compressibility index (Carr's index):

The flow ability of powder can be evaluated by comparing the bulk density (BD) and tapped density (TD) of powder and the rate at which it is packed down. According to the specification Carr's index values ranging between 5-15 indicate excellent flow and between 12-16 indicate good flow whereas Values between 33-38 indicate very poor and greater than 40 indicate extremely poor flow.

The compressibility index (Carr's index) of prepared Dalfampridine sustained release granules was calculated by following the formula [14]

$$\text{Carr's index (\%)} = \frac{TD - BD}{TD} \times$$

100

Hausner's ratio

It is another method used for the determination of flow properties of granules and all the formulations of prepared Dalfampridine sustained release granules; it was determined by using the following formula.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

According to specifications values, less than 1.25 indicates good flow (=20% of Carr's index), whereas greater than 1.25 indicates poor flow (=33% of Carr's index). Between 1.25 and 1.5, a glidant needs to be added to improve flow. [15]

Evaluation of post-compression parameters of Dalfampridine sustained release matrix tablet formulations

Average thickness

Measurement of thickness is a process used to estimate the uniformity in the formulation, as well as

physical appearance, can be estimated. The thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo dial thickness Gauge, Japan) and the results were expressed as mean values of ten readings, with standard deviations. From each formulation of Dalfampridine sustained release tablets; ten tablets were randomly selected and used for thickness determination. According to the specification, tablet thickness should be controlled within a $\pm 5\%$ variation of the standard value. [16]

Tablet hardness

Tablet hardness testing, is a laboratory technique used by the pharmaceutical industry to test the breaking point and structural integrity of a tablet "under conditions of storage, transportation, and handling before usage". The breaking point of a tablet is based on its shape. The hardness of all the formulations of prepared Dalfampridine sustained release tablets was measured by using a Monsanto hardness tester (Cad Mach). According to the specifications of USP; hardness values of 4 to 5 kg/cm² are considered an acceptable limit for sustained-release tablets. From each formulation, the crushing strength of ten sustained release matrix tablets with known weights was recorded in kg/cm² and the averages were calculated with standard deviation. [17]

Friability

Friability is the tendency for a tablet to chip, crumble, or break following compression. This tendency is normally confined to uncoated tablets and surfaces during handling or subsequent storage. Throughout the pharmaceutical industry, friability testing has become an accepted technology, and the instrument used to perform this process is called Friabilator or friability Tester. For any compressed uncoated tablet; friability loss of less than 0.1 to 0.5 % and a maximum up to 1% of the tablet weight are considered acceptable. Previously weighed ten tablets (W_i) from each batch of Dalfampridine sustained release tablets were taken in Roche friability (Roche friability, Secor India). After a hundred revolutions of the friabilator; tablets were recovered by cleaning in a soft cloth to make them free from dust and the total remaining weight (W_f) was recorded. Friability was calculated by using the following formula. [18]

$$\%F = \frac{(W_i - W_f)}{W_i} \times 100$$

Weight variation test

Uniformity of weight is an in-process test parameter that ensures consistency of dosage units during compression. All the formulations of Dalfampridine sustained release tablets were assessed for weight variation as per the USP monograph. Twenty tablets from each batch were weighed collectively and

individually using an electronic balance. The average weight was calculated with the percent variation of each tablet and the process was repeated thrice to calculate the standard deviation. According to the USP monograph, the weight variation tolerance limit for the uncoated tablet having an average weight of 130 mg or less is 10% whereas for an average weight between 130-324 mg is 7.5%, and for an average weight of more than 324 mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviates from the average weight by not more than 7.5% and no tablet deviates by more than 15%. [19]

Content uniformity studies

For determination of content uniformity of all formulations of Dalfampridine sustained release tablets; twenty tablets from each batch were triturated to form powder. Powder equivalent to one tablet was taken and dissolved in 100 ml of HCl buffer pH 1.2 and heated at 37 °C for 60 min with constant stirring. The solution was cooled, and filtered and after suitable dilution, the Dalfampridine content was measured by using a UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 262 nm. Each measurement was carried out in triplicate and the average drug content in each formulation was calculated. [20]

Swelling Index (SI)

The swelling behaviour of all formulations of Dalfampridine sustained release tablets were measured by studying its weight gain in the dissolution medium under study. The swelling index was determined by placing the tablets in the basket of the dissolution apparatus containing 100 ml of phosphate buffer pH 6.8 as a dissolution medium maintained at 37 ± 0.5 °C. After every one-hour interval and up to 12 h, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120). The experiment was performed in triplicate for each time point. The swelling index was calculated using the following formula: [21]

$$\text{Swelling Index (SI)} = \frac{W_f - W_i}{W_i} \times 100$$

W_f and W_i are wet and dry weights of the tablet respectively.

In vitro drug release study

The *in vitro* release studies were conducted for all Dalfampridine sustained release matrix tablet formulations using eight stations USP dissolution rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India.) maintaining at 37 ± 0.5 °C. To

simulate the physiological conditions of GIT, the first 2 h of dissolution was carried out in 900 ml of simulated gastric fluid (SGF, 3.2 mg/ml pepsin in 0.05M HCl, pH 1.2) and the rest of the time in 900 ml of simulated intestinal fluid (SIF, 10 mg/ml pancreatic fluid in phosphate buffer, pH 6.8). At regular intervals of time (every 1 h interval), the aliquots were withdrawn and analyzed for drug using the UV-visible spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at λ_{max} 262 nm both for HCl buffer pH 1.2 and phosphate buffer pH 6.8. After each sampling, an equal volume of fresh dissolution media was added to the dissolution medium. All the dissolution studies were repeated thrice and mean and standard deviation were calculated. The obtained mean percentage of cumulative drug release was plotted over time. [22]

In vitro drug release kinetic studies

The rate and mechanism of release of Dalfampridine from prepared sustained-release tablets were analyzed by fitting the dissolution data of optimized formulation (DF₁₁) into the following exponential equations.

Zero order release equation is calculated by the following equation.

$$Q = K_0 t$$

Where Q is the amount of drug released at time t and K₀ is the zero order release rate constant.

The first-order equation is calculated by following the equation.

$$\log(100 - Q) = \log 100 - \frac{K_1 t}{2.303}$$

Where K₁ is the first order release rate constant. When the data are plotted as logarithm of cumulative percent drug remaining versus time, it yields a straight line, indicating that the release follows first order kinetics. The constant K₁ can be obtained by multiplying 2.303 with the slope.

The dissolution data was fitted to the following Higuchi's equation.

$$Q = K_2 t^{1/2}$$

Where K₂ is the diffusion rate constant. When the data are plotted as accumulative drug released versus square root of time, it yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to K₂.

The dissolution data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behaviour from polymeric systems.

$$\log \left(\frac{M_t}{M_\infty} \right) = \log K + n \log t$$

Where M_t is the amount of drug released at time t , M_∞ is the amount of drug released after infinite time, K is a release rate constant and n is the diffusion exponent indicative of the mechanism of drug release.

For matrix tablets, if the exponent $n < 0.5$, then the drug release mechanism is quasi-fickian diffusion (If $n = 0.5$ then fickian diffusion and if the value is $0.5 < n < 1$, then it is anomalous diffusion coupled with erosion. An exponent value of 1 is indicative of Case-II Transport or typical zero-order and $n > 1$ non-fickian super Case II). The diffusion exponent was based on Korsmeyer-Peppas equation.

