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Research Article

Formulation and Evaluation of Delayed Release Coated Tablet of Dalfampridine for the Treatment of Multiple Sclerosis

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A B S T R A C T

The study aimed to develop delayed release coated tablets of Dalfampridine for treating multiple sclerosis. Dalfampridine core tablets were prepared using wet granulation method with various excipients. Pre-compression parameters and flow characteristics were evaluated to ensure smooth tablet production. Post-compression studies included weight variation, thickness, hardness, friability, drug content, and In-vitro drug release. Coating was applied to the core table formulation using a 5% coating solution consisting of Eudragit L100-55, PEG-600, talc, color concentrate, IPA, and acetone. Coating parameters such as inlet temperature, spraying rate, and pan rotation were optimized using a 2^3 factorial design. The stability study confirmed the formulation's stability at room temperature and 40°C/75% RH for one month. The coated tablets showed no drug release in acidic environments (pH 1.2) but released the drug in intestinal environments (pH 6.8). Formulation E2, coated under specific conditions i.e. inlet temperature of 50°c, spay rate of 2ml/min and pan rotation of 15 rpm was identified as the best formulation based on % weight gain, coating process efficiency, and release time in the intestine.

Key words: Delayed release coated tablet, Dalfampridine, Multiple sclerosis, coating parametrers, Eudragit L-100 55

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INTRODUCTION

Dalfampridine is a neurofunctional modifier that enhances walking speed in individuals with multiple sclerosis (MS). It acts as a broad-spectrum lipophilic potassium channel blocker, favorably binding to the open state of potassium channels in the central nervous system (CNS). Its target in MS patients is the potassium channels. Dalfampridine does not prolong the QTc interval. By inhibiting voltage-gated potassium channels in the CNS, it maintains transmembrane potential and prolongs action potential, ensuring sufficient current for conduction in demyelinated axons typical in MS. Additionally; it aids neuromuscular and synaptic transmission by alleviating conduction blocks in demyelinated axons [1].

The oral route is widely used for drug administration due to its convenience and effectiveness. Formulation design aims to overcome limitations, including controlled/sustained release systems [2]. Enteric coatings play a crucial role in site-specific drug delivery to the intestine by preventing medication release before reaching the small intestine. These coatings remain insoluble in low pH but become soluble as pH increases in the gastrointestinal tract, allowing controlled release. Materials for enteric coatings include CAP, CAT, PVAP, HPMCP, fatty acids, waxes, shellac, plastics, and plant fibers [3].

Main reasons for preparing enteric coating tablets may be enumerated as [4]:

- Shielding the stomach lining from drug-induced harm.
- Safeguarding drugs from degradation by gastric contents.
- Facilitating site-specific drug release for intestinal absorption.

Tablet coating is a complex process influenced by several factors like spray rate, inlet air temperature, rotating speed of the pan, and percentage solid content. Each of these variables

affects the quality and uniformity of the final product. Controlling these parameters is crucial to ensure proper drying, minimal moisture content, and uniform coating, which in turn enhance product consistency and stability while minimizing the risk of degradation [5].

The aim of the present work is to optimize the process parameters during preparation of Dalfampridine enteric coated tablet.

Experimental

Materials:

Dalfampridine API was gifted by Alkem laboratories baddi, Himachal pradesh, MCC PH 101, MCC PH 102, lactose monohydrate, SSG, pvk-30, calcium carbonate, talc, magnesium stearate, starch, Eudragit L-100-55, PEG 600, acetone, isopropyl alcohol used were of analytical grade.

Methods:

Fourier Transform Infrared Spectroscopy for Analysis of Drug and Excipients [6]:

FT-IR spectra of the pure drug and polymer were obtained at room temperature using a Shimadzu FTIR-8400S spectrophotometer in transmittance mode. Samples were ground, mixed with Nujol, and compressed between two KBr plates to form thin films. These plates were then placed in the spectrometer, and scanning was conducted between wave numbers 4000-400 cm^{-1}.

Evaluation of powder blend (pre-compression parameters) [7, 8]

Angle of Repose

The angle of repose is the maximum angle formed by a pile of powder when it's poured onto a surface. It's a useful measure for assessing particle flow properties, which are related to packing densities and mechanical arrangements. To determine the angle of repose, powder is placed in a funnel so that it flows freely onto a surface. The angle is calculated from the diameter of the resulting cone of powder.

