ASSESSMENT OF SELF-EXTRACTED CELLULOSE FROM *ORYZA SATIVA* FOR DESIGN OF CONTROLLED DRUG DELIVERY SYSTEM OF DALFAMPRIDINE

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ABSTRACT

Objectives: The main objective of the present work includes extraction of cellulose from *Oryza sativa* (OS), characterization of cellulose, development of controlled release tablet dalfampridine using cellulose of OS, and *in vitro* evaluation.

Methods: Dry powdered OS husk sample was extracted with a mixture of hexane and methanol (2:1, v/v) using soxhlation method and was characterized by solubility, melting point determination, differential scanning calorimetry (DSC), and Fourier-transform infrared (FTIR) analysis. Compatibility between dalfampridine and the mixture of cellulose with dalfampridine was confirmed by FTIR and DSC analysis. Then, controlled drug delivery system of dalfampridine were prepared as directly compressed tablets using various compositions containing OS cellulose, hydroxypropyl methylcellulose (HPMC), dicalcium phosphate, and magnesium stearate (8 nos. F1 to f8) and were evaluated.

Results: Cellulose was extracted from OS extract to possess its ideal characteristics. Dalfampridine and its mixture with cellulose were compatible according to FTIR and DSC analysis. Directly compressed tablets made with 10 mg of dalfampridine and OS cellulose, HPMC, dicalcium phosphate, and magnesium stearate evidenced prolonged and controlled drug delivery of dalfampridine for 12 h. Formulation made with OS cellulose 250 mg, HPMC 20 mg, dicalcium phosphate 40 mg, and magnesium stearate 5 mg was ideal without burst release.

Conclusion: Cellulose extracted from OS is used successfully for the production of directly compressed tablets of dalfampridine to elicit optimum characteristics including controlled drug delivery for 12 h.

Keywords: Cellulose from *Oryza sativa*, Soxhlation method, Fourier-transform infrared, Compatibility, Dalfampridine, Controlled delivery.

INTRODUCTION

Synthetic polymers and celluloses are generally utilized for the design of controlled or novel drug delivery systems. There are chances of toxic effects produced from synthetic polymers or celluloses. At this juncture, natural polymers reported with less toxicity and high biodegradability can be taken as a choice for the design of formulations of drugs. Cellulose is one of the polymers used in biomedical applications. It was reported that all-cellulose composites possess an intriguing combination of high strength and biodegradability [1].

Therefore, in the present research work, we have exploited cellulose from *Oryza sativa* (OS) for the design of drug for the treatment of multiple sclerosis (MS) as there are no reports for utilization of this cellulose in the development of drug delivery systems. Formulations.
OS (RH) is one of the major agricultural residues generated as a by-product during the rice milling process. According to Jackson, OS consists of 33% cellulose, 26% hemicellulose, and 7% lignin. Cellulose is a polysaccharide made of d-glucose connected through -1,4-glycosidic bonds and is a promising raw material for producing important chemicals, including cellulosic ethanol, hydrocarbons, and starting materials to produce polymers [2].

At present, the model drug selected is dalfampridine which is recently approved by the FDA in January 2010 for symptomatic treatment of MS patients with a specific indication for improvement in walking. In the past, 4-aminopyridine has been used as an experimental agent which presumably enhances nerve conduction of demyelinated axons through its effects on potassium channels for the treatment of fatigue in MS.

Moreover, now, dalfampridine is used successfully. Hence, it is aimed to design in the form of controlled-release tablets.

The work involves four objectives such as extraction of cellulose from OS, characterization of cellulose, development of controlled release tablet dalfampridine, and *in vitro* evaluation.

MATERIALS AND METHODS

Materials
Dalfampridine was purchased from Simpson Pharmacy, Mumbai. n-Hexane, methanol, hydrogen peroxide, liquid nitrogen, KBr, hydroxypropyl methylcellulose (HPMC), dicalcium phosphate, and magnesium stearate were purchased from SD Fine Chemicals Ltd.

Methods

Isolation of cellulose from OS
Dry powdered OS husk sample was extracted with a mixture of hexane and methanol (2:1, v/v) using soxhlation method for 10 h for removal of oil/wax, etc. Then, the delignification is done a follow-up with using two-step processes usually. At first, the extractive-free OS husk (10 g) was soaked in 300 ml different alkalis (5%, w/v) with a ratio of liquor to the material (30:1) and heated to 80°C for 5 h. Then, the collected slurry can cool. Then, it is treated with 10% H_2SO_4 to neutralize the solution. Then, it adjusts to 3–4 of pH value at 50°C [3,4].

After extraction, residual biomass was separated by filtration through Buchner funnel connected to a vacuum pump. The residual biomass was undertaken for bleaching treatment using 2% H_2O_2 solution with adjusting pH value 9 and the ratio of liquor to the materials (30:1) and

stirred for 5 h at room temperature [5]. Then, the biomass was cleaned with distilled water specifically for many times to attain chemical free product including H_2O_2. The collected samples were filtered and, in an oven, sieved through 40 mesh screen and stored in the airtight container to prevent oxidation for the future use.

Characterization of cellulose

Extracted cellulose was characterized by solubility, melting point determination, differential scanning calorimetry (DSC), and Fourier-transform infrared (FTIR) analysis.

