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Research Article

Formulation Development and Evaluation Of Wax Incorporated Floating Beads Of Dalfampridine

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ABSTRACT

In this study, the Dalfampridine multi-unit sustained release gastric drug delivery system was developed from a purely aqueous medium, avoiding the use of any organic solvents, thereby releasing the drug over a short period of time. time. The emulsion gelation technique is used to prepare the beads. Edible oil pearls are made by mixing and homogenizing olive oil and water containing pectin and molten wax, then extruding them into a solution of calcium chloride. The effects of carnauba wax on smoking efficacy, variation in delay, morphology, and drug release have been studied. Carnauba wax was found to be sufficient to promote drug release at gastric pH. The results show that these particles can trap drugs in large enough quantities and can also successfully deliver drugs to the stomach for a long time without the use of organic solvents.

INTRODUCTION

The oral route is one of the oldest and most widely used routes of administration, providing a convenient method of obtaining local and systemic effects. The different approaches taken in formulation design will overcome the limitations of conventional dosage forms, including controlled / sustained release drug delivery systems. Multi-unit flotation systems may be an attractive option because they have been shown to reduce interindividual and intrasubject drug absorption, as well as the risk of dose release. 2 different flotation delivery system approaches as multi-unit gas containment system, hollow microspheres (microspheres) prepared by the solvent emulsion diffusion method, 3 low-density foam-based microparticles of powder, prepared granules by the method of gelatin emulsion, etc. it could be widely distributed across the GIT, offering the potential for more reliable and sustainable drug delivery.

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Granule formation occurs due to the crosslinking of calcium ions with pectin to form calcium pectinate. Studies on morphology, buoyancy, swelling, drug content, the effect of smoking and the study of drug release were conducted. The aim of this study was to investigate the effect of conjugated wax, prepared with the emulsion gelation method, on the release profile of the drug.

MATERIALS AND METHODS

Materials

Dalfampridine was purchased from Simson Pharma. Pectin, Olive oil, Carnauba wax, Calcium chloride used were of laboratory grade and available at institute.

Preparation of floating wax beads

The emulsion of pectin, olive oil and Dalfampridine was prepared in distilled water using a high speed homogenizer (IKA T25) at 3000 rpm. The weighed amount of the wax was melted on the water bath at the temperature of more than 50C of melting point of the wax. The molten wax was dispersed in the previously heated homogenized emulsion of pectin, olive oil and Dalfampridine and mixed until the homogeneous mixture was obtained. The hot melted mixture was extruded in the 2% w/v Calcium chloride solution through 22G syringe. The beads formed were allowed to remain in the calcium chloride solution for 10 – 20 mins for the hardening of the beads. The beads formed were then filtered and washed thoroughly with water to remove the excess of calcium from the surface of the beads.4

Composition of formulation

Table 1: Composition of formulation

Formulation code	Drug	Pectin	Olive oil	Carnauba wax	Water Q.S
F1	500	4	30	4	100
F2	500	4	30	8	100
F3	500	4	30	12	100
F4	500	4	30	16	100

Micromeritic properties

All the prepared formulations of floating beads were evaluated for bulk density, tapped density, Carr's index and Hausner's ratio.5,6

Percentage yield

All the prepared formulations of floating beads were evaluated for the percentage yield by using following formula. 5,7

Determination of drug content and drug entrapment efficiency

50 mg of beads were weighed and crushed in a pastel mortar and the crushed material was dissolved in 25 ml of 0.1 N Hydrochloric acid. The solution was kept for 24 hrs. Volume of this solution was made up to 50 ml with washings of mortar. Then it was filtered. The filtrate was assayed by spectrophotometically using a UV spectrophotometer (Schimadzu, UV, 1800). The drug content and the entrapment efficiency were determined.8