Tan θ = h/r

Where, h = height of the powder heap
R = radius of the powder heap
θ = angle of repose

Determination of Bulk Density and Tapped Density

An accurately weighed amount of powder (W) was poured into a graduated cylinder, and the initial volume (V0) was measured. The cylinder was then sealed and placed in the tap density tester (according to USP standards). The apparatus was set for 100 tablets, and the final volume (Vf) was measured. The process continued until two consecutive readings were equal. Bulk density and tapped density were calculated using the following formulas.

Bulk density = W/ V0

Tapped density = W/ Vf

Where, W= Weight of the powder
V0 = Initial volume
Vf = final volume

Compressibility Index (Carr's Index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less Compressible a material the more flowable it is.

CI = (TD-BD)/TD×100
Where, TD = Tapped density
BD = bulk density

Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, As such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow Properties.

Hausener's Ratio = Tapped density/Bulk Density

Formulation development of core tablet of Dalfampridine:

Dalfampridine core tablets were formulated using the wet granulation method. Initially, Dalfampridine and lactose were sieved through a #40 size mesh. These materials were then mixed for 10 minutes using a mortar and pestle. Sodium starch glycolate was sieved through #40 and added to the blend. A binder solution was prepared by dissolving PVPK-30 in purified water understirring.
The former blend was granulated using this binder solution, along with additional purified water or isopropyl alcohol if necessary, until dough mass was achieved. The granules were dried in a hot air oven at 48°C to 55°C until the loss on drying (LOD) was less than 2%. After drying, the granules were sifted through a #20 screen.
Extra granular materials were added and mixed for 10 minutes. This blend was then lubricated with magnesium stearate for 3 minutes. Finally, the blends were compressed into tablets using an 8/6″ round shallow convex punch on a multipunch rotary tablet machine. The prepared tablets were stored in tightly closed glass containers and evaluated for various parameters.

Table 1: Formulation table for core tablet of Dalfamridine

Sr. No.	Ingradients (F1)	Quantity (mg)
1	Dalfamridine	10
2	MCC PH 101	63.4
3	Lactose monohydrate	35.8
4	SSG	8.85
5	Pvpk-30	6.5
Lubrication		
6	MCC PH 102	62.4
7	SSG	5.5
8	Calcium carbonate	4.8
9	Talc	0.25
10	Magnesium stearate	4.5
11	starch	6.85
Total=200 mg		

Post-compression evaluations [9, 10]

Hardness

The hardness of tablet was measured by Monsanto hardness tester. The hardness was measured in kg/cm^2. Ten tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Thickness

The thickness of the tablet was measured by placing tablet between two arms of vernier calliper, which permits accurate measurements and provides information on the variation between Tablets. Ten tablets were taken and their thickness was measured.

Weight variation

Twenty tablets were selected randomly from each formulation and weighed individually using a Shimadzu Digital balance. The individual weights are compared with the average weight for the weight Variation.

Friability

The friability of the sample of ten tablets was determined using Roche friabilator. Pre-weighed ten tablets were placed in the plastic chambered friabilator attached to motor revolving at a speed of 25 ± 1 rpm. Rotate the drum 100 times. The tablets were then dedusted and reweighed and percent Loss was calculated. It was calculated using the following equation.

% Friability = (W1 – W2)/W1×100

Where, W1 = Initial weight of the 10 tablets

W2 = Final weight of the 10 tablets after testing.

Percent friability of tablets less than 1% is considered acceptable.

Disintegration Test

The disintegration test was carried out according to I.P procedure on six tablets using disintegration test apparatus with disks in Phosphate Buffer (pH 6.8) maintained at 37^{0}C ± 5^{0}C. The disintegration time of each tablet was recorded.

Determination of drug content

Dalfampridine tablets were subjected to drug content analysis. Three tablets from each formulation were powdered after being weighed. Approximately 10 mg equivalent of Dalfampridine was precisely weighed and dissolved completely in pH 6.8 phosphate buffer. The resulting solution was then filtered, and 1 ml of the filtrate was diluted to 100 ml with pH 6.8 phosphate buffer. The absorbance of this solution was measured using a UV spectrophotometer at 261 nm.

