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FORMULATION AND EVALUATION OF DELAYED DRUG RELEASE OF DALFAMPRIDINE

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Abstract:
The present study aimed to develop and evaluate a delayed drug release formulation of Dalfampridine to achieve controlled and prolonged drug release. A total of eight formulations (D1–D8) were prepared using different polymers and polymer ratios. Formulations D1 to D4 were prepared using Eudragit S100 as the polymer, while D5 to D8 were formulated using Hydroxypropyl Methylcellulose (HPMC) in varying concentrations to study their effect on the drug release profile.
All the prepared formulations were evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose to assess the flow properties of the powder blend. The compressed tablets were further evaluated for post-compression parameters including hardness, friability, weight variation, thickness, and drug content. The results indicated that all formulations complied with the Indian Pharmacopoeia (IP) limits, indicating good tablet quality and uniformity.
In-vitro dissolution studies were carried out to determine the drug release behaviour of the formulations. Among all the formulations, D4, containing Eudragit S100 in an optimized ratio, showed the best drug release profile with 99.68% drug release over 12 hours. Therefore, D4 was considered as the optimized formulation due to its satisfactory physicochemical properties and controlled drug release characteristics.
The study concludes that the formulated delayed release tablets of Dalfampridine using Eudragit S100 can effectively provide prolonged drug release and may enhance therapeutic efficacy and patient compliance.
Keywords: *Dalfampridine, Eudragit S100, Hydroxypropyl Methylcellulose (HPMC).*

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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 characterized 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.

Hydrophilic 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.

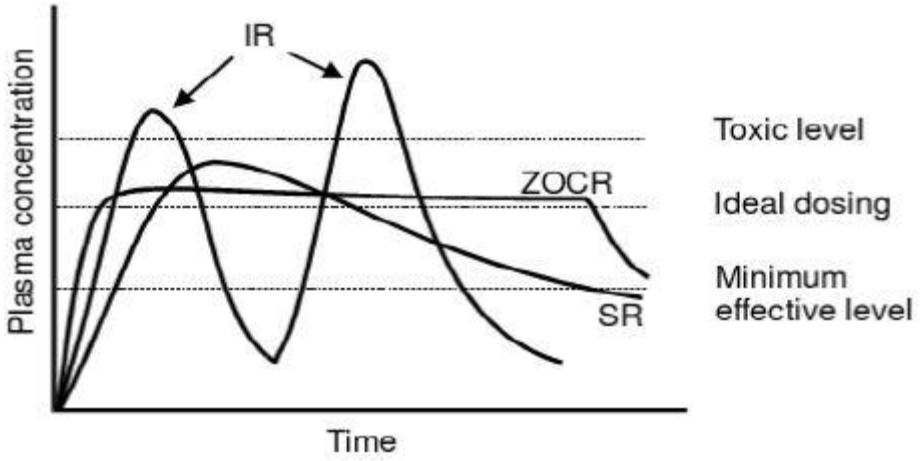


Fig.1.1 Diagram shows characteristic representation of plasma concentrations of a conventional immediate relese dosage form (IR), a sustained release dosage form (SR) and an idealized zero-order controlled release (ZOCR) dosage form (in combination with a start-up dose).

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].

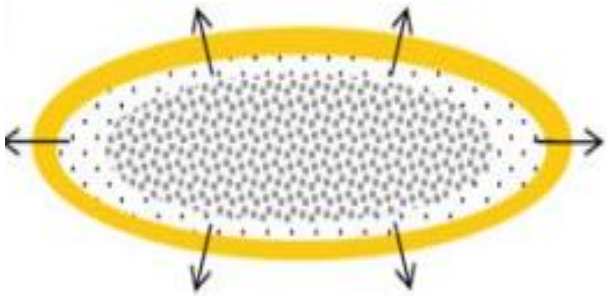


Fig.1.2 Membrane diffusion controlled release. Drug in core (granulated pattern) dissolves to form saturated solution (dilute dots). Drug then diffuses across membrane (thin tipped arrows). Zero order release persists as long as there is sufficient drug in core to form saturated solution.[2]

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

METHODOLOGY:

Analytical method development:

7.1.1 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.

7.1.2 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 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

7.2. Pre formulation 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.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Table 7.1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticle interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

Table 7.2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

7.3. Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3. 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 100mg.