Floating lag time and floating time

The formulated bead sample (n=20) were placed in a beaker filled with 0.1N HCl (pH 1.2) solution. Temperature was maintained at 37 ^{0}C. The floating time of beads were observed for 12 hrs. The preparation was thought of to possess buoyancy in the test solution only when all the beads floated in it. The time the formulation took emerge on the surface of the medium (floating lag time) and the time for which the formulation remains floating on the surface of the medium (floating time) were noted.9

Swelling studies

Beads were studied for swelling characteristics. Only those batches were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug loaded beads were taken, weighed and placed in wire basket of USP dissolution apparatus I. The basket containing beads put in a beaker containing 100 ml of 0.1N HCl (pH 1.2) maintained at 37 0C. The beads were periodically removed at predetermined intervals

and weighed. Then swelling ratio was calculated as per the following formula. 10

Particle size determination

The particle size of beads was determined by the dry state using optical microscopy method. The stage micrometer and eyepiece micrometer were used for the measurement of the particle size. The size of the beads present in the 1cm3 area of the slide was counted. 11

Surface characterization

Surface characterization of beads were examined with a scanning Electron Microscopy (Diya labs, airoli, Mumbai) beads were mounted on metal grids using double-sided tape and coated with gold under vaccum. 12

Differential Scanning Calorimetry (DSC)

The DSC measurements were performed on a DSC 60, Shimadzu, Japan differential scanning calorimeter with thermal analyzer. All accurately weighed samples were placed in a sealed aluminium pans, before heating under nitrogen flow (10 ml/min) at a scanning rate of 10^0C per min from 25 to 300^0C. An empty aluminium pan was used as reference.13

Fourier Transform Infrared Spectroscopy (FTIR)

The compatibility study was carried out by using Fourier transform infrared spectrophotometer (BRUKER). FTIR study was carried on pure drug and physical mixture of drug and polymer. Physical mixtures were prepared and samples were kept for 1 month at room temperature. Infrared absorption spectrum of Dalfampridine was recorded over the wave number 4000 to 400 cm-1 using Fourier Transform spectrophotometer. 13, 14

In- vitro drug release study

The release of Dalfampridine from sustained release floating wax bead was determined using USP dissolution apparatus I at 50 rpm. The dissolution medium used 900ml of 0.1N HCl (pH1.2) and temperature was maintained at 37 0C. A sample (5ml) was withdrawn from the dissolution apparatus at 0 min., 1hr, 2hr, 4hr, 6hr, 8hr, 10hr, 12hr. The samples were filtered through Whatman filter paper and analysed using UV method. Cumulative % drug release was calculated and observed. The dissolution of the formulation was compared with the 250mg of the capsule containing 5mg of the drug.4

Best fit kinetic model for optimized formulation

The data obtained from study of diffusion kinetics of the optimized formulation was studied to obtain the best fit model. The best fitted model is the one which gives the highest R2 value and least slope value. Stability study Stability study of the formulation which gave maximum dissolution rate was carried out to point out any visual physical or chemical change made in the formulation after storing it at elevated temperature and humidity conditions. The optimized formulation was store in ambient colour bottle and stored at 400 C ± 20C and 75% ± 5% Relative humidity for three months. Floating wax beads was analysed for the drug content.15

Statistical Analysis

Results of ex-vivo experiments are reported as SEM analysis. The classical zero order release curve was found to be linear. The curves plotted according to Higuchi model were also found to be linear. The drug release occurs probably by diffusion and erosion and dissolution. From the above tables it was seen that the best fit model for formulation was Zero order kinetic, such type of model was applicable when sustained release dissolution mechanism are seen.

RESULTS AND DISCUSSION

Micromeritics properties

From the study of the micromeritics properties of the formulation it was found that the bulk density of the formulation lied within range of 0.3604 – 0.4804 g/cm3, tapped density within range of 0.5563- 0.4693. The Carr's index lies within range of 6.76 – 11.70 and Hausner's ratio within range

of 1.2658 – 1.1277 which indicates that the prepared formulation have good flow property (Table 2).