In-vitro Drug Release Studies

In vitro drug release from various formulations was assessed using the USP dissolution apparatus type II. A dissolution medium of 900 ml phosphate buffer at pH 6.8 was employed for 1 hour. Tablets were placed into the basket and subjected to a temperature of 37 ± 0.5°C with stirring at 100 rpm. At predefined intervals, samples were withdrawn and replaced with fresh dissolution medium. The collected samples were analyzed using a UV spectrophotometer at 261 nm against a blank prepared in pH 6.8 buffer. The release studies were conducted in triplicate, and the average values were plotted against time.

Enteric coating of Dalfampridine core tablet

Coating carried out within R&D coater, where tablets of precise weights are introduced into a coating pan. The process continues until the desired weight gain, typically set at 5%, is achieved.

Preparation of Enteric coating solution

Mix equal amounts of IPA and acetone, stirring them with a magnetic stirrer until a vortex forms. Then, add Eudragit L100-55, PEG600, talc, and color concentrate to the vortex and stir for 25 minutes. Make sure there are no air bubbles. Finally, use this solution to coat 100 tablets according to the formula provided in Table No. 2.

Table 2: Formula for Preparation of 5%Enteric Coating Solution

Ingredients	Quantity (gm)
Eudragit L100-55	3.16
PEG 600	1.6
Talc	0.2
Color concentrate	0.01
IPA:Acetone	1:1

A 2^3 full factorial design is applied for the optimization of the coating parameters. Outlet temperature (X1), spray rate (X2), rotation of pan (X3) was taken as independent variable. The dependent variables selected are percentage weight gain and coating process efficiency (%) to find out effect of independent variables on dependent variable.

Table 3: Selection of levels for independent variables and coding of variable

Code value	Outlet temperature	Spray rate/ml	Rpm of pan
-1 (low)	50^0c	2 ml/min	8 rpm
+1(high)	70^0c	4ml/min	15 rpm

Table 4: Formulation Table for Coating Parameters by 2^3 Factorial design

Formulations code	Code value		
	X1	X2	X3
E1	-1	-1	-1
E2	-1	-1	+1
E3	-1	+1	-1
E4	-1	+1	+1
E5	+1	-1	-1
E6	+1	-1	+1
E7	+1	+1	-1
E8	+1	+1	+1

Table 5: 2^3 full factorial design layout for optimization of coating parameters

Formulation	Inlet Temp.	Spray Rate(ml/min)	Pan Rotation (rpm)
E1	50 ^{O}C	2 ml/ min	8
E2	50 ^{O}C	2ml/min	15
E3	50 ^{O}C	4ml/min	8
E4	50 ^{O}C	4ml/min	15
E5	70 ^{O}C	2ml/min	8
E6	70 ^{O}C	2ml/min	15
E7	70 ^{O}C	4ml/min	8
E8	70 ^{O}C	4ml/min	15

Evaluation of Enteric coated tablet for dependent factors [11, 12]:

Percent weight gain (%)

"Percent weight gain in coating" signifies the increase in tablets' weight post-coating application. It's calculated as a percentage of the tablets' initial weight before coating.

% wga = [(wta – wtb)wtb] ×100%

Where, wtb and wta are the total batch weights before and after coating, respectively.

Coating process efficiency

The efficiency of the coating process (CPE) was evaluated by comparing the actual percent weight gain to the theoretical percent. If there were a perfect transfer of coating to the tablets (100% theoretical), it would indicate no loss of coating material. The coating process efficiency was calculated using the following formula.

CPE = (%wga /%wgt) ×100%

Where wgt is the theoretical percent weight gain, which in this experiment was 5% in every coating trial, and wga is the actual percent weight gain

Evaluation of optimized Enteric coated tablet [13, 14]:

Hardness: The hardness of tablet was measured by Monsanto hardness tester. The hardness was measured in kg/cm^2. Ten tablets Were randomly picked from each formulation and the mean and standard deviation values were calculated

Friability: Tablet strength was tested by Roche Friabilator. Pre-weighed tablets were given 100 revolutions in 4 min and were dedusted. The percentage Weight loss was calculated by reweighing the Tablets.