Solubility of cellulose

Pretreatment of cellulose: Ethanol acid pre-treatment
In a water bath, add several liters of cold distilled water to remove unnecessary chemicals and for cooling. Ethanol was pre-heated to 60°C. Then, when thermal equilibration was reached, hydrochloric acid (37wt.%) was added. 16 g of cellulose pulp was added to ensure homogeneous dispersion of the cellulose in the ethanol-acid medium, especially under continuous stirring that the performed reaction was stopped after 30 min. Then, to remove any residuals of ethanol and HCl completely, the collected biomass was filtered and washed with distilled water [6].
Solubility:
As cellulose is insoluble in water, a freshly prepared solvent system ($NaOH/H_2O$) pre-cooled to −1°C was tried test solubility [7]. The solution was kept in a freezer at 0°C. Then, the cellulose was added to the solvent in a cooled container refrigerated through circulation

of a water-polyethylene glycol solution. Each solution was stirred for 20 min at 500 rpm. The temperature was kept at −1°C during the first couple of minutes and then increased to +4°C.

Melting point

Melting point of prepared cellulose was determined by open capillary tube method [6]. The capillary tube was closed at one end by fusion and was filled with the drug on the other end by repeated tapings. The capillary tube was placed on apparatus. The instrument was set to automatically increase the temperature of the heating bath at a rate of 1°C per minute. The temperature at which the drug started melting is recorded. This was performed thrice, and their average was taken as a result.

DSC

DSC analysis was carried out for the cellulose of OS using DSC (Mettler, Toledo, Switzerland) and scanned for a range of 10°C/min under static air atmosphere.

FTIR

FTIR spectrum of extracted cellulose was obtained using IR spectrophotometer (Bruker, JAPAN) by KBr pressed pellet technique. The scanning range was 4000–400 cm⁻¹ and the resolution was 1 cm⁻¹.

## Drug-excipient interaction study of dalfampridine with cellulose of OS

As the present work was to develop controlled drug delivery system of dalfampridine using the self-extracted cellulose of OS, drug-

Table 1: Composition of dalfampridine controlled-release tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Dalfampridine	10	10	10	10	10	10	10	10
RH cellulose	150	125	200	200	_	250	300	_
HPMC	29	89	30	_	105	20	_	120
Dicalcium phosphate	131	106	80	110	205	40	10	190
Magnesium stearate	5	5	5	5	5	5	5	5
Total	325	325	325	325	325	325	325	325
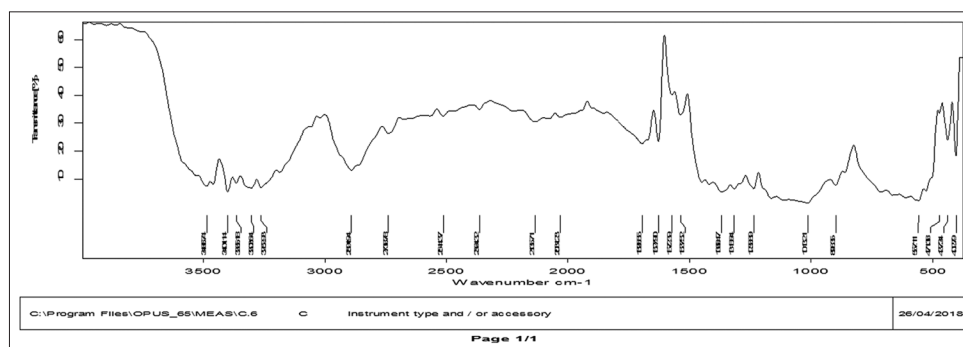
Fig. 1: The alkali (liquid ammonia)-treated *Oryza sativa* cellulose Fourier-transform infrared
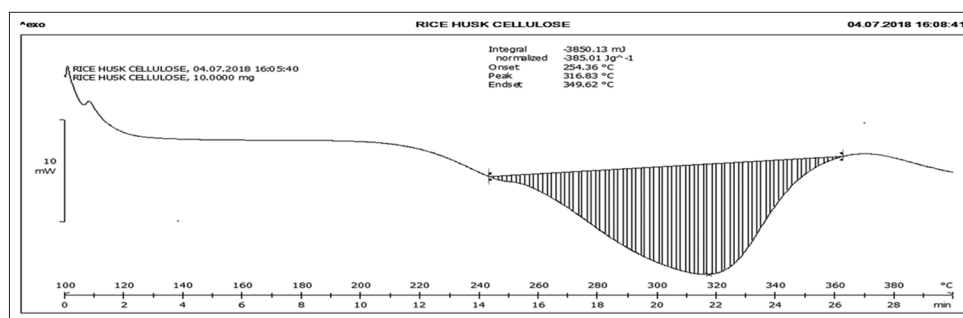
Fig. 2: Differential scanning calorimetry of *Oryza sativa* cellulose

Table 2: *Oryza sativa* cellulose functional group identification

Functional groups	Reference wave number	Observed wave number
OH Stretching	3990	3386
C=O Stitching	1751	1896
C-H Bending	1369	1315.84
C-O Stretching	1220	1236.89
C-O-C Pyranose ring	1384	1388.47
β-glycoside linkage	910	858.35
O-H Bending	1384	1388.47

Table 3: IR absorption peaks of pure dalfampridine and its mixture with *Oryza sativa* cellulose

Functional group	Reference wave number (cm^{-1})	Wave number (cm^{-1})
NH-Stretching	3437.37	3304.56
CH (aromatic) stretching	3031.66	3061.13
C=N	1648.46	1648.76
C=C	1504.49	1505.20
CH-Bending	1433.83	1433.43

excipient interaction studies were carried out to assess compatibility between them. Hence, DSC thermogram and FTIR spectrum were taken for the mixture of dalfampridine and cellulose of OS and were compared.

