

DESIGN, CHARACTERIZATION AND EVALUATION OF HYDROGEL BEADS OF DALFAMPRIDINE USING SYNTHETIC POLYMERS

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ABSTRACT

The current research deals with formulation and evaluation of hydrogel beads of Dalfampridine by using Synthetic polymers. These hydrogel beads were prepared with the objective to enhance bioavailability and to produce sustained release of dalfampridine. More over the Hydrogel beads of Dalfampridine are prepared by ionotropic gelation method. In the present work, a total of nine formulations were formulated, using synthetic polymers like sodium CMC, HPMC K4M, Carbopol along with sodium alginate as a gelling agent. The formulated Dalfampridine Hydrogel beads were then assessed for various parameters viz., FTIR, SEM, particle size, size distribution, % yield, drug content, entrapment

efficiency, *in vitro* dissolution, release kinetics. The invitro dissolution data for best formulation F9 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsmeyer-peppas equation. Optimized formulation F9 shows R^2 value 0.974. As its value nearer to the '1' it is conformed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot. The 'n' value is 1.020 for the optimised formulation(F9) i.e., n value was >0.89 this indicates Super case transport. From the drug release kinetics of the Dalfampridine hydrogel beads it was concluded that the formulation F9 follows Zero order release with super case transport mechanism.

KEYWORDS: Dalfampridine, Hydrogel beads, Ionotropic gelation method, FTIR, SEM, Entrapment efficiency, In vitro dissolution.

INTRODUCTION

Dalfampridine is a neurofunctional modifier that helps improve walking speed in patients with multiple sclerosis (MS). Dalfampridine is a broad-spectrum lipophilic potassium channel blocker and binds favourably to the open state than closed state of the potassium channel in the CNS. Its pharmacological target are the potassium channels exposed in MS patients. Does not prolong the QTc interval. Dalfampridine inhibits voltage-gated potassium channels in the CNS to maintain the transmembrane potential and prolong action potential. In other words, dalfampridine works to make sure that the current available is high enough to stimulate conduction in demyelinated axons that are exposed in MS patients. Furthermore, it facilitates neuromuscular and synaptic transmission by relieving conduction blocks in demyelinated axons.

The relatively high water content of hydrogels makes them also permeable to small molecules like oxygen, nutrients, and metabolites. This high solute permeability makes them ideal materials of choice as devices for the controlled release of many drugs and other active agents.

The purpose of this work is to develop a novel sustained release hydrogel beads with natural polymers to enhance bioavailability of Dalfampridine.

Various approaches for preparation of Hydrogel beads include Homopolymeric hydrogel beads, co-polymeric hydrogel beads, Semi inter penetrating network hydrogel beads, inter penetrating network hydrogel beads, ionotropic gelation technique, Emulsion Internal Ionotropic Gelation Technique, Polyelectrolyte Complexation Technique, Coacervation Technique.

Hydrogel beads is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery system is desirable for enhancing the bioavailability and produce prolonged action in GIT. Orally-administered dalfampridine is rapidly and completely absorbed from the gastrointestinal tract. T_{max}, immediate release form is 1 hour; T_{max}, extended release form is 3.5 hours; C_{max}, 10 mg extended release is 17.3 - 21.6 ng/mL; Relative bioavailability of 10 mg extended-release tablets compared to aqueous oral solution is 96%. The terminal elimination half life is about 5-6hrs. So to enhance the bioavailability of Dalfampridine, sustained release hydrogel beads were formulated by using ionotropic gelation method.

MATERIALS AND METHODS

Materials

Dalfampridine purchased from Spectrum pharma labs Hyderabad,HPMCK4M, Carbopol, Sodium CMC, Sodium alginate, Calcium chloride and Hydrochloric acid were used. All the reagents used are of LR grade.

Methods

The method used for preparation of hydrogel beads is Ionotropic gelation method.

Accurate quantity of polymer was dissolved in 25ml of distilled water and stirred to form dispersion. Drug was added to the above dispersion and again stirred for uniform distribution. and stirred until a homogenous mixture was obtained. The mixture was extruded through a 23G syringe needle into calcium chloride solution (1% w/v). The beads were allowed to remain in the same solution for 30 min to improve their mechanical strength. The formed beads were separated, washed with water and allowed to dry at room temperature overnight.