Uniformity of weight: Randomly selected twenty tablets from the formulation were weighed individually and together on Electronic balance .The average weight was noted.

Drug content studies: The drug content in Tablets were determined by randomly choosing ten tablets from enteric coated Formulation and powdered using mortar & Pestle. A quantity equivalent to 10 mg of Dalfampridine. It was weighed and Dissolved in Phosphate buffer pH 6.8 (diluted if Necessary), then absorbance was taken on 261 Nm on (Shimadzu Corp., Japan) at wavelength 261 nm.

Swelling studies: Swelling of tablet excipient particles involves the absorption of a liquid increasing weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and binds to large molecules, breaking the hydrogen bond and resulting in the swelling of particles. The extent of swelling can be measured in terms of % of weight gain by the tablet.

$$\text{Swelling Index} = \frac{Wt - Wo}{Wo}$$

Where,Wt = Weight of tablet at time t

Wo = Weight of tablet before placing in the beaker

Disintegration time: Disintegration time was Determined using the disintegration apparatus in 0.1 N HCl for 2 h and then

in phosphate buffer pH 6.8 For 1 hour maintaining the temperature at 37±2°C .

***In-vitro* drug release:** USP dissolution apparatus type II was employed to study the in vitro drug release from optimize d formulation. The dissolution medium used was 900 ml of acidic buffer of pH 1.2 for 2 h and phosphate buffer of pH 6.8 for 1 hrs. The tablet was kept in to the basket. The temperature was maintained at 37 ± 0.5°C and the stirring rate was 100 rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV spectrophotometer at 261 nm (pH 1.2) and at 261 nm (pH 6.8) against a blank. The release studies were conducted in triplicate and the mean values were plotted versus time.

Kinetics of the optimized formulation [15]:

To study the *In-vitro* release kinetics of the optimized formulations of Dalfampridine Delayed release coated tablet, data obtained from dissolution study were plotted in various kinetic models i.e. Zero order kinetics, First order kinetics, Higuchi kinetics,Hixson and Crowell erosion kinetics and Korsmeyer – Peppas kinetics.

Accelerated Stability Studies [16]: The stability of the drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic, and toxicological specifications.

In the present study, an accelerated stability study was carried out at 40°C ± 2°C / 75 RH ± 5% for 1 month for the optimized formulation. The optimized formulation was analyzed for its physical appearance, In-vitro drug release study, and % Drug content.

RESULTS:

Fourier Transform Infrared Spectroscopy for Analysis of Drug and Physical Mixture:

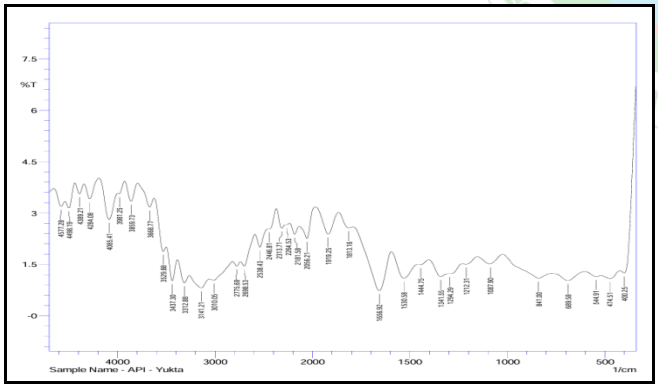

Figure 1: FTIR spectrum of Dalfampridine

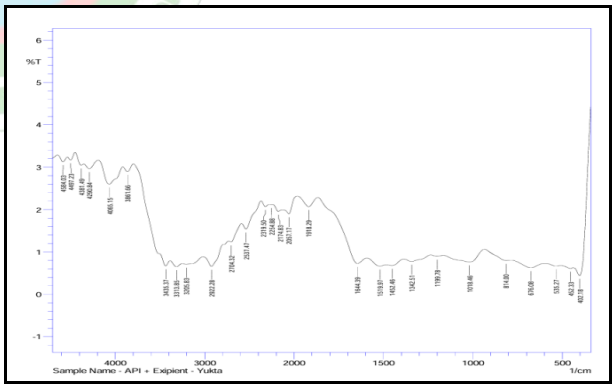

Figure 2: FTIR spectrum of Physical mixture

Pre-compression evaluation of factorial batches of Dalfampridine core tablet

Table 6: Pre-compression evaluation of core table

Formulation		Bulk density	Tapped density	Carr's index	Hausner's ratio
F1	32.15 ± 1.14	0.81 ± 0.5	0.925 ± 0.5	12.43 ± 0.4	1.14 ± 0.9