Preparation of dalfampridine tablets
Controlled release tablets containing 10 mg of dalfampridine were prepared using self-extracted OS cellulose by direct compression [6]. Eight formulations, F1–F8, were tried and their composition is given in Table 1. The ingredients necessary for the preparation of 100 were accurately weighed and mixed in a polyethylene bag. Then, the material was sieved through #40 and determined for micromeritic properties. Lubricated blend was then compressed into tablets using oval-shaped B tooling punches using 13 KP pressure to get 325 mg in 10 station rotary compression machine (Rimek, Mumbai).

Evaluation of pre-compression characteristics
Pre-compression parameters such as angle of repose, bulk density, and tapped density were determined for the blend of all the formulations to assess free flow characteristics [6]. Then, the prepared compressed tablets were evaluated by different tests.

The angle of repose
The angle of repose "θ" is determined by fixed funnel and free-standing cone method using the following equation:

$$\theta = \tan^{-1}(h/r)$$

Where θ = angle of repose, h=height of the pile, and r = radius of the pile.

Carr's compressibility index and Hausner's Ratio
Bulk density was measured by filling the powder in measuring cylinder and the tapped density was determined by tapping method [6]. Compressibility index and Hausner's ratio are calculated using the following equations:
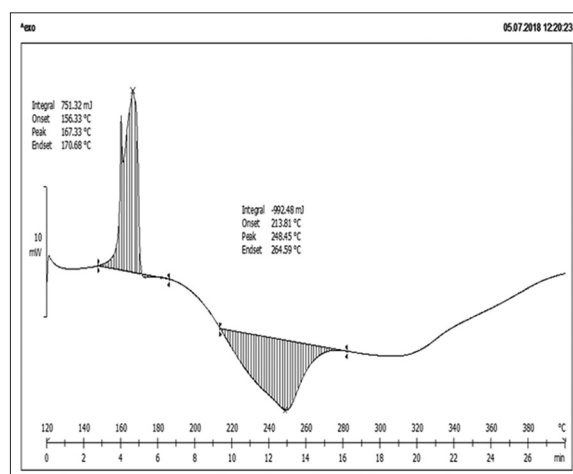
$$\text{Carr's compressibility Index} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio is calculated as the simple difference between the tapped density and bulk density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{bulk density}}$$
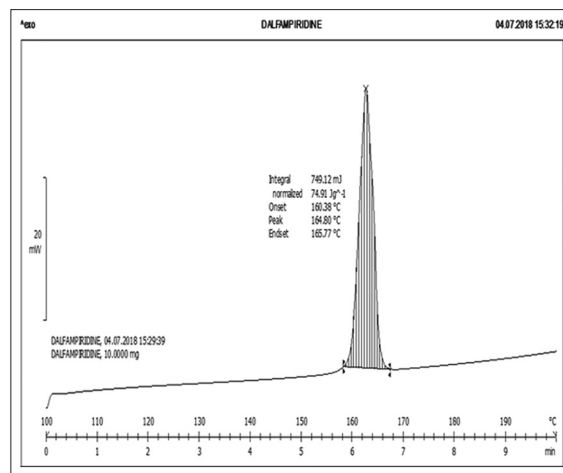
Fig. 3: Differential scanning calorimetry of dalfampridine

Fig. 4: Differential scanning calorimetry of *Oryza sativa* cellulose and dalfampridine

As all powder blends of all formulations evidenced good flow properties, tablets were compressed for all F1–F8.

Evaluation of compressed tablets
The compressed tablets were evaluated by thickness, hardness, friability, drug content uniformity, and *in vitro* drug release studies.

Thickness was determined by Vernier caliper. Hardness was tested using Monsanto hardness tester, and friability test was carried out using Roche Friability Apparatus (Veego Instruments Ltd., India).

Drug content uniformity
Drug content estimation was carried out by collecting ten tablets from each batch at random [8]. The tablets were powdered, and the fine powder (equivalent to 10 mg of dalfampridine) was transferred to a 100 ml volumetric flask and dissolved in water. The solutions were made up to the volume, filtered, and suitably diluted, and drug contents were estimated using UV-visible spectrophotometer (Systronics, India) at 262 nm.

Disintegration test
The disintegration time of tablets was determined for 6 tablets using Thermionic Tablet Disintegration Test Apparatus [8]. pH 7.4 phosphate buffer maintained at 37±0.5°C in isothermal water bath was used as a medium.