EVALUATION PARAMETERS

Surface morphology (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry Dalfampridine gel beads were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of Dalfampridine hydrogel beads were taken by random scanning of the stub.

Percentage yield

Percentage practical yield of Dalfampridine hydrogel beads was calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Dalfampridine beads recovered from each batch in relation to the sum of starting material.

The percentage yield of Dalfampridine beads prepared was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug Content

To determine the drug content and encapsulation efficiency of the beads, 40 mg beads were crushed using a porcelain mortar and a pestle, and dispersed in suitable solvent. The dispersion was sonicated for 15 minutes and left overnight for 24 hrs, then the dispersion was filtered. A 1 ml sample was taken and diluted with suitable solvent, and drug content assayed using a UV-visible spectrophotometer at λ_{max} of 262 nm. The drug content of each formulation was recorded as mg / 200 mg of gel beads.

Drug Entrapment Efficiency

The drug entrapment efficiency of prepared beads was determined by using the following equation.

$$\text{EE (\%)} = \text{Actual Drug Content} / \text{Theoretical Drug Content} \times 100$$

In-vitro dissolution studies

Procedure for In-vitro dissolution study^[64]

The release rate of Dalfampridine Hydrogel beads was determined by employing USP XXIII apparatus II (paddle method). The dissolution test was performed using 900 ml 0.1N HCL, for 2 hours and at 6.8pH buffer for 10 hours, at $37 \pm 0.5^\circ\text{C}$ at 50 rpm. Dalfampridine hydrogel beads equivalent to 40 mg of Dalfampridine was used for the study. At various time points (hourly) 5ml of the sample solution was withdrawn from the dissolution apparatus for up to 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at 262nm. Dissolution profiles of the formulations were analyzed by plotting cumulative percentage drug release versus time. The data obtained were also subjected to kinetic treatment to understand release mechanism.

Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [$\text{Log}(Q_0 - Q)$ v/s t], Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsmeyer Peppas double log plot ($\text{log } Q$ v/s $\text{log } t$) respectively, where Q is the cumulative percentage of drug released at time t and $(Q_0 - Q)$ is the cumulative percentage of drug remaining after time t.

In short, the results obtained from *in vitro* release studies were plotted in four kinetics models of data treatment as follows.

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. \sqrt{T} (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

RESULTS AND DISCUSSION

Drug polymer interaction (FTIR) study

FTIR Spectra were obtained for Dalfampridine, physical mixture, Dalfampridine and polymers. The characteristic peaks of the Dalfampridine were compared with the peaks obtained for physical mixture of Dalfampridine and polymer. From the obtained spectra it appeared that there were no interaction between Dalfampridine and polymers.

Surface morphology (SEM)

The surface morphology of the Dalfampridine beads was studied by SEM. SEM photographs of the optimized formulation was shown in the Fig.1.3. Surface smoothness was observed with guar gum incorporated Dalfampridine beads.

Frequency distribution analysis

As the ratio of polymer was increased, the mean particle size of Dalfampridine beads had also decreased (Table 1.2). The significant decrease may be due to the increase in the viscosity of the droplets. Dalfampridine beads having a size range of 1.0 to 1.5 mm with normal frequency distribution was obtained.

Percentage yield

The percentage yield for Dalfampridine hydrogel beads were given in table 1.3.

Percentage drug entrapment efficiency

Entrapment efficiency increased with increase in the polymer concentration. From the results it can be inferred that there is a proper distribution of Dalfampridine in the beads and the deviation were within the acceptable limits.

By increasing the polymer concentration, the encapsulation efficiency was increased. The entrapment efficiency of high in beads that were formulated by using carbopol.

***In vitro* dissolution studies**

The *in vitro* performance of Dalfampridine hydrogel beads showed prolonged and controlled release of Dalfampridine. The results of the *in vitro* dissolution studies showed controlled release in a predictable manner. As the polymer concentration was increased, the drug release from the hydrogel beads were found to decrease. Compared to sodium CMC and HPMC K4M, Carbopol retarded drug release more effectively, hydrogel beads had an optimum release at the end of 12th hour. The *in vitro* release profiles of all the formulations (F1 to F9) are shown in tables 1.4 and Fig. 1.4 to 1.7.