Hixson-Crowell recognized that the area of the particle is proportional to the cubic root of its volume, and derived an equation as follows

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

Where W_0 is the initial amount of drug, W_t is the remaining amount of drug in dosage form at time t , and K_s is a constant incorporating the surface volume relation. The graphs are plotted as the cube root of the percent drug remaining versus time. [23]

Stability studies of optimized formulation

Stress testing of the active pharmaceutical ingredient can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating the power of the analytical procedures used. The accelerated condition chosen for the stability study was $40 \pm 2^\circ\text{C} / 75\% \pm 5\% \text{ RH}$ (Climatic zone III condition for accelerated testing) using humidity control oven NEC 210R10 (Newtronic Instruments, India) for 90 days. The tablets of the optimized batch (DF₁₁) were packed in air-tight bottles and subjected to accelerated stability studies according to ICH guidelines. The sample was withdrawn from the humidity control oven on the 30th day, 60th day, and 90th day for evaluation of physicochemical parameters *i.e.* physical appearance, weight variation, hardness, friability, swelling index, drug content, and *in vitro* drug release characteristics. [24]

4. RESULTS AND DISCUSSION:

4.1 Drug and Polymers Compatibility Studies

FTIR Analysis:

Figures 1 to 3 display the FTIR spectra of Dalfampridine in its purest form as well as Dalfampridine combined with HPMC and Eudragit.

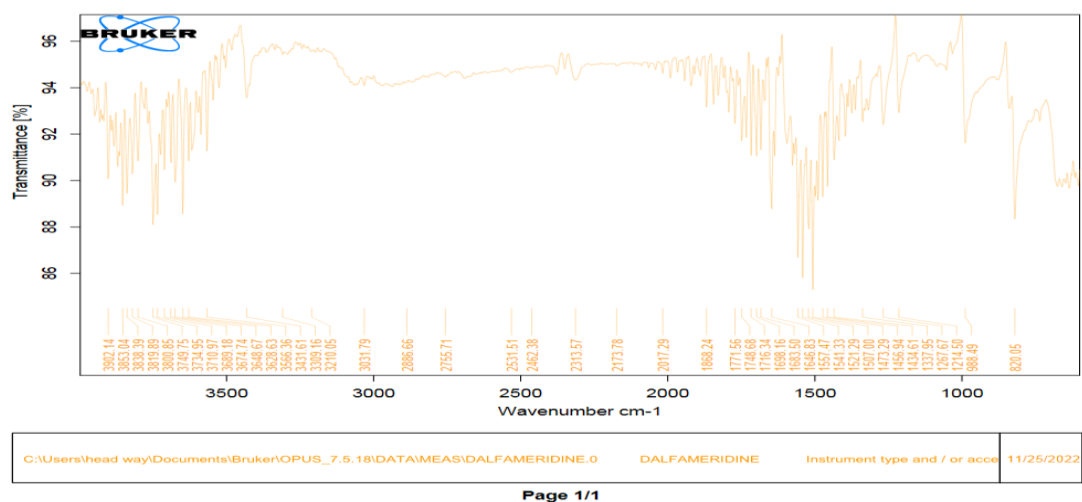
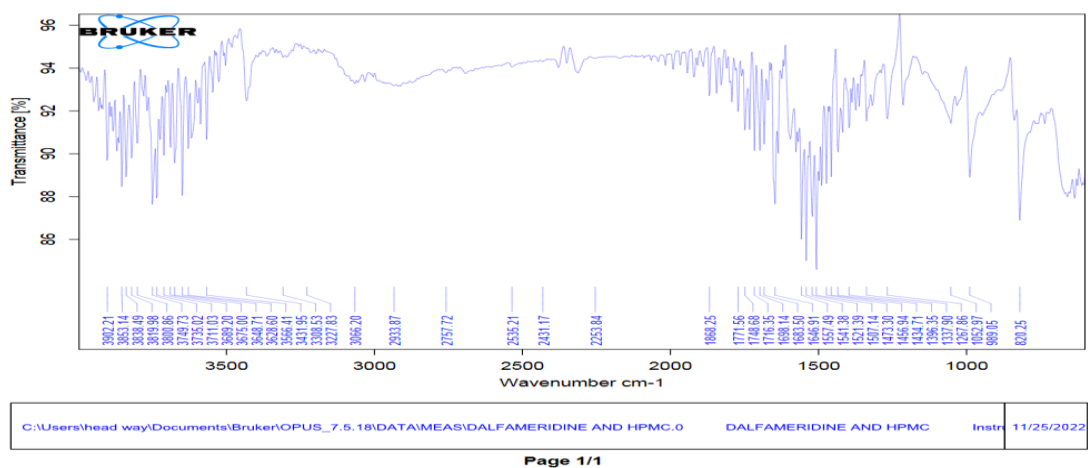


Fig. 1: A Pure Dalfampridine Drug's FTIR Spectra



2: Dalfampridine FTIR Spectra with HPMC

Fig.

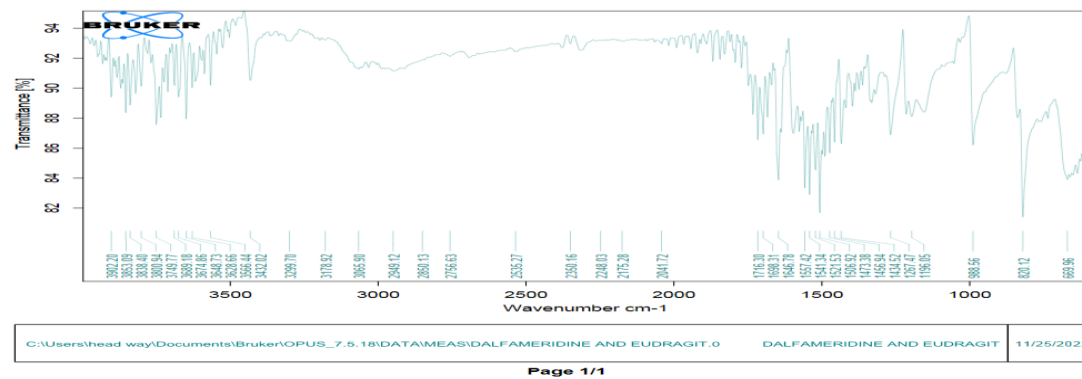
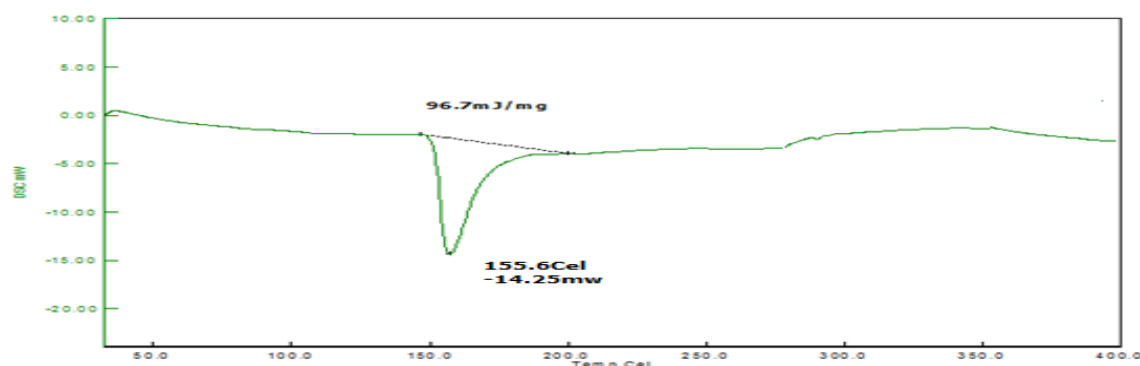