***In vitro* drug release studies of prepared tablets**
In vitro dissolution release studies were carried out for the prepared tablets of flutamide and glimepiride in comparison with the commercial
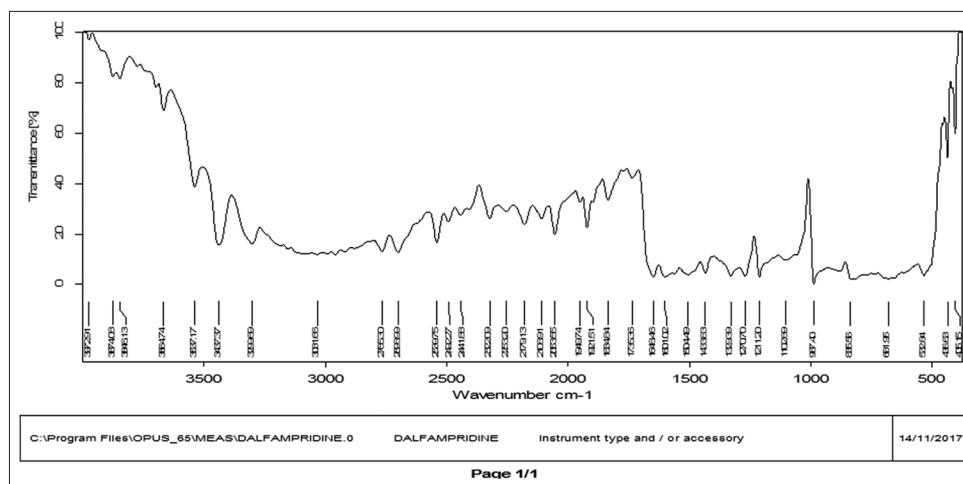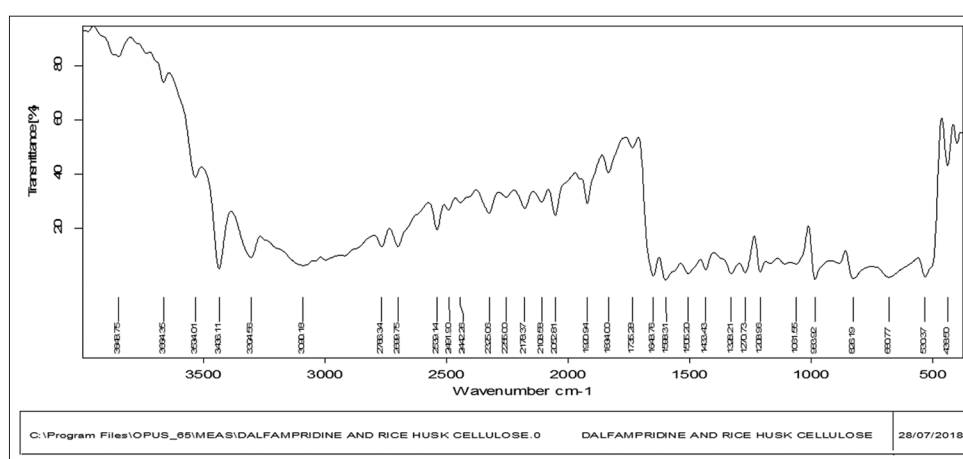
Fig.5: Fourier-transform infrared of dalfampridine

Fig. 6: The alkali (liquid ammonia)-treated *Oryza sativa* cellulose Fourier-transform infrared

Table 4: Pre-compression parameters of formulation, F1–F8 (n=3±SD)

Formulation code	Bulk Density (g/mL)	Tapped Density (g/mL)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.80±0.13	0.942±0.2	15.07±1.2	1.14±0.01	25.12±0.94
F2	0.78±1.0	0.931±0.6	16.21±0.2	1.19±0.19	25.86±0.35
F3	0.81±0.7	0.932±0.1	13.09±0.3	1.15±0.32	25.21±0.58
F4	0.80±0.2	0.936±0.8	14.52±0.4	1.17±1.09	25.23±0.21
F5	0.78±0.9	0.925±0.5	15.06±0.7	1.18±0.07	25.21±0.98
F6	0.80±0.2	0.931±0.9	14.07±0.2	1.16±0.03	26.45±0.43
F7	0.82±0.3	0.928±0.1	11.63±0.6	1.13±0.05	26.23±0.74
F8	0.80±1.4	0.927±0.3	13.70±0.3	1.15±0.08	25.88±0.97

Table 5: Evaluation parameters of formulation, F1–F8 (n=3±SD)

Formulation Code	Hardness in (Kg/Cm²) (n=3)	Friability % (n=6)	Thickness (mm) (n=3)	Disintegration time (min) (n=6)	% drug content (n=10)
F1	7.94±0.12	0.405±0.40	4.231±0.01	7±0.3	87±0.02
F2	7.84±0.86	0.405±0.40	4.233±0.01	6.56±0.2	90±0.05
F3	8.01±0.14	0.420±0.07	4.248±0.02	6.48±0.2	94±0.09
F4	6.10±0.11	0.012±0.10	4.244±0.01	7.52±0.3	95±0.03
F5	7.41±0.14	0.015±0.01	4.256±0.02	7.45±0.3	97±0.06
F6	8.14±0.29	0.007±0.06	4.246±0.01	7.80±0.1	96±0.07
F7	4.25±0.10	0.422±0.52	4.234±0.01	8.50±0.1	94±0.02
F8	5.10±0.05	0.006±0.04	4.248±0.01	8.41±0.3	92±0.07

tablets of both the drugs [9]. The test was carried out using USP XXI Dissolution Testing Apparatus Type II, (Electrolab, India) using 900 ml of pH 6.8 phosphate buffer maintained at 37±0.5°C as medium. Stirring speed was maintained at 50 rpm. Aliquot samples were withdrawn at

pre-determined time intervals and filtered through 0.45 μm Millipore filter, suitably diluted wherever necessary, and were analyzed for the drug content by UV-visible spectrophotometer (Systronics, India). The volume withdrawn at each time interval was replaced with fresh dissolution medium maintained at the same temperature. Each study was performed in triplicate and mean values are reported.