Release kinetics of Dalfampridine hydrogel beads

The *in vitro* dissolution data for best formulation F9 were fitted in different kinetic models i.e., zero order, first order, Higuchi and korsmeyer-peppas equation. Optimized formulation F9 shows R² value 0.974. As its value nearer to the '1' it is conformed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot.

The 'n' value is 1.020 for the optimised formulation(F9) i.e., n value was >0.89 this indicates Super case transport.

TABLES AND GRAPHS

Table 1.1: Formulation design for Dalfampridine hydrogel beads using different ratios of drug and polymers.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dalfampridine	100	100	100	100	100	100	100	100	100
Sodium Alginate	250	500	750	250	500	750	250	500	750
Sodium CMC	250	500	750	-	-	-	-	-	-
HPMC K4M	-	-	-	250	500	750	-	-	-
Carbopol	-	-	-	-	-	-	250	500	750
Calcium chloride(%)	1	1	1	1	1	1	1	1	1

Drug polymer interaction (FTIR) study

From the spectra of Dalfampridine, physical mixture of Dalfampridine and polymer, Dalfampridine and blank beads, it was observed that all characteristic peaks of Dalfampridine were present in the combination spectrum, thus indicating compatibility of the Drug and polymer.

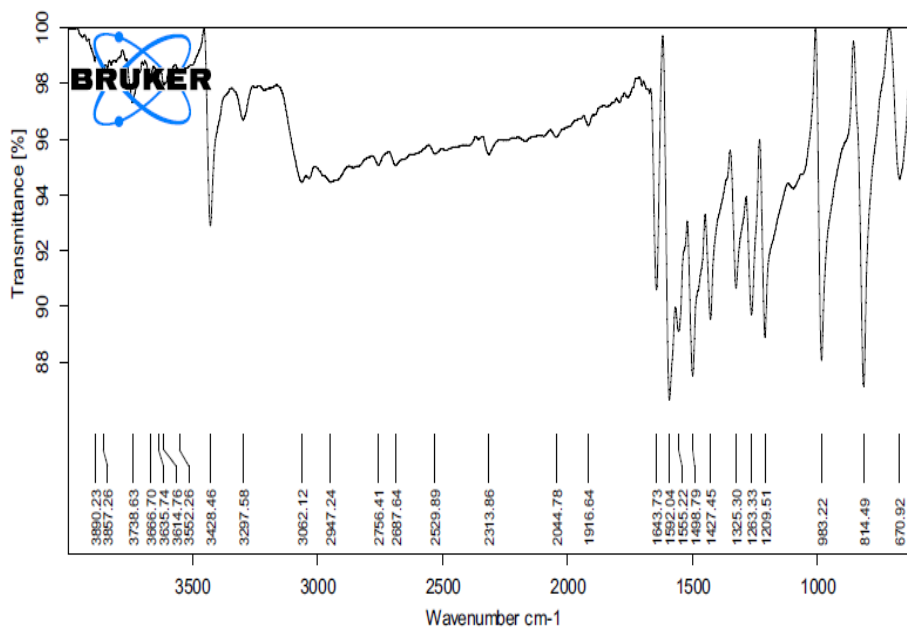


Fig 1.1 IR spectra of Dalfampridine

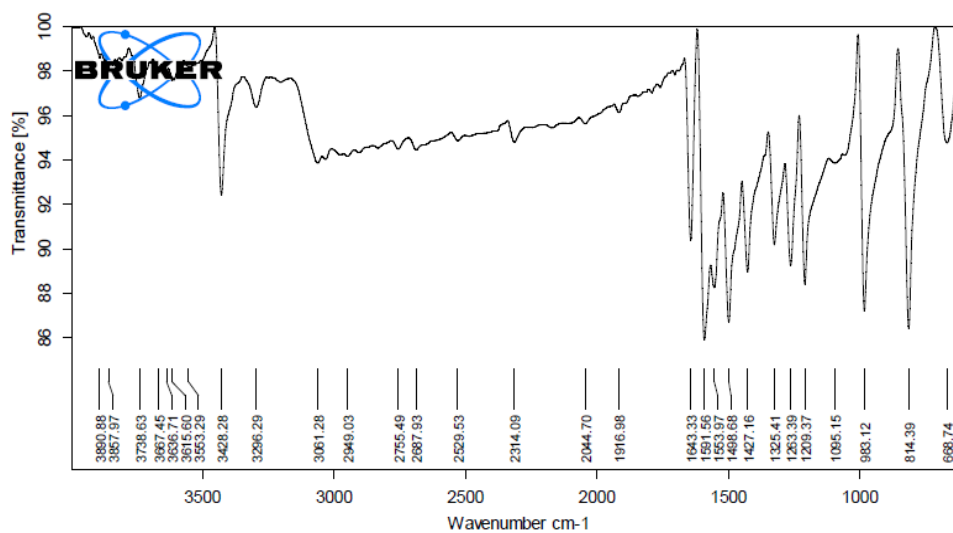


Fig 1.2 IR spectra of optimized formulation.

Surface morphology - Scanning Electron Microscopy (SEM)

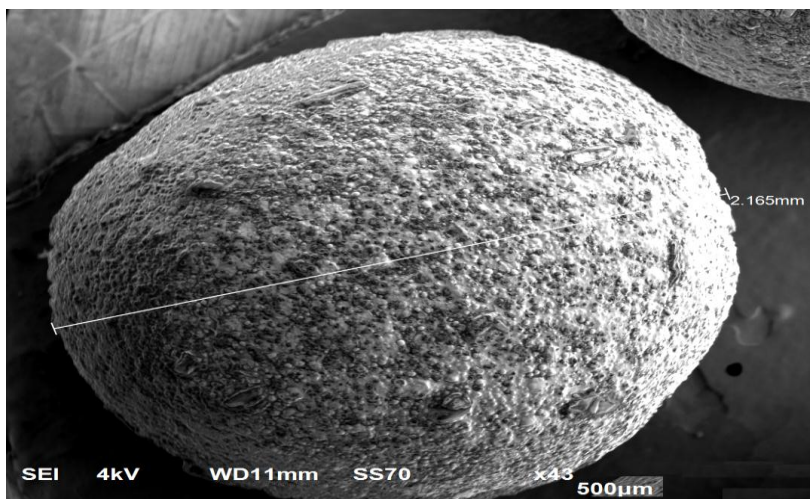


Fig 1.3 SEM photographs of Hydro gel beads using sodium alginate and Carbopol.

Determination of Average particle size

Table 1.2 Average particle size of Dalfampridine Hydrogel beads.

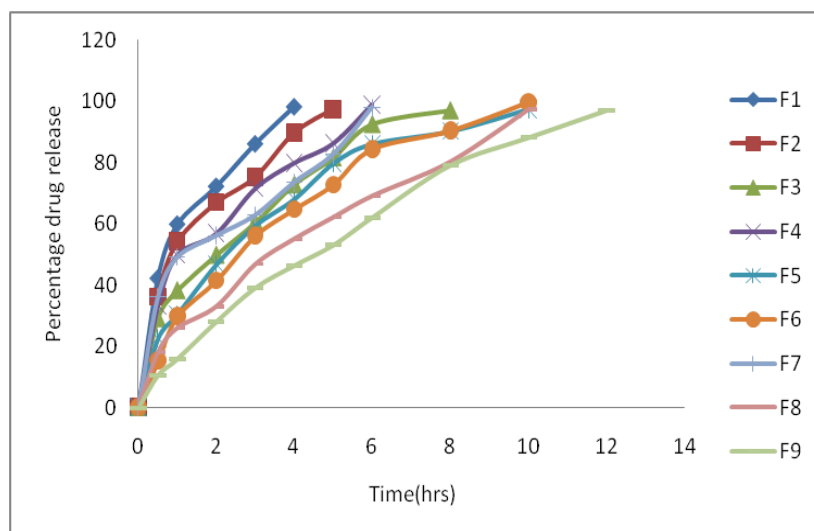
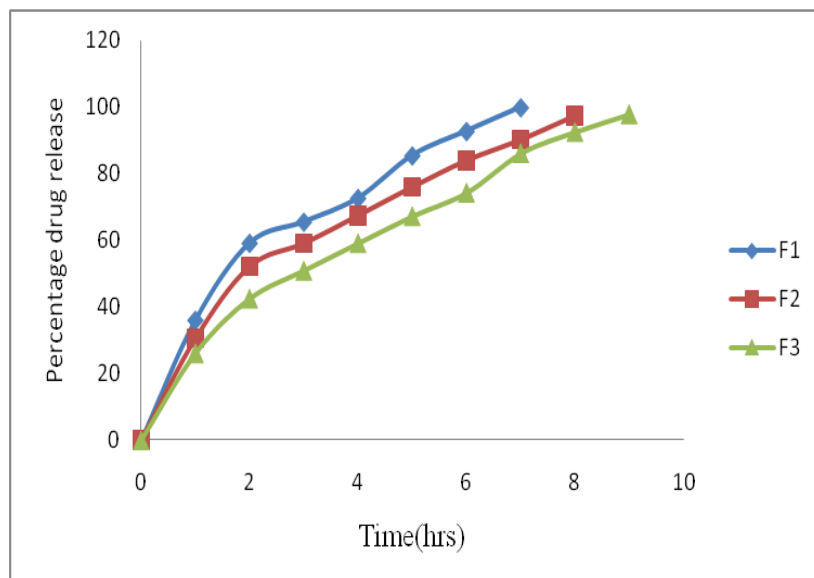
Sl. No	Formulation code	Average size (mm)
1	F1	1.2
2	F2	1.3
3	F3	1.2
4	F4	1.4
5	F5	1.5
6	F6	1.2
7	F7	1.5
8	F8	1.3
9	F9	1.2