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 7.3: Formulation composition for tablets

INGREDIENTS	FORMULATION CHART							
	D1	D2	D3	D4	D5	D6	D7	D8
Dalfampridine	10	10	10	10	10	10	10	10
Eudragit S 100	10	20	30	40	-	-	-	-
HPMC	-	-	-		10	20	30	40
PVP K 30	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3
Mg Stearate	3	3	3	3	3	3	3	3
Mcc	68	58	48	38	68	58	48	38
Total weight	100	100	100	100	100	100	100	100

All the quantities were in mg

7.4. Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table 7.4: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche Friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the Friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content:

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Dissolution parameters:

Apparatus -- USP-II, Paddle Method

Dissolution Medium -- 0.1 N HCl, pH 6.8 Phosphate buffer

RPM -- 50

Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,9,10,11,12

Temperature -- 37°c ± 0.5°c

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl were removed and pH 6.8

phosphate buffer was added process was continued up to 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at required wavelength using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:
Various models were tested for explaining the kinetics of drug release. To analyse 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.

Zero order release rate kinetics:
To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time 't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.
In Higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:
The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K\ t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for super case II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$$(100\text{-}Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.
Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

7.5. Drug – Excipient compatibility studies
Fourier Transform Infrared (FTIR) spectroscopy:
The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 400cm^{-1}.

RESULTS AND DISCUSSION:

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

8.1. Analytical Method
Graphs of Dalfampridine were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 262 nm and 265 4respectively.

Table 8.1: Observations for graph of Dalfampridine in 0.1N HCl (262)

Concentration (µg/ml)	Absorbance
0	0
2	0.122
4	0.235
6	0.344
8	0.458
10	0.569

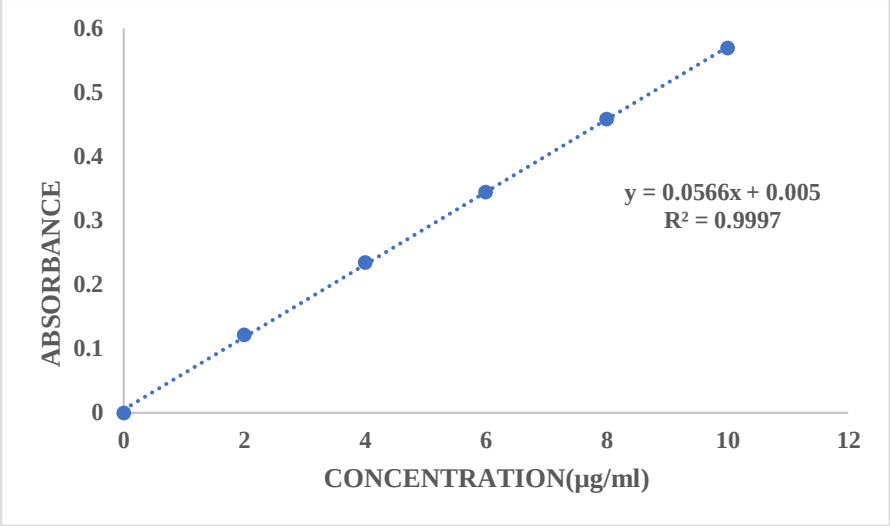


Figure 8.1: Standard graph of Dalfampridine in 0.1N HCl

Table 8.2: Observations for graph of Dalfampridine in pH 6.8 phosphate buffer (265nm)