*n=3

Post-compression evaluations of Factorial batches of core tablets

Table 7: Post-compression evaluation of core tablet

Formulation	Weight	Hardness	Thickness	Friability	Disintegration	% Drug
F1	210 ± 0.2	4.39± 0.09	2.54 ± 0.15	0.34± 0.03	6.68 ± 0.47	98.23±0.06

*n=3

In-Vitro drug Release of core tablet

Table 8: *In-vitro* drug release of core tablet

% CDR	
Time (min)	***F1***
0	0
5	9.21±0.34
10	27.18 ± 0.64
15	48.75± 0.27
20	74.61± 0.71
30	86.72± 0.45
40	96.72± 0.32
50	-

*n=3

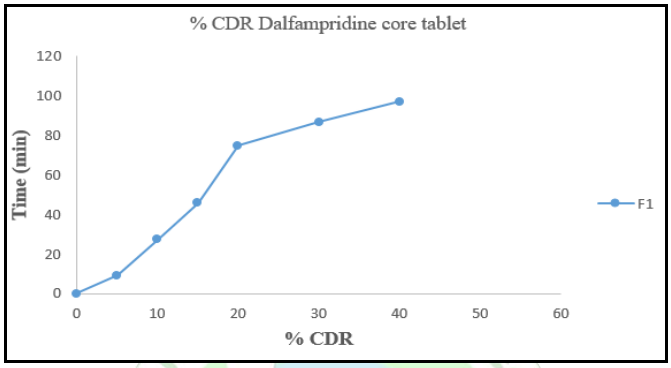

Figure: 3 In-vitro Drug Release for Dalfampridine core tablet (F1)

Evaluation of Enteric Coated Tablets

Table 9: Evaluation of Enteric Coated Tablet

Formulation	% Weight gain	Coating process efficiency %
E1	3.17± 0.34	63.4± 0.23
E2	4.1± 0.18	82± 0.11
E3	1.4± 0.24	28.5± 0.47
E4	1.49± 46	29.8± 0.16
E5	1.19± 51	23± 0.51
E6	0.87± 0.71	17.46± 25
E7	-	-
E8	-	-

*n=3

Evaluation of optimized Delayed Release Coated Tablet

Table 10: Result of optimized Delayed Release Coated Tablet

Formulation	Thickness	Hardness	Uniformity of weight	Friability	Drug content	Disintegration
E2	2.96±0.76	6.53±0.31	219±1.36	0.24±0.03	96.84±0.02	9.35±0.45

*n=3

Swelling studies

Table: 11 Swelling study of optimized E2 batch

Time (Hrs)	E2
0	0
1	11.43 ± 0.05
2	15.62 ± 0.4
3	48.85 ± 0.32
4	80.53 ± 0.16
5	96.71 ± 0.68

*n=3

In-Vitro drug Release of Optimized Dalfampridine Delayed Release Coated Tablets

Table 12: In-Vitro drug Release of Optimized E2 batch

Dissolution Media	Sampling Time	% Cumulative Drug Release
		E2
Simulated gastric fluid (0.1 N HCL)	0	0
	1 hrs	0
	2 hrs	0
Simulated pH 6.8	10 mins	9.45 ± 0.15
	15 mins	18.7 ± 0.48
	20 mins	45.46 ± 0.65
	30 mins	72.25 ± 0.52
	40 mins	84.23± 0.37
	60 mins	95.86 ± 0.76