Table 2: Micromeritics properties of the formulation

Batch Code	Bulk density (gm/ml) ± SD	Tapped density (gm/ml) ± SD	Carr's index ± SD	Hausner's ratio ± SD
F1	0.3920 ± 0.0013	0.4693 ± 0.0021	11.70 ± 0.0578	1.1904 ± 0.0085
F2	0.4804 ± 0.0045	0.5563 ± 0.0049	6.76 ± 0.0357	1.1277 ± 0.0010
F3	0.4312 ± 0.0020	0.5182 ± 0.0016	9.22 ± 0.0441	1.1834 ± 0.0058
F4	0.3604 ± 0.0011	0.4569 ± 0.0025	8.10 ± 0.0482	1.2658 ± 0.0011

Percentage yield

All formulations F1 – F4 found percentage yield 97.14 – 95.20% which lied in the normal range in (Table 3).

Table 3: Percentage yield of the formulations

Sr. No.	Batch Code	Percentage Yield (%)
1	F1	96.84
2	F2	97.14
3	F3	95.65
4	F4	95.20

Drug content and drug entrapment efficiency

The percentage drug content of all prepared formulations was found to be in the range of 95.21-96.89%. Therefore uniformity of drug content was maintained in all formulations (Table 2). Therefore entrapment efficiency was found to be less due to the diffusion of the drug into the calcium chloride solution during the formation of the microspheres (Table 4).

Table 4: Drug content of the formulation

Sr. No.	Batch Code	Contents(%)±SD
1	F1	96.81± 0.2743
2	F2	96.89 ± 0.8369
3	F3	96.22 ± 0.7968
4	F4	95.21 ± 0.5750

Floating lag time and floating time

Floating lag time in the range of 1.12 – 1.37 min. and floating time >12hr for all formulations F1-F4. This is due the increase in the concentration of the carnauba wax. (Table 5).

Table 5: Floating lag time and floating time of formulations

Sr. No.	Batch	Floating lag time (min.)	Floating time (hrs.)
1	F1	1.37 ± 0.04630	> 12
2	F2	1.12 ± 0.09391	> 12
3	F3	1.21 ± 0.00707	> 12
4	F4	1.25 ± 0.04221	> 12

Swelling studies

For all prepared batches (F1-F4), percent swelling ratio was found to be in the range of 10 – 20.66 %. The F1 batch showed the maximum swelling index. This is because of the lipophilic nature of the carnauba wax which affected the swelling of the beads. (Table 6).

Table 6: Swelling Index of formulations

Sr. No.	Batch Code	Swelling ± SD
1	F1	15.68 ± 0.02471
2	F2	20.66 ± 0.05241
3	F3	14.66 ± .0254
4	F4	10.25 ± 0.01679

Particle size determination

For F1-F4 batches average particle size was found to be in the range of 1.21 – 1.51 mm (Table 7).

Table7: Particle size determination of formulation

Sr. No.	Batch Code	Particle size (mm) ± SD
1	F1	1.51 ± 0.0251
2	F2	1.21 ± 0.0163
3	F3	1.46 ± 0.0258
4	F4	1.27 ± 0.0355

Surface characterization

The SEM result showed that the particle size of formulation was found to have regular and spherical shape with rough and uneven surface (Figure 1).