Fig. 3: Dalfampridine with Eudragit FTIR Spectra

When the spectra of pure Dalfampridine and Dalfampridine with HPMC and Eudragit are compared, it can be seen that the sharp peaks at 2886 cm⁻¹ that appear in the pure Dalfampridine spectrum also appear at 2850 cm⁻¹ due to -CH stretching and the broad peak at 3566 cm⁻¹ that appeared at 3566 cm⁻¹ due to N-H stretching in the Dalfampridine with HPMC and Eudragit spectrum. Due to CH stretching, the broad peak that initially emerged at 3031 cm⁻¹ also emerges in Dalfampridine with HPMC and Eudragit at 3065 cm⁻¹ (Alkene). The physical mixture of Dalfampridine with HPMC and Eudragit also contained the characteristic IR absorption peaks of Dalfampridine at 1646 cm⁻¹ (C=N stretching), 1557 cm⁻¹ (N-H bending), 1337 cm⁻¹ (CH bending (alkane)), 1267 cm⁻¹ (C-N vibration), and 820 cm⁻¹ (CH bending (aromatic)) with no shifting in the major peaks, and there were no additional peaks formed in the optimized formulation.

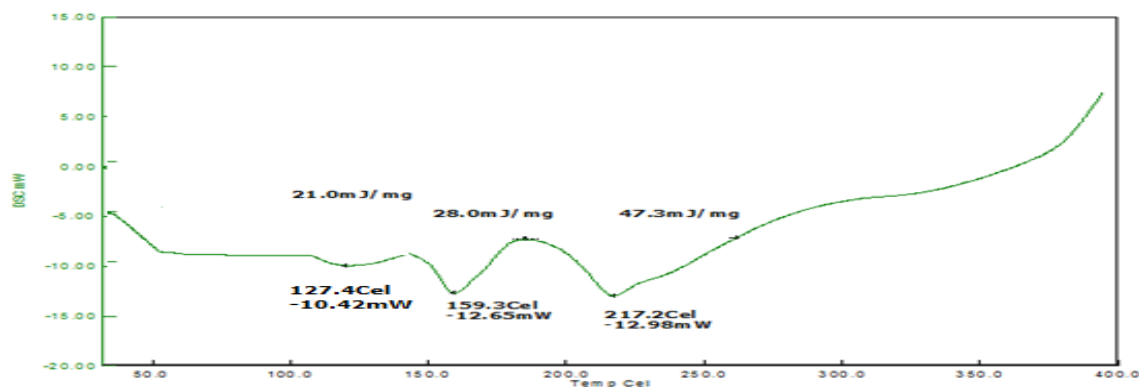
DSC Analysis:

Figure 4 & 5 DSC thermogram of Dalfampridine pure Drug and physical mixture of excipients and the Dalfampridine medication used for preparation of sustained release tablets.



DSC thermogram of Dalfampridine pure drug

Fig. 4: DSC thermogram of Dalfampridine Pure Drug



DSC thermogram of Dalfampridine with polymers

Fig. 5: DSC thermogram of Dalfampridine with polymers

The DSC thermogram of the pure drug Dalfampridine and the physical mixture of Dalfampridine with polymers used for formulation both showed endothermic peaks at 155.6 °C and 159.3 °C, respectively, because the formulation required a little bit more heat than the pure drug due to the presence of various excipients and polymers used for formulations. This suggests the

thermodynamic stability of the physical mixture of polymers and dalfampridine. When dalfampridine is physically mixed with polymers, such as HPMC and Eudragit, endothermic peaks can be seen at 217.2 °C and 127.4 °C on the DSC thermogram, respectively.

Pre-compression Parameters

Precompression parameters such as bulk and tapped density, Hausner's ratio, Carr's index, and angle of repose were measured in order to better understand the flow characteristics of granules for the ease of tablet formulation fabrication. This demonstrated the granules' effective packing capacity. The density of granules is based on particle packing and varies when the granules consolidate, per observations of bulk and tapped densities. When Carr's index is less than 16%, it typically means that all of the formulations have adequate flow properties. Higher Carr's index values could be attributed to formulations with more tiny particles and inconsistent powder sizes. A quick and easy way to gauge the flow parameters and gauge how cohesive a granule column is to use the Hausner's ratio. Hausner's ratios for all Dalfampridine sustained-release tablet formulations were in the low

ranges, showing good granule flowability. In general, granules with a Hausner's ratio value below 1.25 have excellent flow properties, and this was the case for all of the formulations of Dalfampridine sustained-release granules under investigation. The relevant phenomenon to employ in estimating the flow properties of particles larger than 150 micrometers is the angle of repose. Angles of repose of 25° show that the material is flowing freely, whereas 40° suggests that the material is not flowing well. Angles of repose were lower than 25° for all formulations. Granules for the dalfampridine sustained-release tablet exhibited exceptional flow characteristics and worked well for compressing tablets. Table 3 provides the precompression parameter results for all Dalfampridine sustained-release tablet formulations.

Table 3: Result of precompression parameters of Dalfampridine sustained release granules

F. No.	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose	Carr's index	Hausner's ratio
DF ₁	0.342±0.02	0.393±0.04	22.35±0.14	12.98	1.15
DF ₂	0.372±0.03	0.412±0.04	20.74±0.12	09.71	1.11
DF ₃	0.383±0.03	0.428±0.03	21.45±0.26	10.51	1.12
DF ₄	0.388±0.05	0.435±0.04	21.62±0.18	10.80	1.12
DF ₅	0.335±0.04	0.372±0.05	20.68±0.16	09.95	1.11
DF ₆	0.370±0.05	0.417±0.05	21.36±0.15	11.27	1.13
DF ₇	0.362±0.04	0.402±0.03	20.52±0.17	09.95	1.11
DF ₈	0.344±0.03	0.389±0.06	21.42±0.15	11.57	1.13
DF ₉	0.352±0.04	0.405±0.05	20.45±0.15	13.08	1.15
DF ₁₀	0.376±0.03	0.423±0.02	22.40±0.14	11.11	1.13
DF ₁₁	0.384±0.04	0.429±0.05	21.50±0.14	10.49	1.12
DF ₁₂	0.361±0.04	0.396±0.04	20.38±0.13	08.84	1.10

All values are expressed as mean± SD; (n=3)

Post-Compression parameters:

All of the Dalfampridine sustained release matrix tablets' physical specifications were deemed to be acceptable. All of the formulations' tablets had the same uniform, white, circular shape, and smooth surface morphology. There were no signs of the typical tablet abnormalities such as capping, picking, or chipping. All of the Dalfampridine sustained release matrix tablet formulations had average thicknesses that ranged from 3.25 mm to 3.47 mm. The variations from the average value were around