Concentration [µg/ml]	Absorbance
0	0
2	0.138
4	0.281
6	0.418
8	0.549
10	0.686

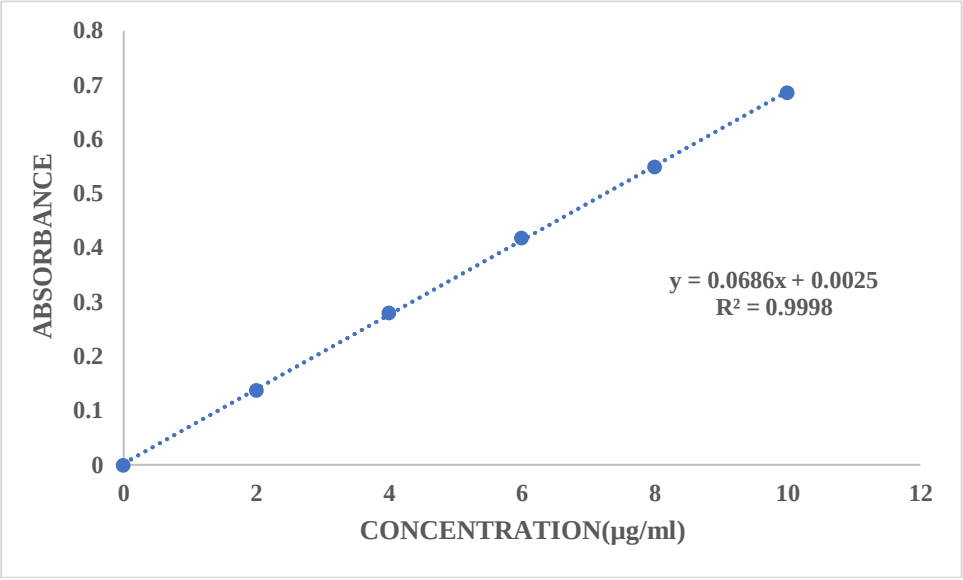


Figure 8.2: Standard graph of Dalfampridine pH 6.8 phosphate buffer (265 nm)

8.2. Preformulation parameters of powder blend

Table 8.3: 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
D1	29.57±0.576	0.41±0.01	0.39±0.006	12.55±0.034	1.10±0.016
D2	27.22±0.115	0.36±0.03	0.41±0.08	14.34±0.012	1.13±0.012
D3	32.05±0.162	0.50±0.011	0.65±0.011	18.14±0.031	1.19±0.001
D4	30.12±0.315	0.45±0.09	0.58±0.03	15.3±0.001	1.21±0.013
D5	26.41±0.431	0.38±0.05	0.44±0.018	17.77±0.02	1.12±0.006
D6	25.96±0.116	0.42±0.08	0.50±0.06	14.12±0.015	1.12±0.011
D7	30.24±0.211	0.48±0.01	0.66±0.013	18.15±0.002	1.20±0.015
D8	28.16±0.326	0.38±0.06	0.45±0.09	15.56±0.006	1.16±0.002

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 0.36±0.03 to 0.50±0.011 (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 0.39±0.006 to 0.66±0.013 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 15.1 which show that the powder has good flow properties. All the formulations have shown the Hausner ratio below 1.25 indicating the powder has good flow properties.

8.3. 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.

8.4. *In-vitro* quality control parameters for tablets

Formulation codes	Weight variation(mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
D1	98.86	2.85	26	1.44	98.12
D2	99.34	2.99	35	1.73	99.31
D3	101.12	2.92	42	1.59	99.08
D4	100.93	2.97	51	1.62	97.22
D5	99.41	2.88	38	1.55	98.64
D6	97.86	2.87	44	1.48	99.83
D7	98.72	2.93	63	1.69	98.43
D8	99.53	2.96	39	1.48	97.66

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 8.4. The average weight of the tablet is approximately in range of 97.86 to 100.93 mg, so the permissible limit is ±7.5% (>100mg). 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 were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 2.85 to 2.99 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-8.4. The result showed that thickness of the tablet is raging from 1.44 to 1.73mm.

Friability:
Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. 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 97.22 -99.83 %.
All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

8.4. *In-Vitro* drug release studies

Table 8.5: Dissolution Data of Dalfampridine Tablets Prepared with Eudragit S 100

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	D1	D2	D3	D4
0	0	0	0	0
1	11.94	13.92	17.94	18.93
2	16.73	19.77	21.72	29.77
3	22.83	26.53	29.83	37.28
4	29.77	31.62	37.12	46.57
5	34.36	36.42	43.33	58.42
6	39.79	43.99	48.79	65.51
7	46.08	52.13	56.05	72.13
8	54.38	66.46	69.35	77.49
9	61.19	72.29	77.73	82.27
10	68.24	79.93	84.24	89.93
11	75.62	84.46	88.43	93.46
12	89.31	87.18	95.62	99.68