Table 1.3: Drug entrapment efficiency of Dalfampridine Hydrogel beads, *In vitro* dissolution studies.

Sl. No.	Formulation Code	Percentage Yield	Entrapment efficiency (%)
1	F1	82.05	82.05
2	F2	87.26	88.48
3	F3	89.41	90.96
4	F4	82.01	88.92
5	F5	86.15	91.52
6	F6	90.52	96.63
7	F7	89.63	88.17
8	F8	90.52	95.02
9	F9	96.42	97.08

Table 1.4: *In vitro* release data of sodium alginate Hydrogel beads of Dalfampridine.

TIME(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	42.15	36.14	29.16	33.18	22.51	15.26	36.15	18.15	10.62
1	59.82	54.09	38.27	49.82	30.52	29.85	49.18	26.18	16.05
2	72.15	66.83	49.85	56.82	46.82	41.52	56.18	33.18	28.18
3	86.05	75.19	60.45	71.52	59.52	56.15	62.85	46.92	39.24
4	98.16	89.62	72.85	79.82	68.18	64.82	73.52	55.18	46.50
5	-	97.26	81.63	86.18	79.82	72.86	82.63	62.18	53.17
6	-	-	92.51	98.85	86.18	81.51	97.96	69.15	62.18
8	-	-	97.05	-	90.32	89.52	-	80.26	79.18
10	-	-	-	-	99.52	98.82	-	99.28	88.18
12	-	-	-	-	-	-	-	-	97.05

**Fig 1.4: %DR of F1-F9.****Fig 1.5: %DR of F1-F3.**

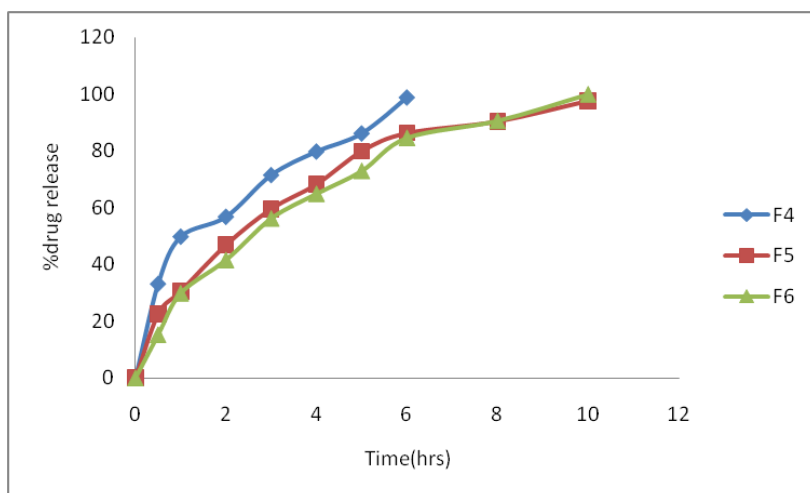


Fig 1.6: %DR OF F4-F6.