5% and within acceptable bounds. Granule flow, applied force, and depth fill of the granules in the die cavity were all consistent throughout the tablet-making process, as seen by the uniformity of tablet thickness. The range of weight changes for various formulations was 3.25±0.30% to 3.52±0.32%. All formulations come within the allowed range of 5% for the typical percentage variation of tablet formulations with weights of 250 mg. Within the deadlines, the average percentage variation of all pill formulations was discovered. As a result, all

formulations met the official standard for weight uniformity by passing the test. The weight variation tolerance limit demonstrated uniformity in tablet compression and, as a result, the medicine content in a single tablet for all formulations within the limits. The pills must be tough to withstand damage from shipping. All of the formulations of Dalfampridine sustained release tablets ranged in hardness from 5.15 ± 0.4 to 5.74 ± 0.3 kg/cm², which suggested that the tablets under study had satisfactory handling and transportation qualities. More uniformity in the compression force used during tablet punching is suggested by less variation in tablet hardness. The percentage of losses that occur during packaging and shipment is often determined using the physical quality of a tablet known as friability. The range of

all formulas' percentage friability was $0.65 \pm 0.02\%$ to $0.58 \pm 0.04\%$. The percentage of friability in the current studies was within the acceptable ranges for all formulations, demonstrating that the product is resistant to damage from handling and transportation. To keep the formulations' bioequivalency, tablets' medication contents must be consistent from one to the next. The drug content percentages for the formulation of Dalfampridine sustained release tablets were found to be between 98.26 ± 1.4 to 101.27 ± 1.4 % (a variation of 4%), which was within acceptable bounds. The value makes sure that the tablet's medication content is evenly distributed. Table 4 lists the physicochemical descriptions of the various Dalfampridine sustained-release tablet formulations.

Table 4: Evaluation of post-compression parameters of Dalfampridine sustained release matrix tablets

F. No.	Hardness (kg/cm ²)	Weight Variation (%)	friability (% w/w)	Thickness (mm)	Content uniformity (%)
DF ₁	5.45 ± 0.3	3.25 ± 0.30	0.65 ± 0.02	3.32 ± 0.12	98.26 ± 1.4
DF ₂	5.37 ± 0.4	3.43 ± 0.21	0.61 ± 0.03	3.25 ± 0.13	99.37 ± 1.2
DF ₃	5.42 ± 0.3	3.31 ± 0.28	0.61 ± 0.03	3.41 ± 0.14	100.34 ± 1.3
DF ₄	5.26 ± 0.2	3.36 ± 0.24	0.60 ± 0.04	3.45 ± 0.13	99.34 ± 1.4
DF ₅	5.15 ± 0.4	3.25 ± 0.34	0.62 ± 0.03	3.47 ± 0.12	99.72 ± 1.2
DF ₆	5.38 ± 0.3	3.46 ± 0.51	0.59 ± 0.04	3.46 ± 0.13	101.27 ± 1.4
DF ₇	5.42 ± 0.2	3.40 ± 0.36	0.62 ± 0.03	3.42 ± 0.12	98.33 ± 1.2
DF ₈	5.50 ± 0.3	3.52 ± 0.32	0.58 ± 0.04	3.44 ± 0.13	99.22 ± 1.3
DF ₉	5.45 ± 0.4	3.47 ± 0.35	0.62 ± 0.03	3.42 ± 0.13	98.39 ± 1.4
DF ₁₀	5.39 ± 0.2	3.50 ± 0.26	0.64 ± 0.02	3.36 ± 0.12	99.72 ± 1.3
DF ₁₁	5.74 ± 0.3	3.43 ± 0.35	0.59 ± 0.03	3.28 ± 0.14	99.43 ± 1.4
DF ₁₂	5.42 ± 0.4	3.52 ± 0.27	0.60 ± 0.03	3.29 ± 0.12	100.26 ± 1.3

All values are expressed as mean \pm SD; (n=3)

Swelling study

Any matrix type-controlled release formulation's swelling index, which characterizes how the medication is released from a dosage form with controlled release, is an essential physical property. A larger swelling index often indicates that the drug was released from the matrix formulation through diffusion over a longer time frame. For all Dalfampridine sustained-release matrix tablet formulations (DF₁ to DF₁₂) up to 12 hours, a swelling study was conducted. Larger swelling indices were seen in the formulations with higher concentrations of HPMC K4M and HPMC K15M because the polymers' increased hydrophilicity caused them to absorb more water. However, because Eudragit RSPO and RLPO are hydrophobic polymers, the

opposite is seen with formulations that contain higher percentages of them. For all Dalfampridine sustained-release matrix tablet formulations (DF₁ to DF₁₂) up to 12 hours, a swelling study was conducted. Larger swelling indices were seen in the formulations with higher concentrations of HPMC K4M and HPMC K15M because the polymers' increased hydrophilicity caused them to absorb more water. However, because Eudragit RSPO and RLPO are hydrophobic polymers, the opposite is seen with formulations that contain higher percentages of them. Even though the formulations that exclusively contained HPMC of different grades had a higher swelling index than other formulations, the maximum swelling did not happen for 9 to 10 hours. Hydrophobic polymers like Eudragit RSPO and RLPO had to be added to

maintain the swelling properties for up to 12 hours. The formulations that combined both HPMC grades in an equal ratio displayed a greater swelling index. DF11, which contains 15% of HPMC K15M and 10% of Eudragit RLPO, outperformed all other formulations in terms of swelling index. Given that Eudragit is a hydrophobic polymer, formulations

DF1, DF4, DF7, and DF10 with higher percentages of Eudragit displayed lower swelling indices than other formulations. Figures 6 to 9 display histograms of the swelling indices across time for all Dalfampridine sustained-release matrix tablet formulations.

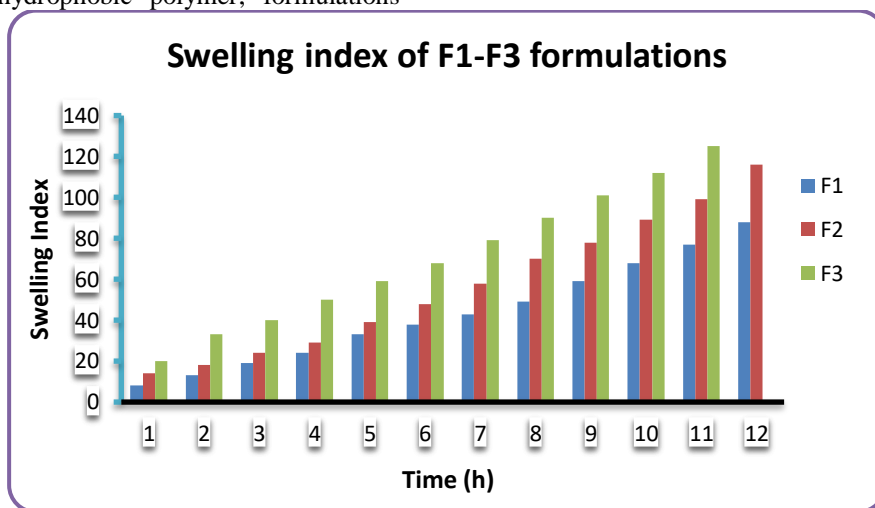


Fig. 6: Histogram displaying the swelling index for the formulations of Dalfampridine continuous release tablets (DF₁ to DF₃)