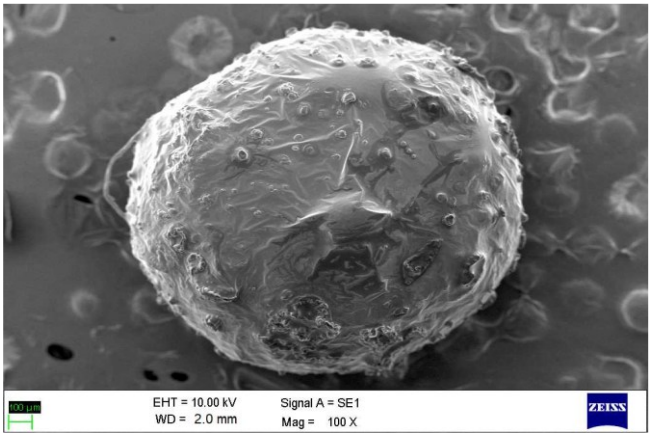

Figure No. 1: Surface morphology of the formulation

Differential scanning calorimetric studies

Dalfampridine was compatible with polymer. There is slightly peak broadening in physical mixture of polymer to pure Dalfampridine (Figure 2). Fourier transform infrared spectroscopy FTIR spectrum of the physical mixture shows that there is no interaction between drug and polymer (Figure 3).

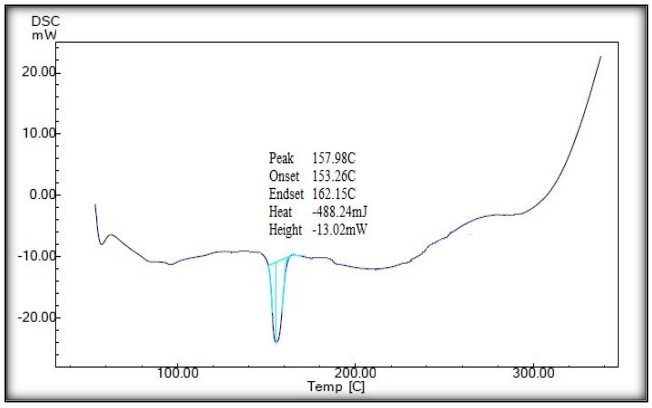

Figure No. 2: DSC thermogram of Dalfampridine

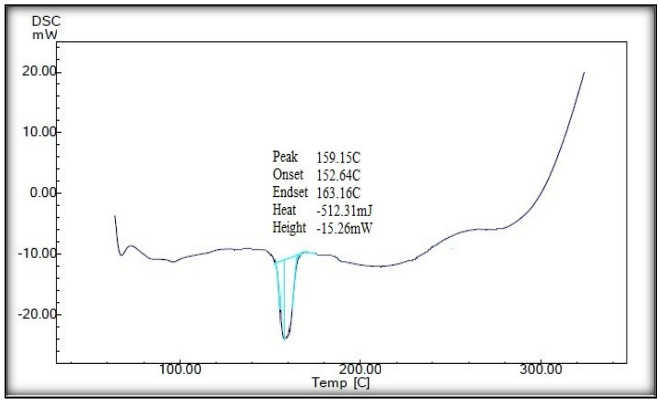

Figure No.3: DSC thermogram of formulation

In vitro drug release

The In vitro drug release study of different formulation maximum drug release 98.51% was shown by F2 batch. The data also suggested that floating beads formulation were capable to produce linear drug release for longer period of time. Drug release profile of formulation F1 to F4 shown in (Figure No. 4) and dissolution profile F1 to F4 signified sustained drug release. Out of four formulations maximum release after 12 hr was found for F2 formulation. (Table 8 and figure 4).

Table 8: In-vitro drug release of different batches of the formulation

Time (hr)	F1	F2	F3	F4
0	**0**	**0**	**0**	**0**
1	10.98 ± 0.032	9.89 ± 0.024	6.73 ± 0.015	6.36 ± 0.020
2	19.81 ± 0.050	20.36 ± 0.088	10.49 ± 0.040	11.81 ± 0.020
4	39.55 ± 0.086	45.03 ± 0.030	19.26 ± 0.020	19.81 ± 0.030
6	50.52 ± 0.020	55.06 ± 0.051	23.10 ± 0.023	28.82 ± 0.030
8	69.71 ± 0.025	84.04 ± 0.061	31.36 ± 0.026	42.56 ± 0.010
10	86.16 ± 0.040	91.65 ± 0.047	34.06 ± 0.021	44.24 ± 0.030
12	91.64 ± 0.050	98.51 ± 0.015	58.74 ± 0.040	45.06 ± 0.020