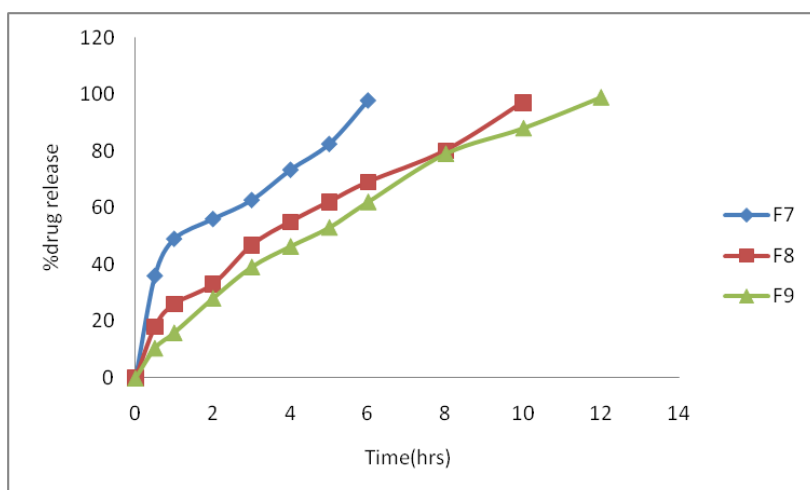


Fig 1.7: %DR OF F7-F9.

ZERO ORDER(F9)

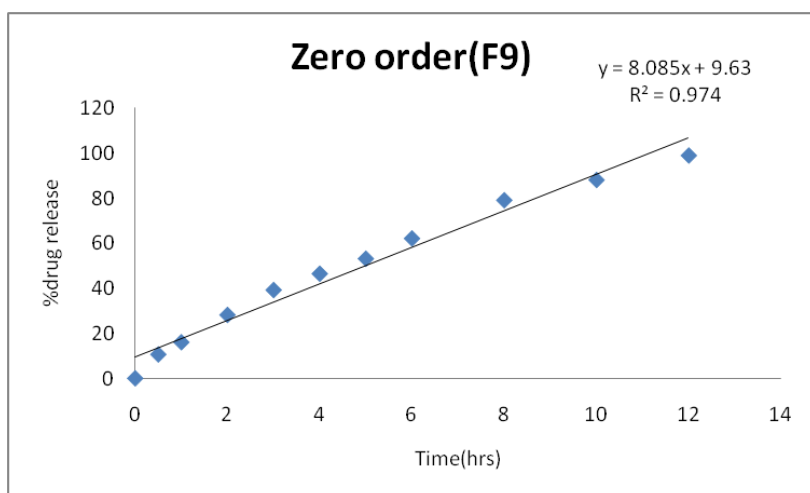
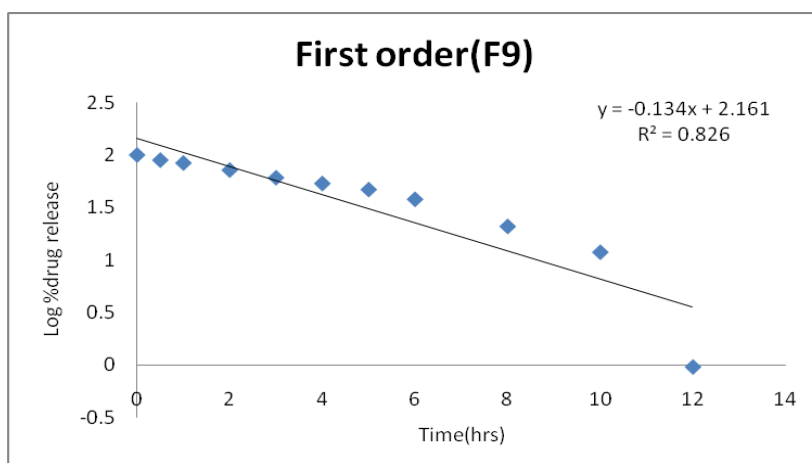
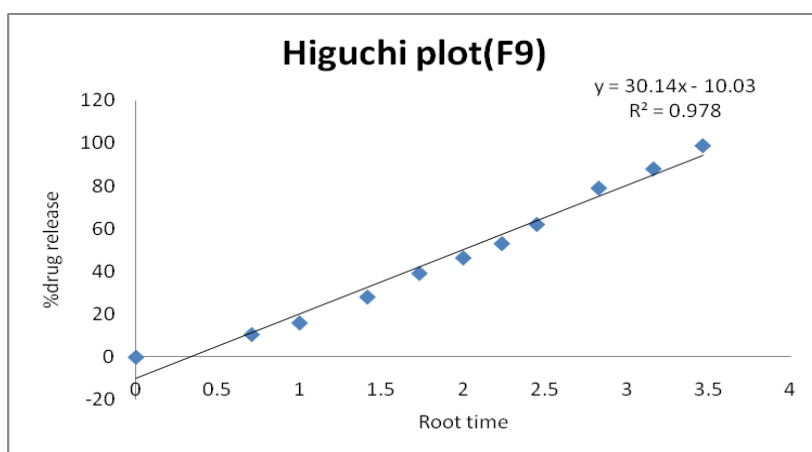
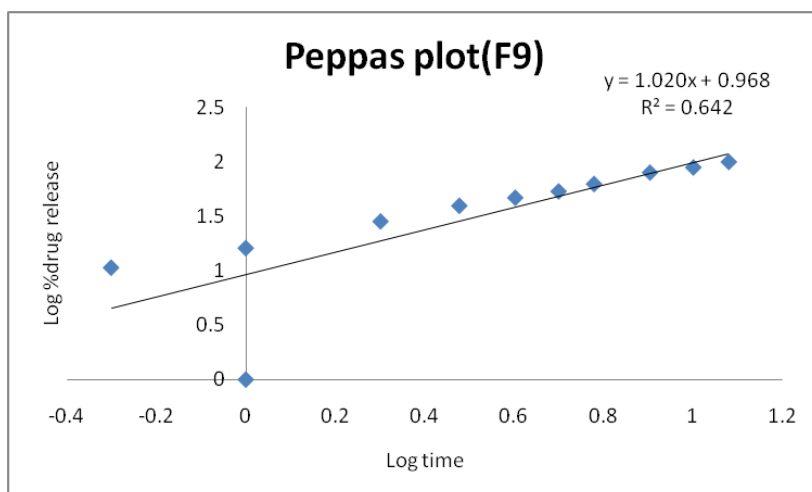