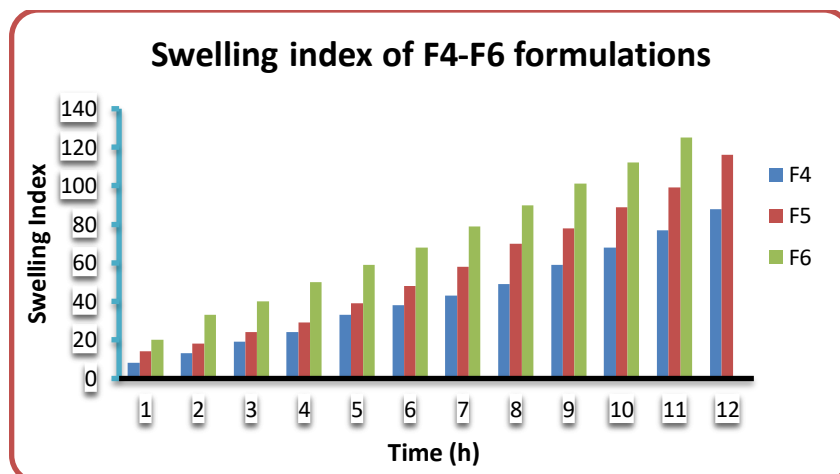


Fig. 7: Histogram displaying the swelling index for the formulations of Dalfampridine continuous release tablets (DF₄ to DF₆)

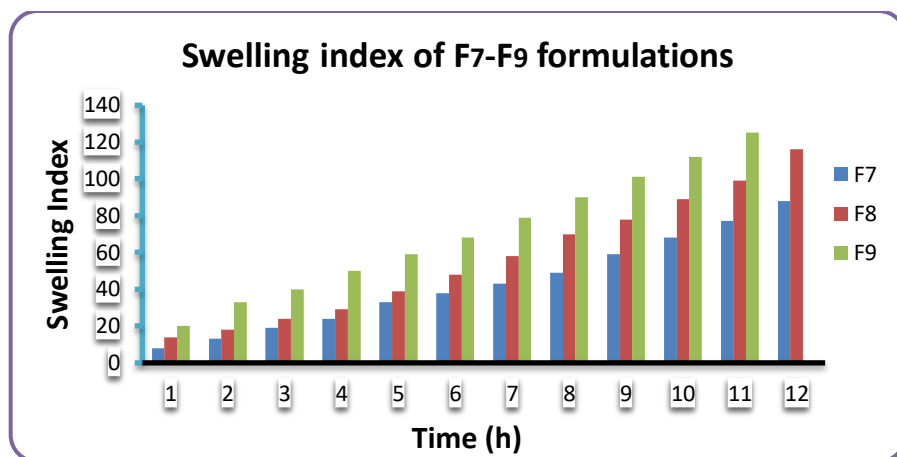


Fig. 8: Histogram displaying the swelling index for the formulations of Dalfampridine continuous release tablets (DF₇ to DF₉)

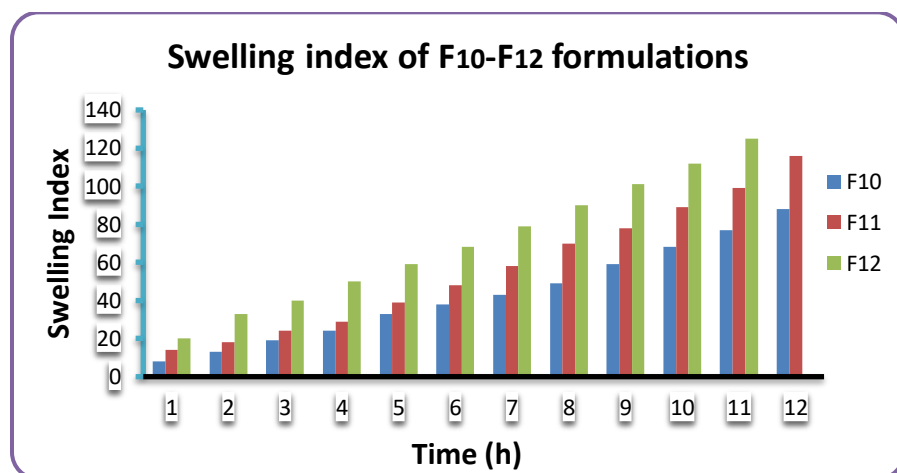


Fig. 9: Histogram displaying the swelling index for the formulations of Dalfampridine continuous release tablets (DF₁₀ to DF₁₂)

***In vitro* drug release profile**

The dissolution studies for all Dalfampridine sustained release matrix tablets were tested for the first two hours in HCl buffer pH 1.2 and the remaining contents were replaced up to 12 hours in phosphate buffer pH 6.8 because the formulations under study were designed to remain in the gastric environment for the first two hours and in the intestine for the following ten hours. To optimise the *in vitro* drug release profile of Dalfampridine sustained released matrix tablets, HPMC K4M, HPMC K15M, and Eudragit RSPO and Eudragit RLPO hydrophobic matrix polymers were used to make twelve different formulations. Different grades of HPMC and eudragit as a polymer are present in formulations DF1 through DF₁₂. Because HPMC K15M has a greater viscosity grade than HPMC K4M, it has a better-controlled release profile when

compared to the two grades of HPMC that were used. The most amount of drug was released for 8–9 hours since the drug is hydrophilic by nature and the HPMC polymer alone initiates the initial burst release. Another hydrophobic polymer called eudragit was added to the sustained release layer to reduce the first burst release. Between the two grades of Eudragit used, Eudragit RSPO exhibited a stronger sustained release impact than Eudragit RLPO. The formulation DF11, which contains 15% of HPMC K15M and 10% of Eudragit RSPO, was chosen as the best formulation since it had a 16.68% initial release and could release up to 99.19% of the drug over 12 hours. Eudragit's concentration increased even though the initial release rate was much slower than planned. So, 10% of Eudragit was thought to be ideal. The drug release profiles of several Dalfampridine SR tablet formulations are displayed by plots displaying

the percentage of CDR concerning time are given in figures 10 to 13.