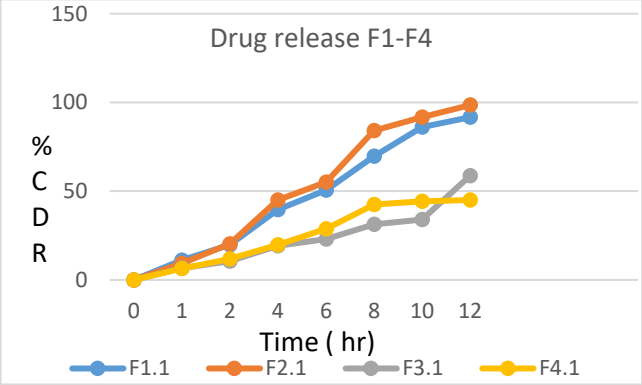

Figure No.4: Drug release profile of formulations F1-F4

From the comparative study of the formulation with capsule containing the dose of 5 mg of Dalfampridine, it was found that the capsule containing drug showed the 98.51% drug release within 60 mins. and marketed formulation showed the 98.51% drug release within 50 min. while the prepared formulation (F2 Batch) showed maximum drug release up to 98.51 % within 12 hrs.

Kinetic model for F2 batch

In order to investigate the mode of release from floating beads data were analysed with following mathematical model.

A. Zero order kinetic
B. First order kinetic
C. Higuchi equation
D. Korsemeyer-peppas equation

The classical zero order release curve was found to be linear. The curves plotted according Higuchi model were also found to be linear. Korsemeyer-Peppas release curves R2 was found to be ≥ 0.947 for all 4 formulations. The drug release occurs probably by diffusion and erosion and dissolution. After comparing the coefficient of regression (r2) values of different kinetic models, drug release kinetics for optimized floating beads best fitted in Zero order kinetic release followed by Higuchi such type of model was applicable when sustained release dissolution mechanism are seen (Table 9 & Figure 5-8).

Table 9: Drug release by using different models by F2 batch

Batch	Kinetic Model			
F2	**Zero Order (r2)**	**First Order (r2)**	**Higuchi Model (r2)**	**Korsemeyer-peppas (r2)**
	0.9992	0.9476	0.9874	0.9886

