Research Article

DESIGN AND DEVELOPMENT OF FLOATING GEL BEADS OF LEVODOPA

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ABSTRACT

Floating gel beads are gastro retentive low density drug delivery systems based on non-effervescent approach. . The objective of the present work is to formulate and evaluate floating gel beads containing Levodopa in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. Floating gel beads of Levodopa were prepared by emulsion gelation method using Sodium Alginate and Coconut oil. The prepared gel beads were evaluated for various parameters like particle size, entrapment efficiency, shape and surface morphology, drug content, *in-vitro* drug release study, *in-vitro* drug release kinetics and stability study. The floating gel beads were found to be spherical by SEM. FT-IR study confirmed the drug-polymer compatibility. All floating gel bead formulations showed good flow properties and Buoyancy percentage was found to be 30.15%-85.70%. Among all formulations, F3 showed appropriate balance between buoyancy and drug release rate (85.70% in 12 hours and 84.13% in 12 hours), hence it is considered as the best formulation. . The data obtained in this study thus suggests that the floating gel beads of Levodopa are promising for sustained drug delivery which can be used for reducing dosing frequency.

Keywords: Floating gel beads, Levodopa, Bioavailability, Buoyancy, Emulsion Gelation, Sodium Alginate.

INTRODUCTION

Oral administration is the most convenient and preferred means of drug delivery. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half life are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity.[1]

To overcome these limitations, various approaches have been proposed to increase gastric retention of drug delivery system in the upper part of the gastrointestinal tract includes floating drug dosage systems, swelling or expanding systems, mucoadhesive systems, modified shape systems, high density systems, and other delayed gastric emptying devices. Dosage forms that can be retained in stomach are called gastro retentive drug delivery systems (GRDDS). GRDDS can improve controlled delivery of drugs that have an absorption window by continuously releasing the drug for time before it reaches its absorption site, thus ensuring its optimal bioavailability.[2]

Levodopa is an anti-Parkinsonism drug used in the treatment of Parkinsonism disease. Levodopa is a prodrug of dopamine. A conventional oral Dopa medication controls the evaluation of Parkinsonism disease adequately about 5 years. It has a biological half life of 0.75-1.5 hours and has a bioavailability of 30%.[3]Coconut oil is added to improve the floating property of gel beads.

MATERIALS AND METHODS

Levodopa was obtained from Yarrow chem products, Mumbai. Sodium Alginate was obtained from Yarrow chem. Products, Mumbai. Coconut oil was obtained from local market.

All the other reagents and chemicals used are of analytical grade.

Methodology

Floating alginate gel beads of Levodopa was prepared by emulsion gelation method. Polymer was dissolved in water with agitation. Drug and oil is then added to the above solution and stirring is continued. The homogenized mixture is then extruded using 21G syringe into 5% Calcium Chloride solution rotated at 800 rpm. The product formed is then washed with water, filtered and dried.[4]

Ingredients	F1	F2	F3	F4	F5	F6
Levodopa (mg)	500	500	500	500	500	500
Sodium Alginate (%w/v)	4	4	4	4	3	2
Calcium Chloride (%w/v)	5	5	5	5	5	5
Coconut oil (%)	-	10	20	30	20	20

Evaluation of floating gel beads

Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Angle of repose (θ) of the gel beads, which measures the resistance to particle flow, was determined by a fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed gel beads were allowed to pass through the funnel freely on to the surface.[5,6]

The height and diameter of the gel beads cone was measured and angle of response was calculated using the following equation,

$$\tan \theta = h / r$$

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

where, h = height of pile
r = radius of the base of the pile
θ = angle of repose.

Drug excipients compatibility studies by FTIR

The pure drug, pure polymer, drug and polymer and physical mixture of drug, polymer and other excipients were prepared and scanned from 4000-400cm^{-1} in FTIR spectrophotometer. The IR Spectrum of pure Levodopa and formulated gel beads were recorded by FTIR spectrophotometer.[7]

Percentage yield

The prepared dried beads of all batches were accurately weighed. The measured weight of prepared gel beads was divided by the total amount of all the excipients and drug used in the preparation of the gel beads, which give the total percentage yield of gel beads.[8,9,10]

It was calculated using the following equation:

$$\text{Percentage yield} = \frac{\text{Weight of the gel beads obtained}}{\text{Total weight of drug and polymer}} \times 100$$

Particle size

Particle size of the formed gel beads were determined using digimatic micrometer (MDC-25S, Mitutoyo, Japan) having accuracy of 0.01mm. The average diameter of 20 beads per batch was determined.