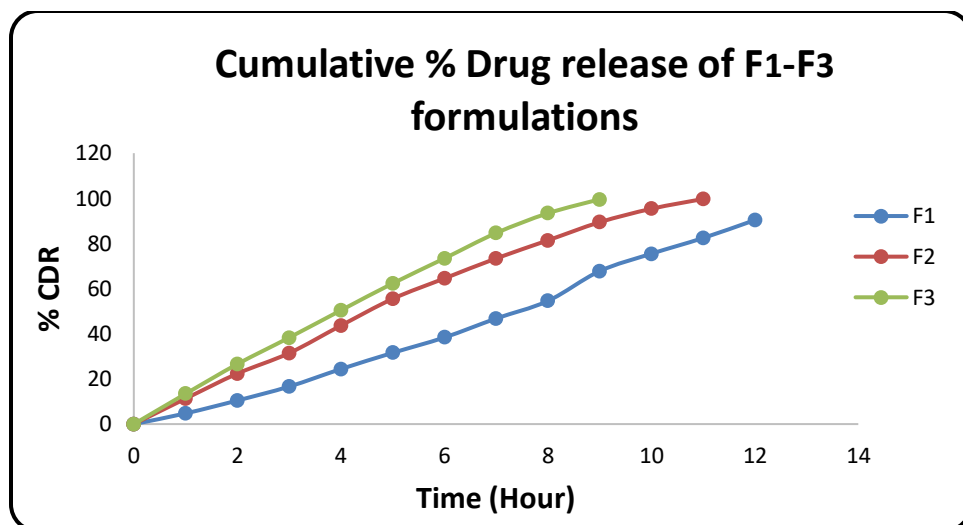


Fig. 10: Study of the Dalfampridine SR formulations' *in vitro* release DF₁ to DF₃

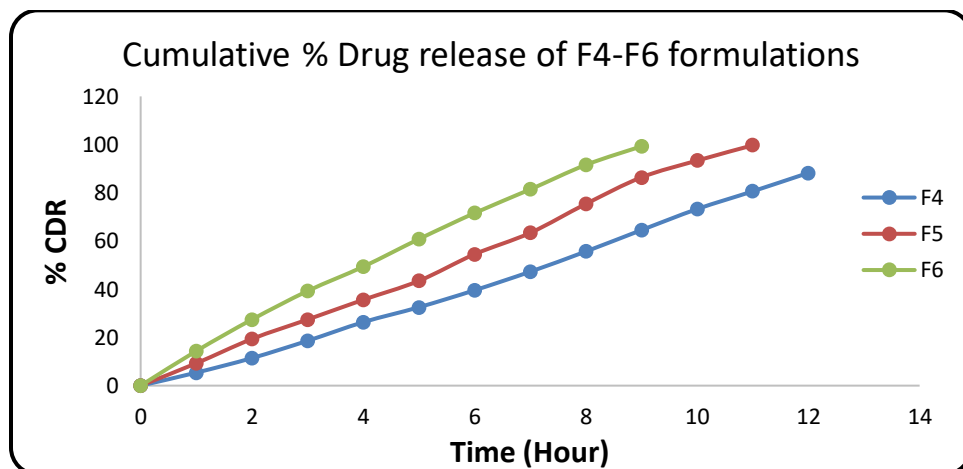


Fig. 11: Study of the Dalfampridine SR formulations' *in vitro* release DF₄ to DF₆

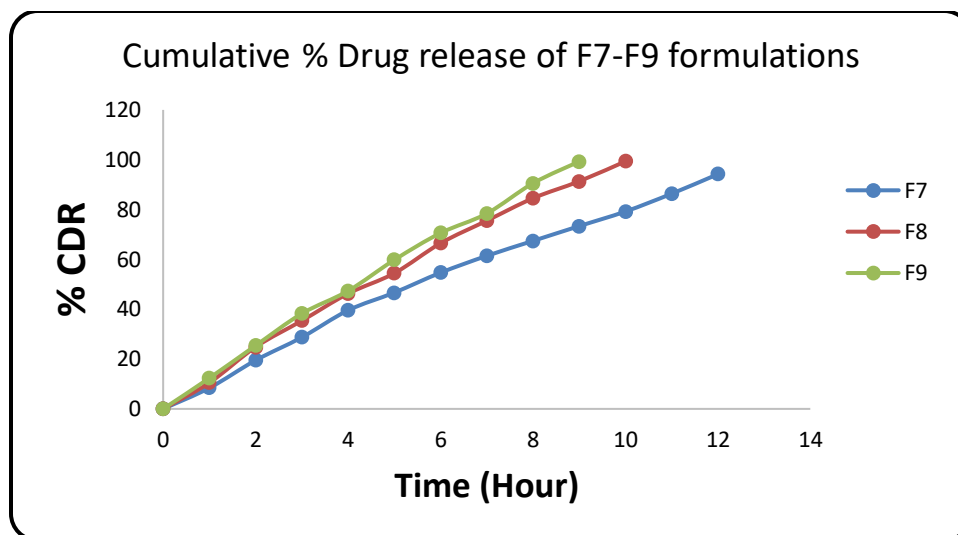


Fig. 12: Dalfampridine SR formulations DF7 to DF9 *in vitro* release studies

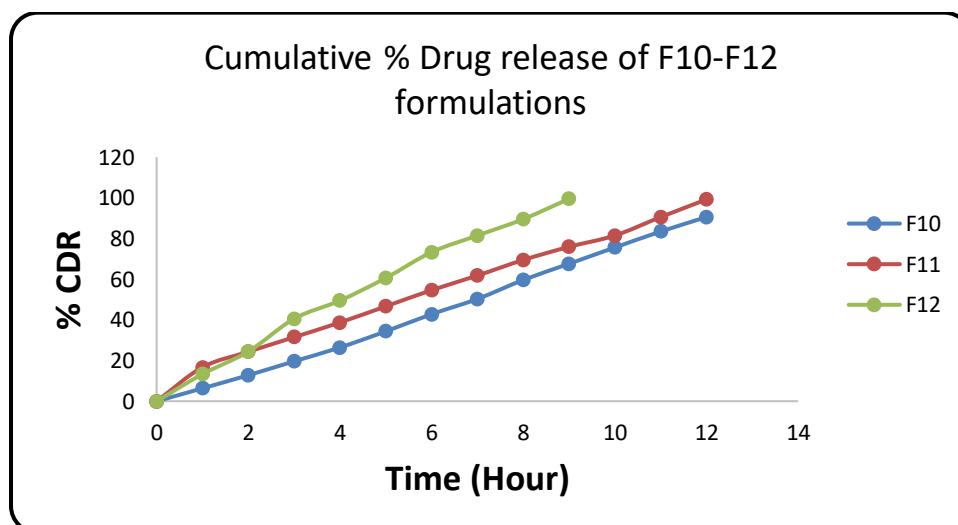


Fig. 13: Dalfampridine SR formulations DF₁₀ to DF₁₂ *in vitro* release studies

***In vitro* dissolution kinetic studies**

The optimized formulation DF₁₁'s *in vitro* dissolution data were fitted to various kinetic models, including the graphs and equation for Peppas's kinetic model of order zero, one, Higuchi, Hixon-Crowell, and Korse-Meyer were plotted (Figure 14 to 18). The zero order release plot's highest regression values (0.993) show that it was found to be fairly linear. For the optimized formulation DF₁₁, the release exponent 'n' was discovered to be 0.732 (0.5 n 1), which seemed to imply an anomalous diffusion associated with erosion. Therefore, zero-order release kinetic models were used in the current study's *in vitro* drug release kinetics of the optimized formulation of Dalfampridine sustained release matrix tablets (DF₁₁), and the drug release mechanism is anomalous diffusion coupled with erosion.