A. Zero order Kinetic

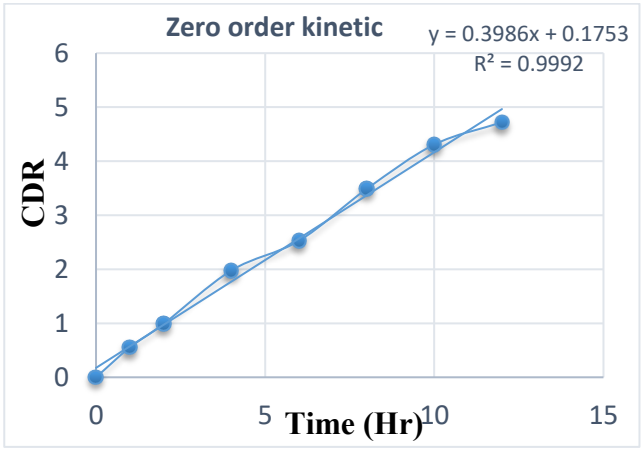

Fig. No. 5: Zero order kinetic study

B. First order kinetic

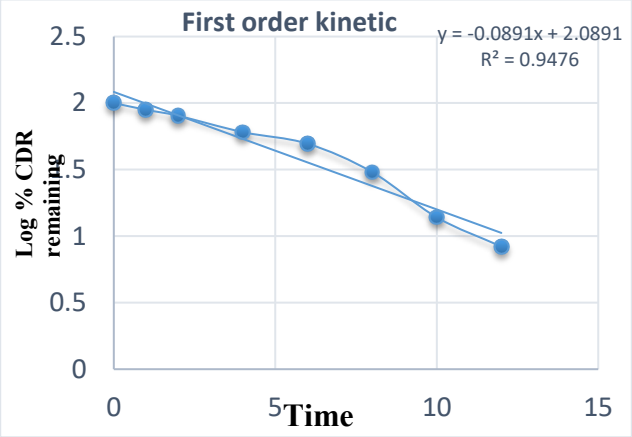

Fig. No. 6: First order kinetic study

C. Higuchi equation

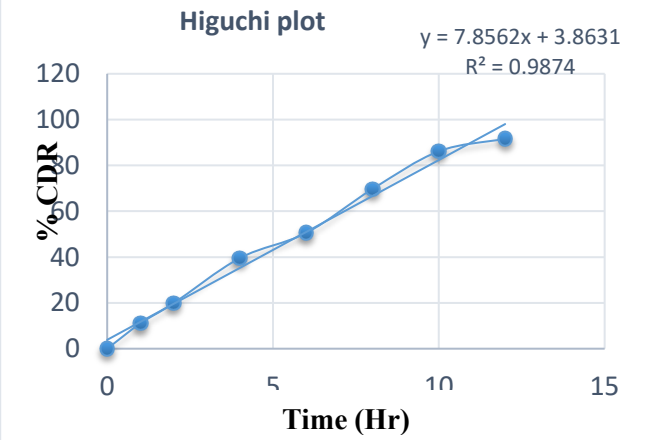

Fig. No. 7: Higuchi plot

B. Korsemeyer-peppas equation

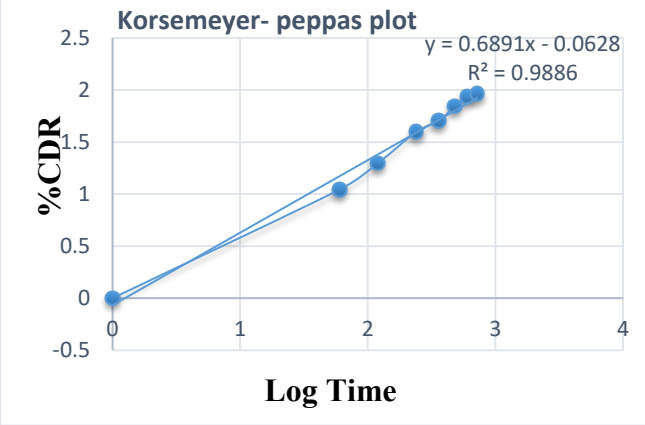

Fig. No. 8: Korsemeyer- peppas plot

Stability study

The sample were withdrawn after 1, 2 and 3 months and subjected to following tests a shown in. The accelerated stability studies (carried for 3 months), at temperature of 40 C ± 2 C and % RH 75% ± 5% RH indicated that the developed 0 floating pectinate microspheres were unaffected after 03 months storage under accelerated condition as no change was observed in the appearance and colour of the formulation. On the basis of these results, it may be concluded that the F2 formulation developed is stable under accelerated condition of 03 months (Table 10).

Table 10: Details of stability study for F2 batch

Test	Before	After		
	0 month	1 month	2 month	3 month
Drug release	93.64 ± 0.246	92.60 ± 0.236	91.07 ± 0.254	90.45 ± 0.251
Floating Lag time	>12 hrs	>12hrs	>12hrs	>12hrs

CONCLUSION

From the above study it may be concluded the use of hydrophobic carriers like waxes can be done for achieving the sustain release action. The low density materials like oils were used to attend the floating of the formulation. The study also suggested that the floating wax microspheres can be implemented as a suitable drug carrier for sustaining the release of the drugs with short biological half life.

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CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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