Assessment of release kinetics of dalfampridine tablets

Rate and mechanism of drug release from matrix tablets were assessed by fitting the data into zero order kinetics ($Q=K_o t$), first-order kinetics ($\log Q=\log Q_0+K_1 t/2.303$), Higuchi's model ($Q=KH t^{1/2}$), and Korsmeyer–Peppas model [10] ($F=(Mt/M)=K t_n$).

RESULTS AND DISCUSSION

Characterization of cellulose

Solubility

Prepared cellulose from OSO was completely soluble in a selected solvent system ($NaOH/H_2O$) pre-cooled to −1°C. This supported the solubility characteristics of celluloses reported in literature [7].

FTIR

FTIR spectrum of OS cellulose is shown in Fig. 1. The absorption peaks are shown in Table 2. As revealed, OH- stretching is at 3386, C=O stretching was observed at 1896, CH-bending was observed at 1315.84, C-O stretching was observed at 1236.89, C-O-C Pyranose ring was observed at 1388.47, and β-glycoside linkage was observed at 888.36. All these values are coinciding with the values of those groups reported for cellulose in the literature [11,3].

Melting point

Melting point observed for the cellulose of OS is 456°C the value which is closer to value reported in literature (467°C) [12].

DSC of OS cellulose

DSC thermogram of cellulose of OS is presented in Fig. 2. It is observed that the melting point is present at 316.83°C. This value is coinciding with the reported range of melting point (315–400°C) for cellulose materials. Hence, it is concluded that the extraction procedure utilized in the present work is suitable to produce cellulose with optimum characteristics to be used in drug development.

Drug-excipient interaction study of dalfampridine with cellulose of OS

DSC thermogram of dalfampridine as presented in Fig. 3 showed a melting peak at 164.80°C, whereas its mixture with dalfampridine with cellulose showed melting peak at 167°C (Fig. 4). This slight modification is ignored and cosidered as incopamatibility.

The FTIR spectrum of dalfampridine and its mixture with cellulose and drug is shown in Fig. 5 and Fig. 6, respectively. Absorption peaks of both are shown in Table 3 for easy comparison. Dalfampridine peaks, NH-stretch at 3437.37, CH-stretch (aromatic) at 3031.66, C=N bond at 1648.46, C=C bond 1504.49, and CH-bending at 1433.83 are not modified appreciably in Fig. 6. Hence, it is considered that there is no incompatibility dalfampridine and OS cellulose mixture [13].

After assessing compatibility between dalfampridine and cellulose of OS, directly compressed tablets of dalfampridine were prepared (8 nos. F1 to F8).

Before compression, pre-compression parameters of blends were assessed and are shown in Table 4. Compressibility index and Hausner's ratio were in the range of 11.63%–16.21% and 1.13–1.19, respectively. The angle of repose between 25.12±0.94 and 26.45±0.43 indicted good flow properties of all prepared formulations, F1–F8.

Hence, all formulations were compressed directly and evaluated. Results of various parameters of F1 to F8 are given in Table 5. Post-compression parameters of prepared directly compressed tablet

Table 6: Dissolution profiles of formulations, F1–F8

Time (h)	% Cumulative Drug Release (n=3 ± SD)							
	F1	F2	F3	F4	F5	F6	F7	F8
30 min	19±0.1	10±0.3	12±0.1	18±0.3	23±0.2	15±0.3	17±0.1	24±0.2
45 min	23±0.2	22±0.2	29±0.1	26±0.2	26±0.1	21±0.3	22±0.1	29±0.1
1	34±0.1	38±0.2	43±0.1	36±1.2	38±0.1	29±0.7	36±0.1	32±0.1
2	38±1.2	38±0.5	55±0.4	40±1.4	40±0.3	29±1.2	36±0.2	38±0.7
3	38±0.3	44±0.8	60±0.8	43±0.8	46±0.4	35±0.2	38±0.3	40±1.2
4	40±0.3	45±0.7	61±0.6	46±0.9	46±0.8	56±0.3	38±0.1	45±0.8
5	46±0.7	45±0.1	63±0.7	48±0.6	46±0.7	63±0.2	40±0.3	56±2.1
6	55±0.6	48±0.1	64±1.2	48±0.1	46±0.1	69±0.5	46±0.8	64±0.8
7	68±1.2	48±0.4	66±1.4	55±0.2	54±0.1	70±0.7	50±0.7	66±0.6
8	76±0.9	51±0.3	70±0.6	66±0.3	65±0.2	74±0.3	55±0.6	70±0.4
9	88±1.2	66±0.3	74±0.8	77±0.3	78±0.3	74±0.3	68±1.2	72±0.2
10	90±1.4	82±0.7	86±1.2	79±0.6	80±0.7	74±0.4	78±1.4	84±0.1
11	95±1.3	89±0.8	88±1.3	85±0.8	85±0.3	87±0.4	78±1.2	88±0.1
12	95±0.1	94±0.2	90±0.1	94±0.1	94±0.2	96±0.5	83±0.8	95±0.2