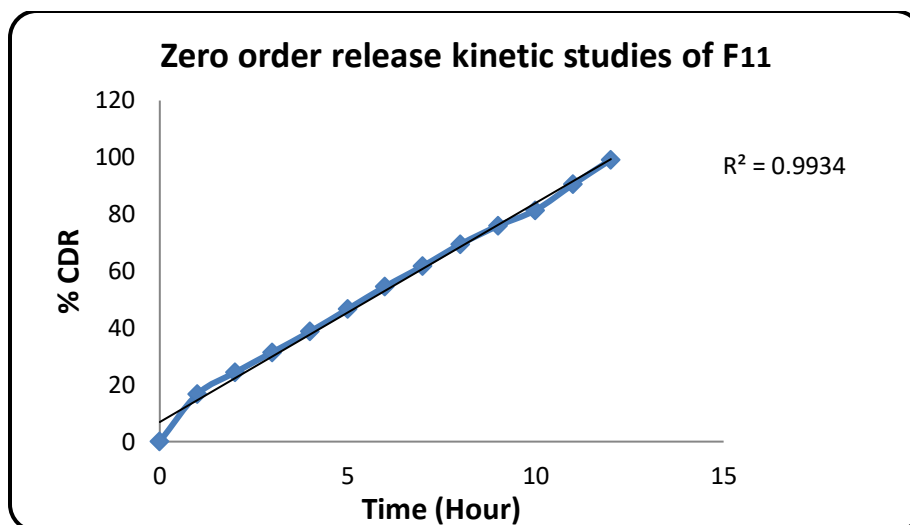


Fig. 14: Zero order release kinetic plot of (DF₁₁)

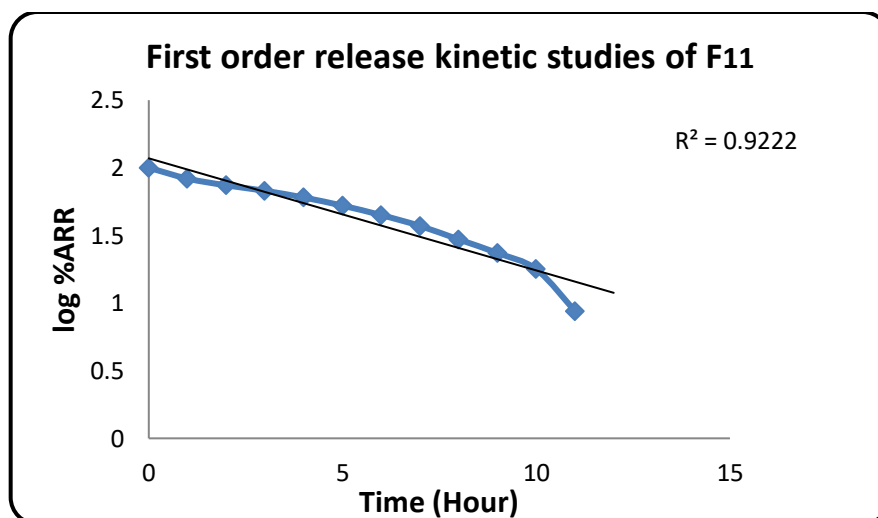
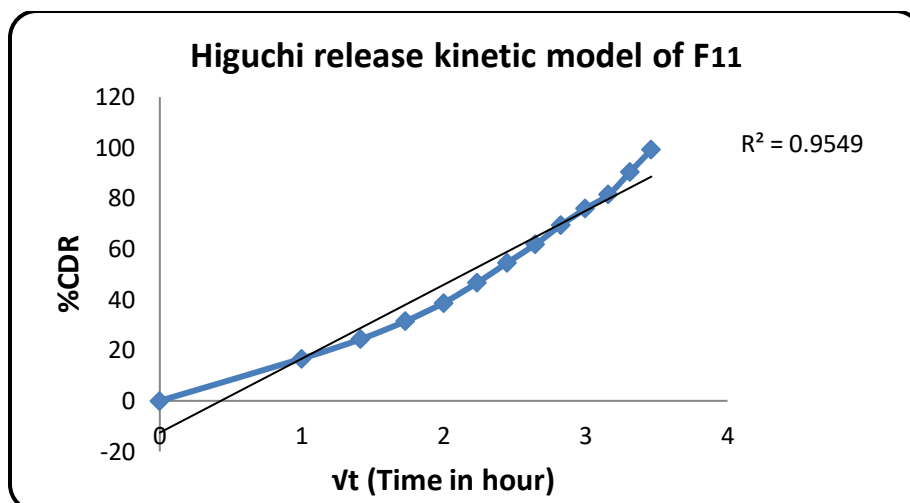
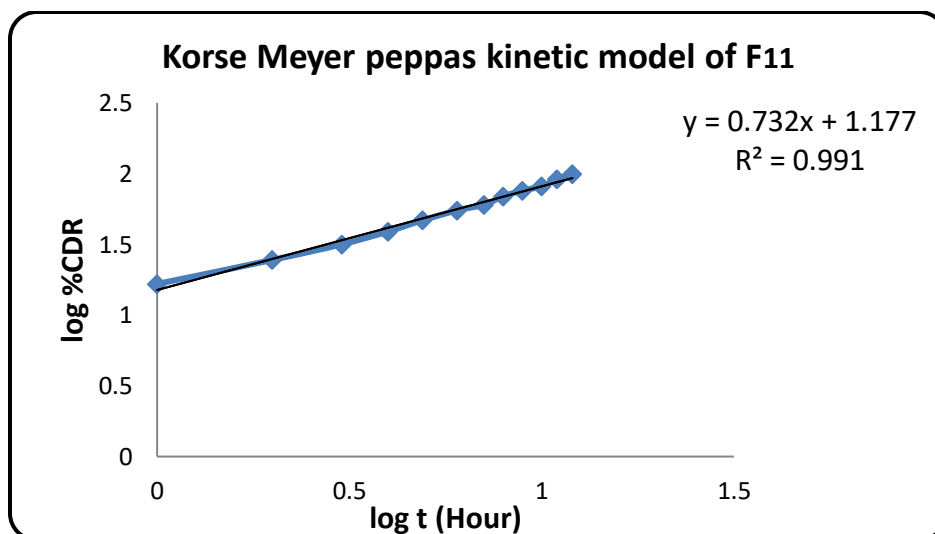
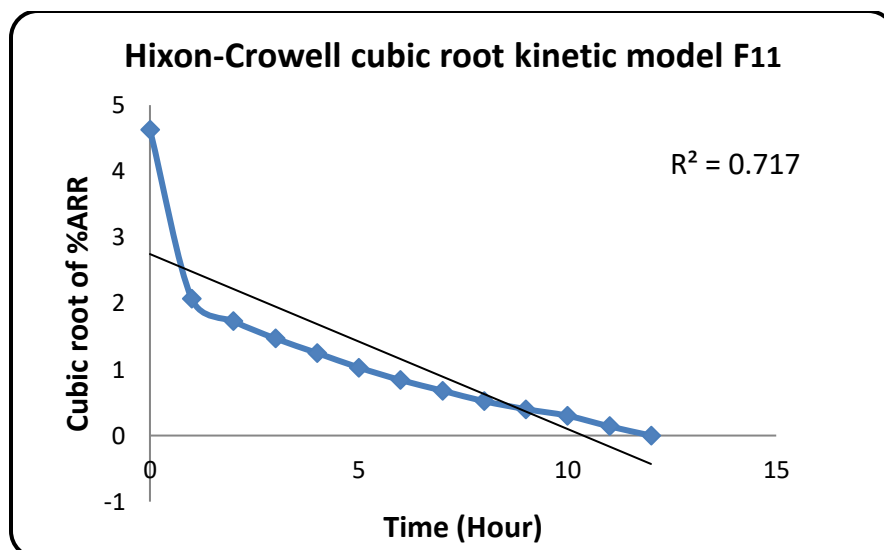


