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Design and development of dalfampridine extended release tablets

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ABSTRACT

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

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

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes. A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimized. A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time. The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms. Oral route still remains the most popular for drug administration by virtue of its convenience to the patient. A sizable portion of orally administered dosage forms, so called conventional, are designed to achieve maximal drug bioavailability by maximizing the rate and extent of absorption. While such dosage forms have been useful, frequent daily administration is necessary, particularly when the drug has a short biological half life. This may result in wide fluctuation in peak and trough steady-state drug levels, which is undesirable for drugs with marginal therapeutic indices. Moreover, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Fortunately, these short comings have been circumvented with the introduction of controlled release dosage forms. These dosage forms are capable of controlling the rate of drug delivery, leading to more sustained drug levels and hence therapeutic action. Hydrophillic matrix systems are among the most commonly used means for oral controlled drug delivery as they can

reproduce a desirable drug profile and are cost effective. The primary mechanism of drug release from hydrophilic matrices occurs when the polymer swells on contact with the aqueous medium to form a gel layer on the surface of the system. The drug then releases by dissolution, diffusion and/or erosion.

MATERIALS AND METHODS

Dalfampridine Provided by SURA LABS, Dilsukhnagar, Hyderabad. Carbapol 934 from Arvind Remedies Ltd, Tamil nadu, India. HPMC K15 from SD Fine Chem. Ltd. (Mumbai, India). Sodium CMC from Yarrow chemicals (Mumbai, India). Microcrystalline cellulose from Chemdyes Corporation (Ahmedabad, India). Magnesium stearate from Shakti Chemicals (Mehsana, India). Aerosil from Kerry laboratories.

Methods

Characterization of Dalfampridine

Organoleptic properties

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

Determination of Dalfampridine Melting point

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

Determination of Dalfampridine Solubility

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

Analytical method development

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.

Determination of Calibration Curve

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

Preformulation parameters

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

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Dalfampridine. Total weight of the tablet was considered as 120mg.

Procedure:

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

Table 1: Formulation composition for tablets

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

All the quantities were in mg

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 2: 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 10 tablets
W2 = Weight of the 10 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, p H 6.8 Phosphate buffer
RPM -- 50
Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature -- 37°c $\pm$ 0.5°c

Procedure

900ml 0f 0.1 N 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 $\pm$ 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.

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 DISCUSSIONS

Organoleptic properties

Table 3: Organoleptic properties

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

Solubility studies

Table 4: Solubility studies of drug in different solvents

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

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

Analytical Method

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

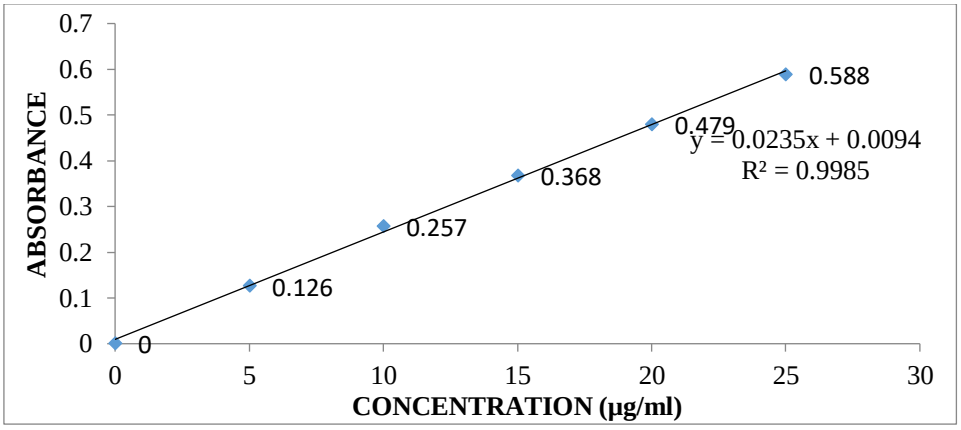

Fig 1: Standard graph of Dalfampridine in 0.1N HCl

Preformulation parameters of powder blend

Table 5: Pre-formulation parameters of Core blend

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

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.382±0.032 to 0.536±0.05 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.462±0.015 to 0.596±0.02 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 17 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.20 indicating the powder has good flow properties.

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.