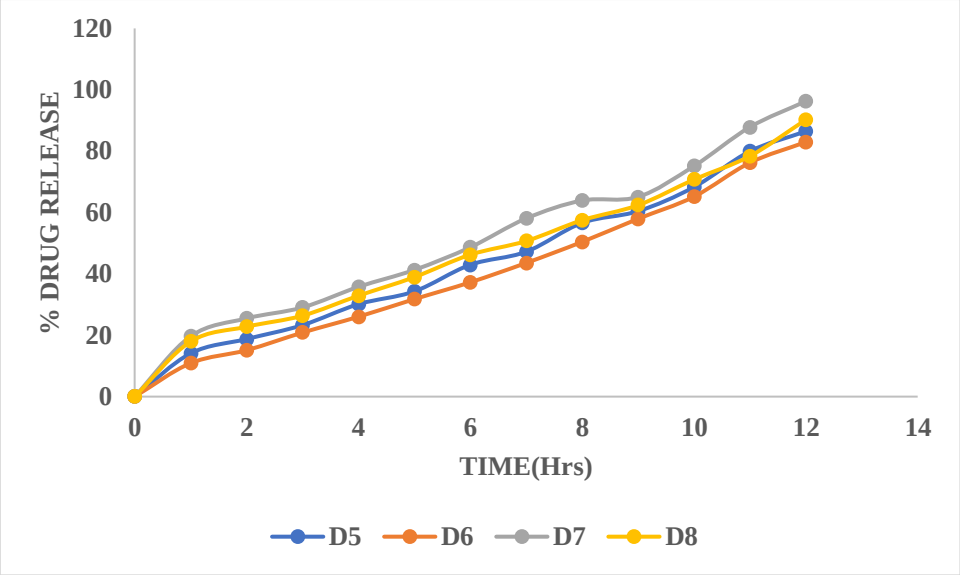


Fig 8.3: Dissolution profile of Dalfampridine (D1, D2, D3 and D4 formulations)

Table 8.6: Dissolution Data of Dalfampridine Tablets Prepared with HPMC

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	D5	**D6**	**D7**	**D8**
0	0	0	**0**	**0**
1	14.08	10.89	19.63	17.93
2	18.76	15.12	25.49	22.77
3	23.29	20.86	29.06	26.37
4	30.12	26.02	35.76	32.87
5	34.29	31.76	41.29	38.93
6	42.96	37.25	48.66	46.25
7	47.22	43.56	58.07	50.71
8	56.62	50.43	63.91	57.49
9	60.43	57.95	65.08	62.38
10	68.29	65.16	75.13	70.75
11	79.94	76.22	87.83	78.39
12	86.46	82.96	96.26	90.22

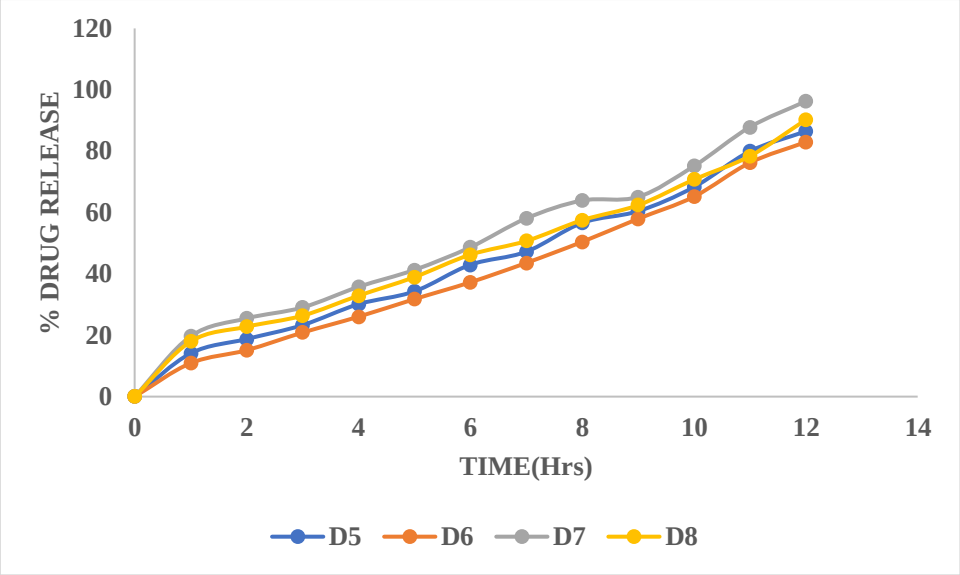


Fig 8.4: Dissolution profile of Dalfampridine (D5, D6, D7 and D8 formulations)

Formulations prepared with Eudragit S 100 retarded the drug release in the concentration of 40 mg (D4Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.68 % in 12 hours with good retardation.

The Formulation Containing HPMC in 30 mg Concentration Showed good retarding nature with required drug release in 12 hours i.e. 96.26%.