*n=3

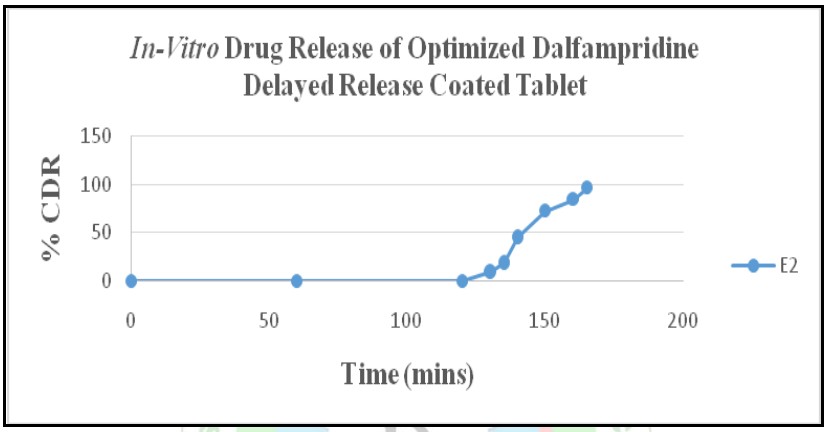

Figure 4: *In-Vitro* Drug Release of Dalfampridine Delayed Release Coated Tablet

Kinetics of Drug Release

Table 13: R^2 Values of various Kinetics Models of Optimized formulation (E2)

Sr. No	*Kinetic Models*	*Coefficient Determination (R^2)*
1	Zero order	0.9822
2	First order	0.9028
3	Higuchi	0.9121
4	Hixon-Crowell	0.9664
5	Kosmeyer-Peppas	-0.3052

Accelerated Stability Studies:

Table 14: Stability studies of optimized formulation (E2)

Sr. No	Parameters	Condition: 40 ± 2^{0}C/75 ± 5% RH	
		Initial	After 1 month
1	Physical appearance	Orange, uniformed coating	Orange, uniformed coating
2	% Drug content	96.84±0.02	96.80 ± 0.03
3	In-vitro Drug Release	95.86 ± 0.76	95.80 ± 0.52

*n=3

DISCUSSION:

The core tablet of dalfampridine was formulated using wet granulation with excipients including MCC PH 101, lactose monohydrate, SSG, PVK-30, MCC PH 102, calcium carbonate, talc, magnesium stearate, and talc. FTIR studies confirmed no interactions between the drug and excipients. Pre-compression studies showed satisfactory flow properties and compressibility. Post-compression evaluation revealed uniform weight, hardness, thickness, friability, and drug content and found to be disintegrated within 6.68 ± 0.47. In vitro dissolution showed 96.72% drug release within 40 minutes. The core tablets were further coated with 5% enteric-coated solution using a 2^3 full factorial design to optimize coating parameters. The coating significantly affected weight gain and coating process efficiency. Formulation E2 exhibited the highest weight gain (4.1%) and coating process efficiency (82%), indicating optimal parameters. The optimized delayed-release coated tablets showed uniformity in thickness, increased hardness due to the protective enteric coating, uniform weight, low friability, and consistent drug content. They remained intact in simulated gastric fluid and disintegrated appropriately in pH 6.8 buffer, demonstrating desired delayed release behavior. The extent of swelling for

the optimized formulation was 96.71% in 5 hours, indicating controlled drug release. In vitro studies confirmed controlled release in simulated gastric and intestinal fluids. Zero-order kinetics best described the release mechanism, indicating controlled release over the required period.Overall, the formulated delayed-release coated tablets of dalfampridine demonstrated satisfactory physical and chemical properties, controlled drug release, and predictable release kinetics. From the accelerated stability studies were performed for optimized E2 formulation. No color or surface changes were observed in the delayed-release coated tablet after storage at 40 ± 2°C/75 ± 5% RH for 1 month. Negligible changes occurred in % drug content and in vitro drug release. The tablet remained stable and suitable for administration, indicating no significant stability issues.

CONCLUSION

The research successfully formulated delayed release coated tablets of Dalfampridine for multiple sclerosis treatment. Dalfampridine enhances nerve impulse transmission disrupted by multiple sclerosis. Due to its stability dependency on pH, Dalfampridine requires delivery into the intestine, hence the formulation of delayed release coated tablets using enteric coating polymers.

The study concluded that a 5% enteric coating solution containing Eudragit L100-55 effectively protected Dalfampridine from gastric pH, releasing it in intestinal pH. Formulation E2, coated under specific conditions, was identified as optimal. Developing Dalfampridine as an enteric coated tablet resolves stability issues in the stomach and ensures drug release in the intestine, overcoming degradation by gastric enzymes and acidic stomach environments.

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