Table 6: *In vitro* quality control parameters for tablets

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

In Vitro Drug Release Studies

Table 7: Dissolution Data of Dalfampridine Tablets

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

Application of Release Rate Kinetics to Dissolution Data

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

Table 8: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
20.1	0.5	0.707	1.303	-0.301	1.903	40.200	0.0498	-0.697	79.9	4.642	4.307	0.335

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

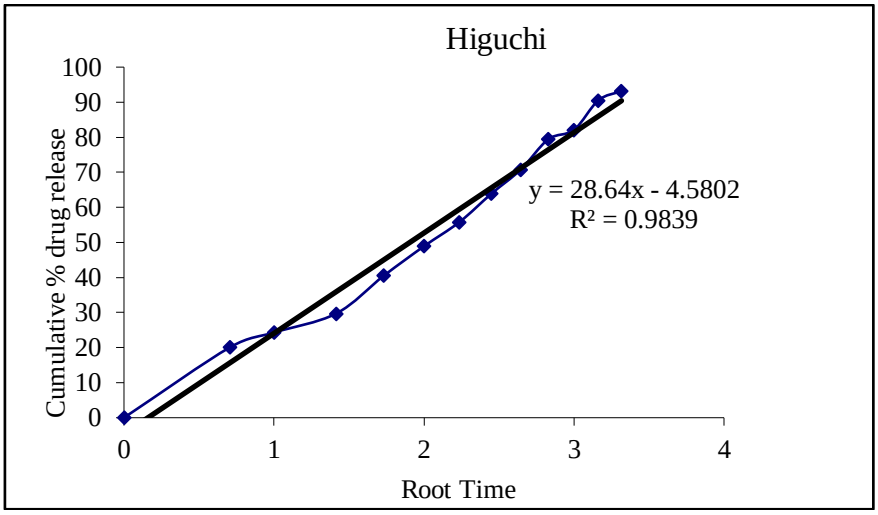

Fig 2 : Higuchi release kinetics graph

Drug – Excipient compatibility studies
Fourier Transform-Infrared Spectroscopy

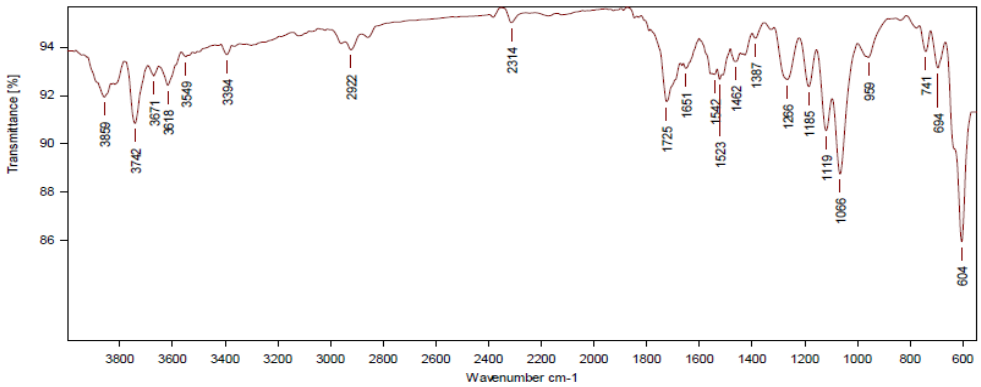

Fig 3: FT-TR Spectrum of Dalfampridine pure drug

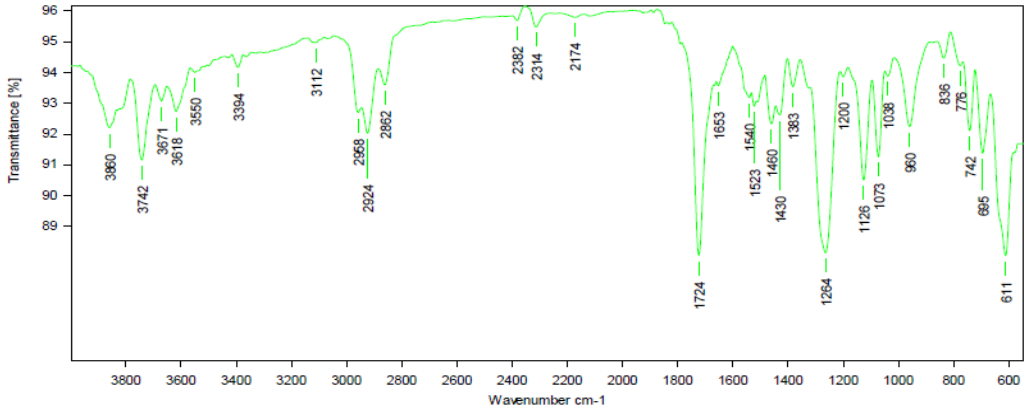

Fig 4: FT-IR Spectrum of Optimised Formulation

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

CONCLUSION

The present research work was successful in improving the efficacy of Dalfampridine oral therapy as the drug release was extended for 12 hours thus reducing dosing frequency thereby improving patient compliance. The extended release matrix tablets of Dalfampridine were prepared by direct compression method. FTIR spectra indicated the absence of probable chemical interaction between the drug and polymers. Dalfampridine tablets were formulated with Carbapol 934, HPMC K15 and Sodium CMC. Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose, bulk density, tapped density, compressibility index and hausner ratio powder has good flow properties. Post compression studies like Weight variation, Hardness, thickness, friability, drug content was determined within IP Formulations under study The FTIR spectra of extended release tablets and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

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

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