From the above results it was evident that the formulation D4is 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 analyse 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 8.7: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	%) REL	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	0	0	0	0	0	0	0	0	0	0
18.93	1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.000
29.77	2	1.414	1.474	0.301	1.847	14.885	0.0336	-0.526	70.23	4.642	4.126	0.516
37.28	3	1.732	1.571	0.477	1.797	12.427	0.0268	-0.429	62.72	4.642	3.973	0.668
46.57	4	2.000	1.668	0.602	1.728	11.643	0.0215	-0.332	53.43	4.642	3.766	0.875
58.42	5	2.236	1.767	0.699	1.619	11.684	0.0171	-0.233	41.58	4.642	3.464	1.177
65.51	6	2.449	1.816	0.778	1.538	10.918	0.0153	-0.184	34.49	4.642	3.255	1.386
72.13	7	2.646	1.858	0.845	0.423	10.304	0.0139	-0.142	27.87	4.642	3.032	1.610
77.49	8	2.828	1.889	0.903	0.452	9.686	0.0129	-0.111	22.51	4.642	2.824	1.818
82.27	9	3.000	1.915	0.954	0.477	9.141	0.0122	-0.085	17.73	4.642	2.608	2.034
89.93	10	3.162	1.954	1.000	0.500	8.993	0.0111	-0.046	10.07	4.642	2.159	2.482
93.46	11	3.317	1.971	1.041	0.521	8.496	0.0107	-0.029	6.54	4.642	1.870	2.772
99.68	12	3.464	1.999	1.079	0.540	8.307	0.0100	-0.001	0.32	4.642	0.684	3.958