Fig 1.8: Zero order graph of F9 formulation.

FIRST ORDER (F9)**Fig 1.9: First order graph of F9 formulation****HIGUCHI PLOT(F9)****Fig1.10: Higuchi plot of F9 formulation.****PEPPAS PLOT(F9)****Fig 1.11: Peppas plot of F9 formulation.**

DRUG RELEASE KINETICS**Table 1.5: Drug Release Kinetics.**

Batch	Zero Order	First Order	Higuchi	Peppas	Peppas
Code	r ²	r ²	r ²	r ²	n
F9	0.974	0.826	0.978	0.642	1.020

CONCLUSION

From the above experimental results it can be concluded that:

Preformulation studies like melting point, solubility and UV analysis complied with standards. The FTIR Spectra revealed that, there was no interaction between Dalfampridine and polymers. Surface smoothness of the Dalfampridine beads was confirmed by SEM. As the ratio of polymer was increased, the mean particle size of Dalfampridine hydrogel beads was decreased. Dalfampridine hydrogel beads with normal frequency distribution were obtained. Entrapment efficiency increased with increase in the polymer concentration. From the results it can be inferred that there was a proper distribution of Dalfampridine in the beads and the deviation was within the acceptable limits. The study also indicated that the amount of drug release decreases with an increase in the polymer concentration. The *in vitro* performance of Dalfampridine Hydrogel beads showed prolonged and controlled release of drug. The *in vitro* dissolution data for best formulation F9 were fitted in different kinetic models i.e., zero order, first order, Higuchi and korsmeyer-peppas equation. Optimized formulation F9 shows R² value 0.974. As its value nearer to the '1' it is conformed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot. The 'n' value is 1.020 for the optimised formulation(F9) i.e., n value was >0.89 this indicates Super case transport.

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