Table 7: Model independent and dependent parameters of dissolution data

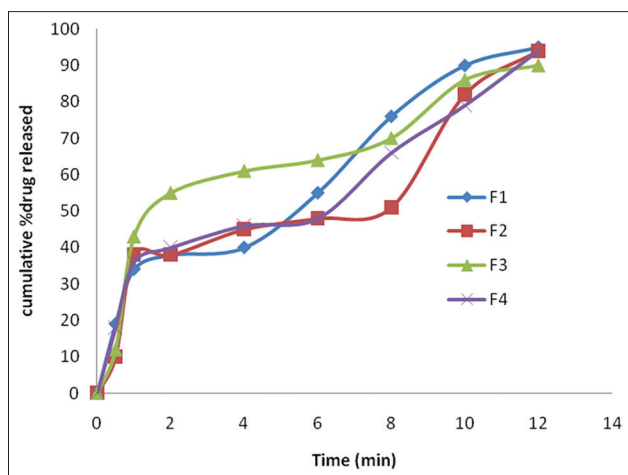| Formulation code	Zero-order R^2 value	First-order R^2 value	Higuchi R^2 value	Korsmeyer	
				R^2	N
F1	0.964	0.905	0.932	0.739	1.36
F2	0.862	0.771	0.830	0.463	1.31
F3	0.812	0.918	0.880	0.417	1.43
F4	0.943	0.811	0.909	0.657	1.38
F5	0.935	0.804	0.879	0.694	1.43
F6	0.925	0.824	0.960	0.752	1.28
F7	0.918	0.876	0.872	0.614	1.36
F8	0.989	0.886	0.970	0.848	1.40

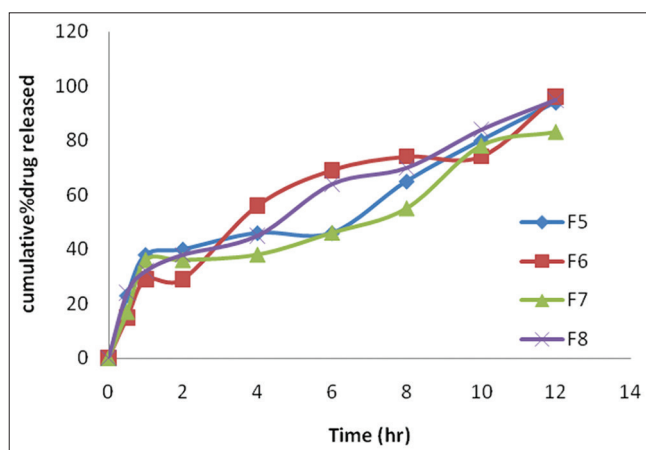**Fig. 7: Percentage drug release profiles of formulations, F1–F4**

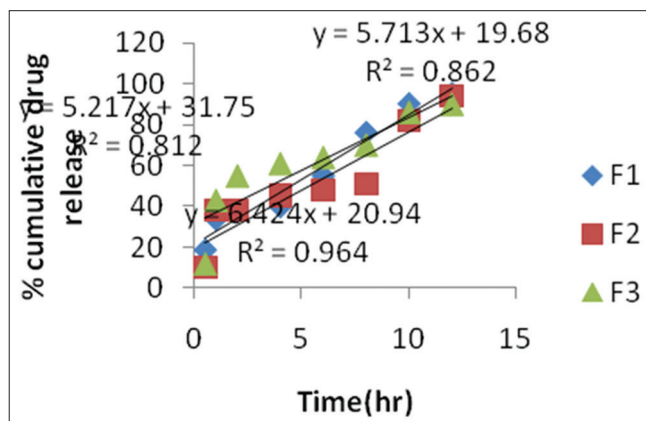**Fig. 8: Percentage drug release profiles of formulations, F5–F8**
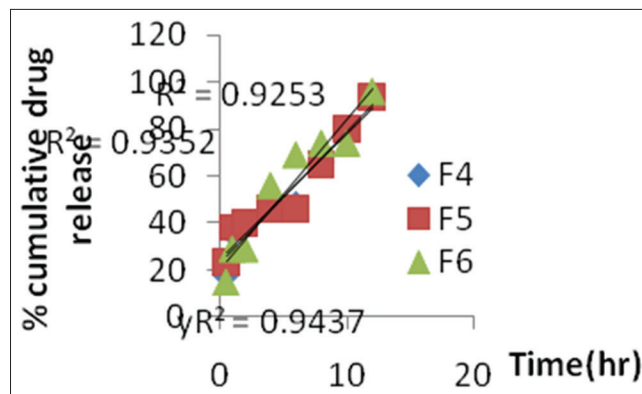