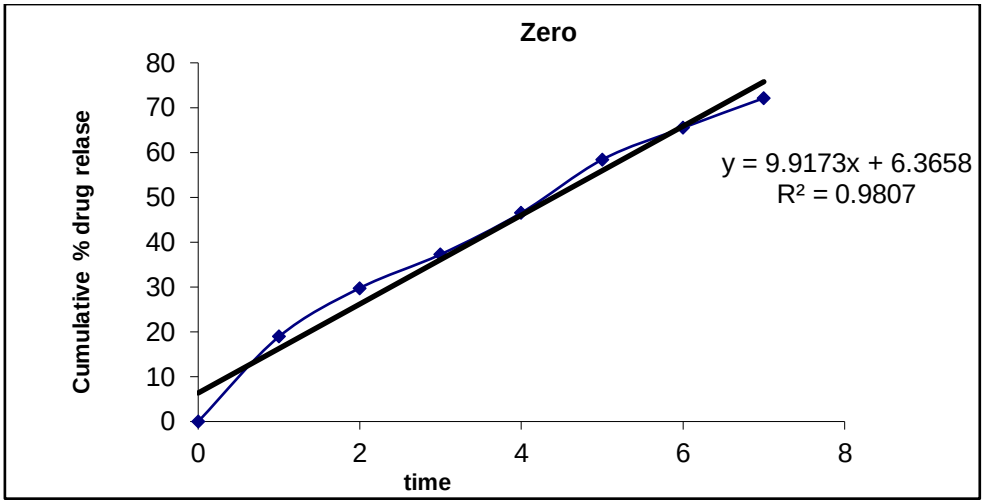


Fig 8.5 : Zero order release kinetics graph

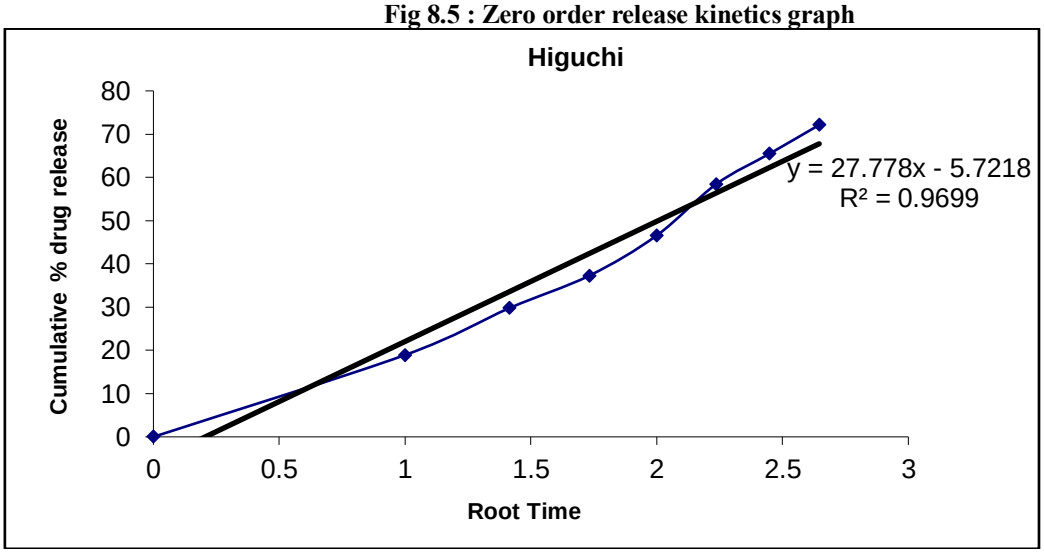


Fig 8.6 : Higuchi release kinetics graph

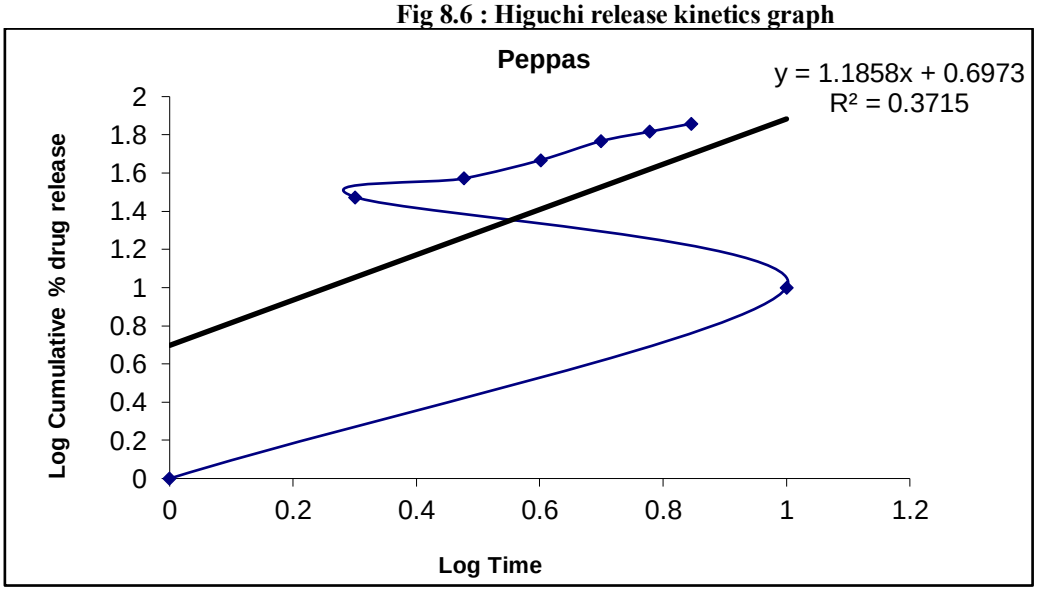


Fig 8.7: Kars Mayer Peppas graph

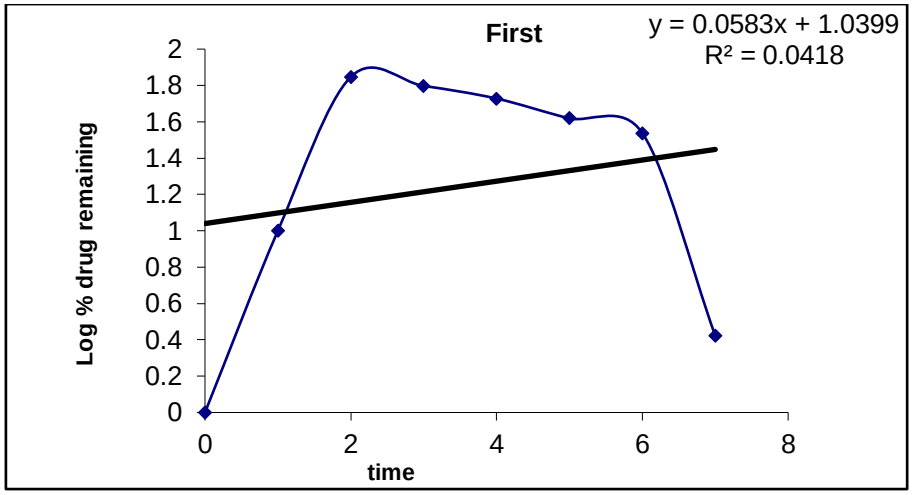


Fig 8.8: First order release kinetics graph

From the above graphs it was evident that the formulation D4 was followed Zero order release kinetics.