Fig. 15: First order release kinetic plot of (DF₁₁)

Fig. 16: Higuchi release kinetic graph of (DF₁₁)Table 17: Peppas release kinetic plot of (DF₁₁)

Table 18: Hixon Crowell release kinetic plot of (DF₁₁)Table 5: Regression values of *in-vitro* release kinetic study of optimized Dalfampridine sustained release matrix tablet (DF₁₁)

Formulation	Zero order (R ² value)	1 st order (R ² value)	Higuchi model (R ² value)	Hixon-Crowell model (R ² value)	Peppas's model (R ² value)	Peppas's model ('n' value)
DF ₁₁	0.9931	0.9220	0.9541	0.7170	0.9910	0.7321

Accelerated stability studies

Accelerated stability studies are a method that can determine the stability of the dosage form in a short amount of time, even when subjected to difficult conditions in terms of temperature and humidity. After submitting the optimized formulations of dalfampridine sustained release tablets (DF₁₁) to the accelerated stressed condition for a period of ninety days, samples were then taken out and evaluated for a variety of physicochemical parameters. These parameters included hardness, weight variation, friability, content uniformity, swelling studies, and *in vitro* drug release characteristics. All of the tablets that were made with the best formulations had increased friability, hardness, and weight variation while having decreased drug content and swelling index values. It was discovered that none of the

physicochemical properties changed significantly and that any changes that did occur were well within the allowable range. The content of the medicine was analyzed, and *in vitro* dissolution tests were carried out for ninety days; the results showed that more than ninety percent of the drug had been maintained. According to the findings of the stability studies, the formulations of dalfampridine with the sustained release that were tested were therefore stable for at least two years. Table 6 lists the results of various physicochemical characteristics that were assessed at various time intervals while under stress for the best Dalfampridine sustained-release tablet formulations. Figure 19 displays the drug release profile plotted taking % CDR with respect to time at various time intervals in an accelerated stressed situation.

Table 6: Comparative physicochemical characterization of optimized batch at accelerated conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$)

Sl. No.	Tablet Properties	Initial	30 days after	Within 60 days	Within 90 days
1	Physical Surfacing	A smooth, concave surface that is light white and free of fractures	the same	the same	the same
2	Weight variation	3.43 ± 0.35	3.48 ± 0.28	3.51 ± 0.41	3.55 ± 0.43
3	Hardness	5.74 ± 0.3	5.25 ± 0.4	5.12 ± 0.4	5.04 ± 0.3
4	Friability	0.59 ± 0.03	0.62 ± 0.05	0.65 ± 0.04	0.72 ± 0.05
5	Swelling index	116 ± 1.2	112 ± 1.1	107 ± 1.0	102 ± 1.3
6	Drug content	99.43 ± 1.4	98.25 ± 1.2	96.36 ± 1.1	95.26 ± 1.0

All values are expressed as mean \pm SD; (n=3)

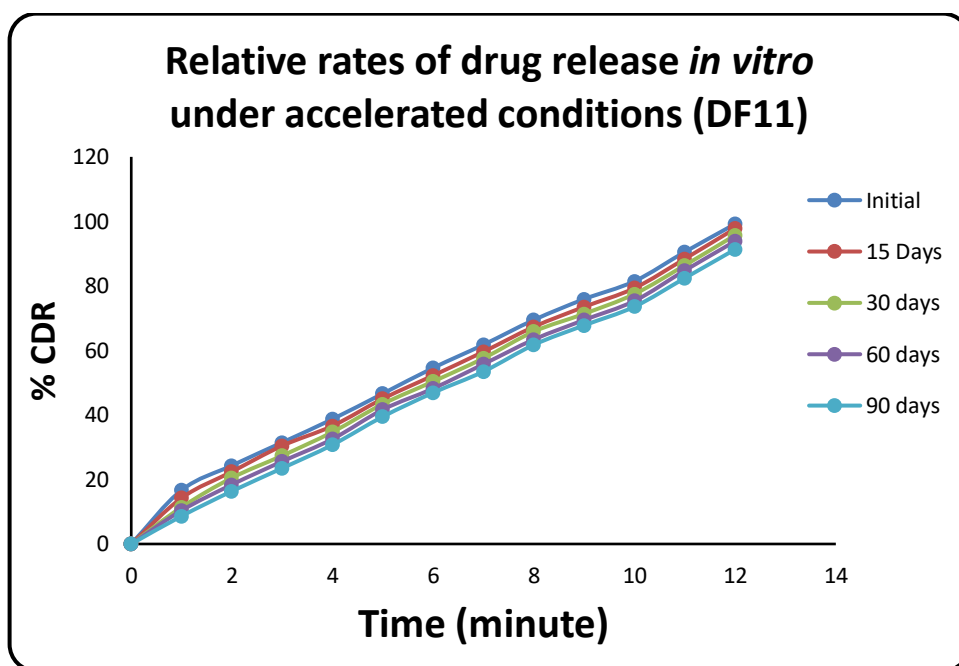


Fig. 19: The dissolution profile of (DF11) *in vitro* under accelerated circumstances was compared and analyzed ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$)

5. CONCLUSION:

Using Dalfampridine, multiple sclerosis patients can walk more easily. Multiple sclerosis is a disease in which the nerves do not function properly, which can lead to issues with vision, speech, and bladder

control, as well as weakness, numbness, and lack of muscular coordination. Dalfampridine is administered orally twice daily in doses of 10 mg with a plasma half-life of 5 to 6 hours. It was decided that the best formulation of dalfampridine would be a

once-daily sustained-release pill in order to cut down on the number of times the medication would need to be administered and to increase patient compliance. Dalfampridine is a component of the BCS categorization system's first class and is soluble in water. Because of the rapid diffusion of the dissolved drug via the hydrophilic gel network as well as an initial burst release of medications, the drug release over an extended period employing a hydrophilic matrix system is restricted. This is especially true for highly water-soluble substances. The purpose of this work was to assess and develop sustained released Dalfampridine matrix tablets by using hydrophilic synthetic polymers such as hydroxyl propyl methyl cellulose (HPMC K4M & HPMC K15M) and hydrophobic synthetic polymers such as Eudragit RSPO and RLPO. Studies using FTIR and DSC have been carried out to ensure that pharmaceuticals and polymers are chemically, thermally, and physically compatible with one another. The Dalfampridine SR tablet was successfully developed in the present study after formulation design and performing pre-compression and post-compression parameters according to specifications. The Dalfampridine SR tablet system thus has a promising future as an alternative to the already marketed conventional, as shown by the results of the current study. To evaluate the effectiveness of this formulation used to treat multiple sclerosis and improve walking in patients, additional clinical studies are necessary.

ACKNOWLEDGEMENT

The authors are thankful to Sunshine Laboratories in Mumbai, India and Glenmark Pharma, Nasik, India for providing gift samples of drug and polymer respectively. Authors are also thankful to the chairman & Principal Anwarul Uloom college of Pharmacy, Hyderabad, Telangana, for permitting to carry out research work.

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