Fig. 9: Zero order for F1–F3
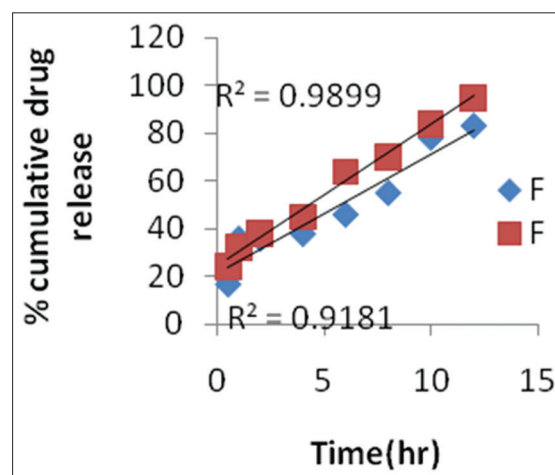

Fig. 10: Zero order for F4–F6
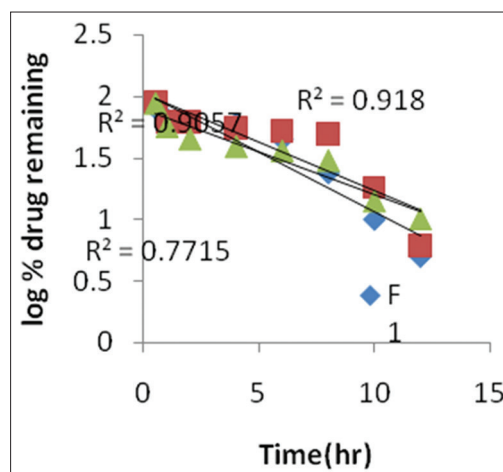

Fig. 11: Zero order for F7–F8

Fig. 12: First order for F1–F3

formulations, F1–F8, of dalfampridine are given in Table 14. Weight variation values are in the range of 0.03–0.09%. Hardness is in between 5.10 and 8.14 kg/cm². Thicknesses are from 4.231 mm to 4.256 mm. Friability is in the acceptable values of 0.007–0.422%. Disintegration time obtained is in a reasonable range of 6.48–8.50 min, and drug content is in 87–97%. Hence, these results indicated that all the parameters of prepared formulations, F1–F8, are in official limits.

***In vitro* drug release studies of prepared tablets**
In vitro drug release data as shown in Table 6 and Figs. 7 and 8 clearly indicate prolonged and controlled drug delivery of dalfampridine for 12 h.

However, there is a ideal controlled release from F6 without exhibiting burst release (≥31%) [14] within 1 h. Hence, from these studies, F6 is considered as best formulation assessed for release kinetics.

Assessment of release kinetics of dalfampridine tablets
Zero order, first order, Higuchi, and Korsmeyer plots are shown in Figs. 9-20 and the corresponding "r" values are in given in Table 7. "r" values closer unity in case of zero-order and Higuchi plots indicate that the release kinetics of dalfampridine from prepared tablets is followed in zero-order and by mechanism of diffusion.
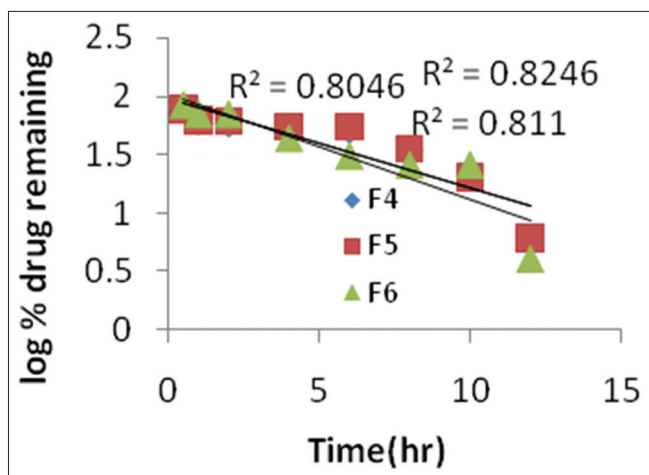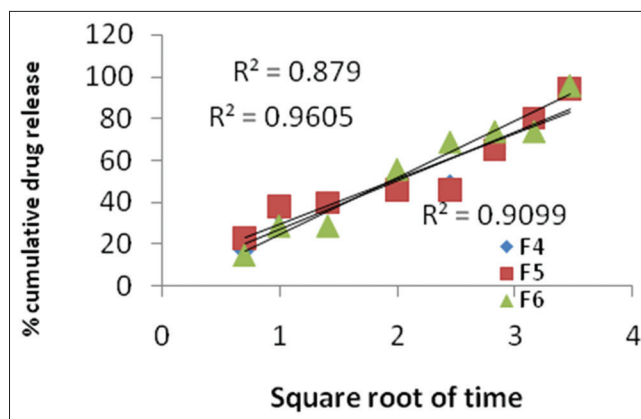
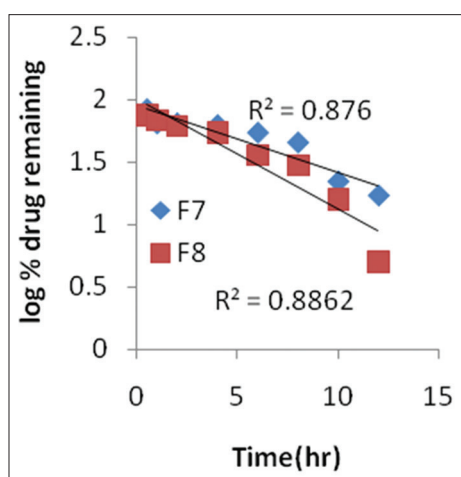**Fig. 13: First order for F4–F6**