8.5. Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy:

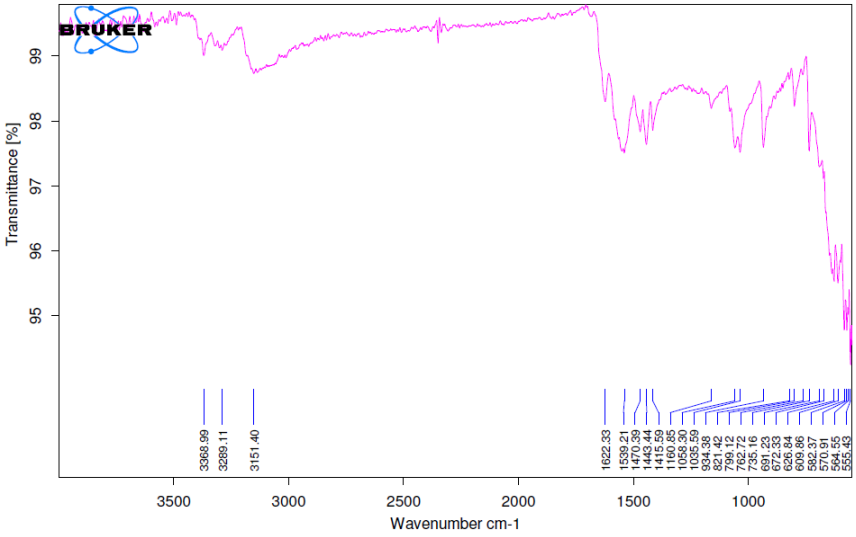


Figure 8.9: FT-TR Spectrum of Dalfampridine pure drug

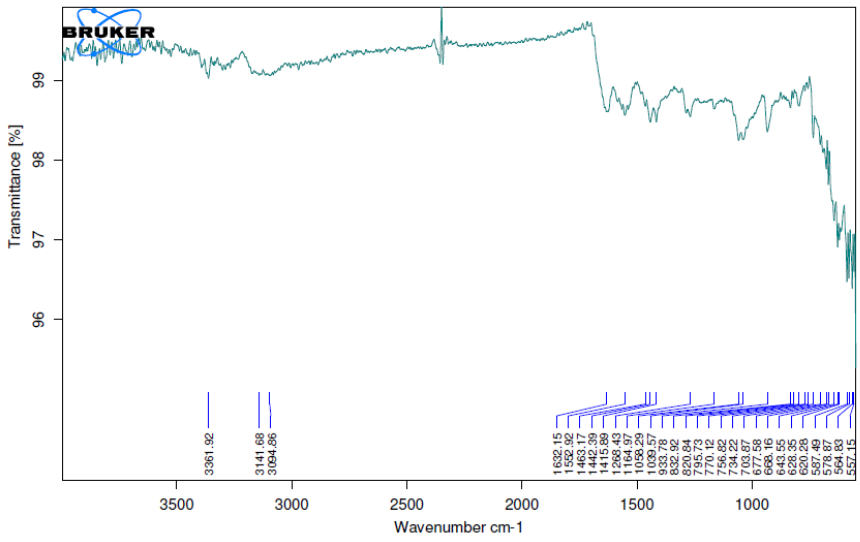


Figure 8.10: FT-IR Spectrum of Optimized Formulation

CONCLUSION:

The present study on the formulation and evaluation of delayed drug release tablets of Dalfampridine successfully demonstrated that a controlled and delayed release profile can be achieved through appropriate selection of polymers and formulation techniques. The prepared formulations were evaluated for various physicochemical parameters such as hardness, friability, weight variation, drug content, and in-vitro drug release, and the results were found to be within acceptable pharmacopeial limits.

The optimized formulation showed a desirable delayed release pattern, effectively preventing immediate drug release and allowing the drug to be released at the intended time. This helps in maintaining a prolonged therapeutic effect, improving patient compliance, and reducing dosing frequency. The dissolution studies confirmed that the polymeric system used in the formulation played a significant role in controlling the release behaviour of Dalfampridine.

Overall, the study indicates that the developed delayed release formulation of Dalfampridine can be considered a promising approach for enhancing therapeutic efficacy and providing sustained

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