Fig. 14: First order for F7 and F8

Fig. 15: Higuchi model for F1–F3
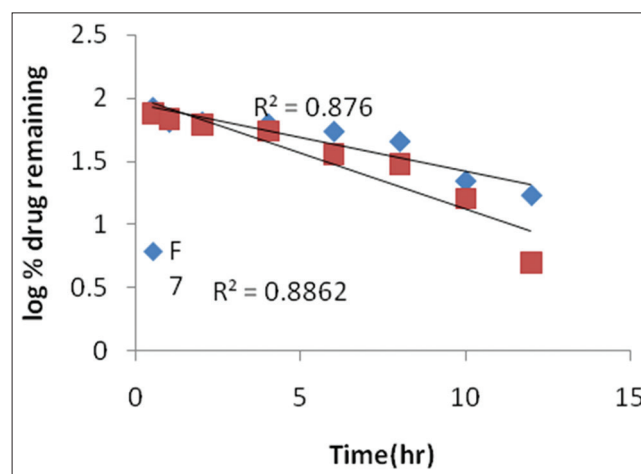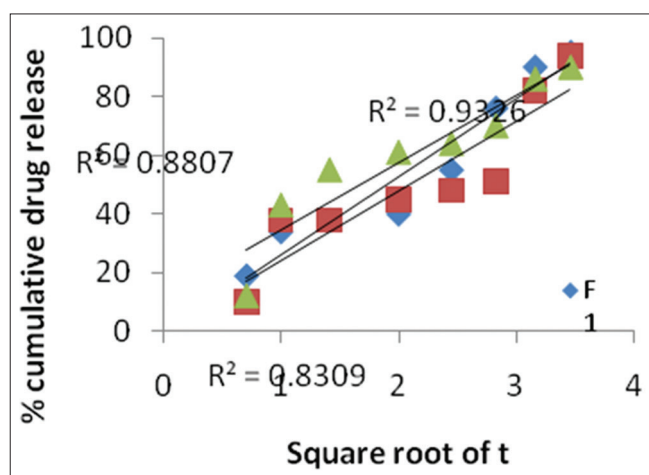

Fig. 16: Higuchi model for F4–F6

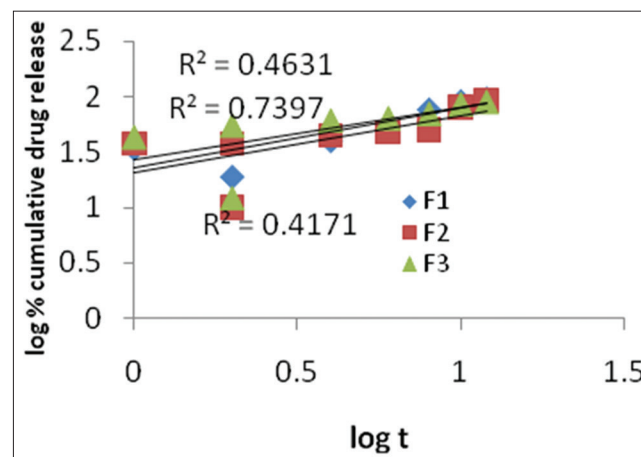**Fig. 17: Higuchi model for F7– F8**

Fig. 18: Korsmeyer model for F1–F3

CONCLUSION

"Hence from these studies, it is concluded that cellulose of OS can be used successfully for the production of directly compressed tablets of dalfampridine to elicit optimum characteristics including controlled drug delivery for 12 h."

AUTHORS' CONTRIBUTIONS

Jeevanajyothi B has designed the plan of present work and responsible for this novel work and preparation of the manuscript. Mounika has done the experiments involved in the research.
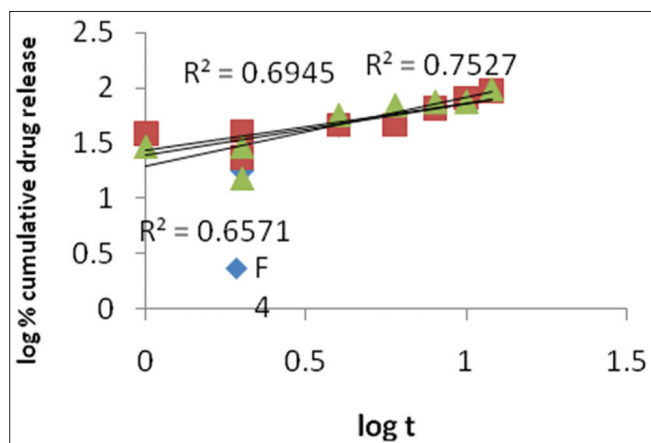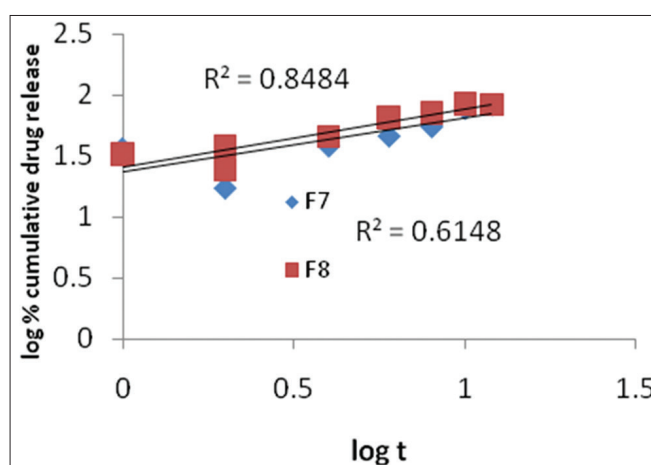
Fig. 19: Korsmeyer model for F4–F6

Fig. 20: Korsmeyer model for F7–F8

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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