Drug content

Prepared gel beads weighed accurately (weight equivalent to 100mg) were crushed in a glass mortar and the powdered gel beads were diluted suitably with 0.1N HCl and analyzed for drug content. The drug content was analyzed by measuring absorbance in UV spectrophotometer at 280 nm using 0.1N HCl as blank. The drug content was calculated using the Equation as follows.[11,17]

$$\text{Drug content} = \frac{\text{Concentration} \times \text{Dilution factor}}{1000} \times 100$$

Shape and surface morphology

The samples for the scanning electron microscope (SEM) analysis were prepared by sprinkling the gel beads on one side of an adhesive stub. Then the gel beads were coated with gold before microscopy. Finally the morphology and size of the gel beads were observed under the scanning electron microscope. Samples were analyzed at 20kv and magnification 40X.[12]

***In-vitro* buoyancy test**

The floating alginate gel beads about 100 mg will be spread over the surface of the dissolution medium of 900 ml stimulated gastric fluid, which will be placed in USP dissolution apparatus type II (paddle). The temperature will be maintained at 37±0.5°C and shall be agitated by paddle at 100 rpm for 12 hours. After agitation the gel beads that float over the surface of the medium and those that will settle down at bottom of the flask will be recovered separately and dried.[12]

The percentage buoyancy of the floating gel beads will be calculated using the formula:

$$\text{Buoyancy \%} = W_f/(W_f + W_s)$$

Where W_f and W_s are the weight of the floating and settled gel beads respectively.

***In-vitro* drug release studies**

The *in-vitro* dissolution studies were carried out using USP Type-I Dissolution apparatus

for up to 10 hours. Sample of floating gel beads equivalent to 100 mg of Levodopa was placed in dissolution apparatus containing 900ml 0.1N HCl which was maintained at 37± 0.5°C and at a stirring speed of 50 rpm. 5ml samples were withdrawn at predetermined time intervals and same volume of fresh medium was replaced into the basket. Aliquot of 5 ml was withdrawn at time intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1 and 12 hours. The concentration of drug released was estimated by using UV spectrophotometer at 280nm. The percent of drug released at various time intervals was calculated and plotted against time.[8,18]

In-vitro drug release kinetics

The dissolution profile of all the batches was fitted to Zero order, First order and Higuchi to ascertain the kinetic modeling of the drug release. 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. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppa's exponential equation).[8,19]

Stability studies

The stability study of the floating gel beads was determined by drug content, *in-vitro* drug release study. The selected batch was packed in an aluminium foil and was kept in a petridish at room temperature (25±2ºC and 60±5% RH) an accelerated temperature (40±2ºC and 70±5% RH) for a period of 60 days.[13,14,15]

RESULT AND DISCUSSION

Percentage Yield

Table 1: Percentage yield of Levodopa loaded floating alginate gel beads

S. No.	Formulation code	Percentage Yield (%w/w)
1.	F1	48.70
2.	F2	53.79
3.	F3	54.89
4.	F4	56.04
5.	F5	53.83
6.	F6	54.73

The results of Percentage Yield are shown in Table 11. The Percentage Yield of the Floating Alginate gel beads were found to be in the range of 48.70% to 56.04%.

Table 2: Micromeritic properties of Levodopa loaded floating alginate gel beads

S. No.	Formulation code	Angle of Repose (θº)
1.	F1	$26^0 56' \pm 0.01$
2.	F2	$28^0 81' \pm 0.01$
3.	F3	$23^0 46' \pm 0.02$
4.	F4	$30^0 96' \pm 0.01$
5.	F5	$27^0 47' \pm 0.02$
6.	F6	$29^0 68' \pm 0.01$

The flow property of the prepared gel beads was studied from the angle of repose and Carr's index value. From this result it could be concluded that the floating alginate gel beads exhibited good flow property.

Drug Excipient Compatability Study by FTIR

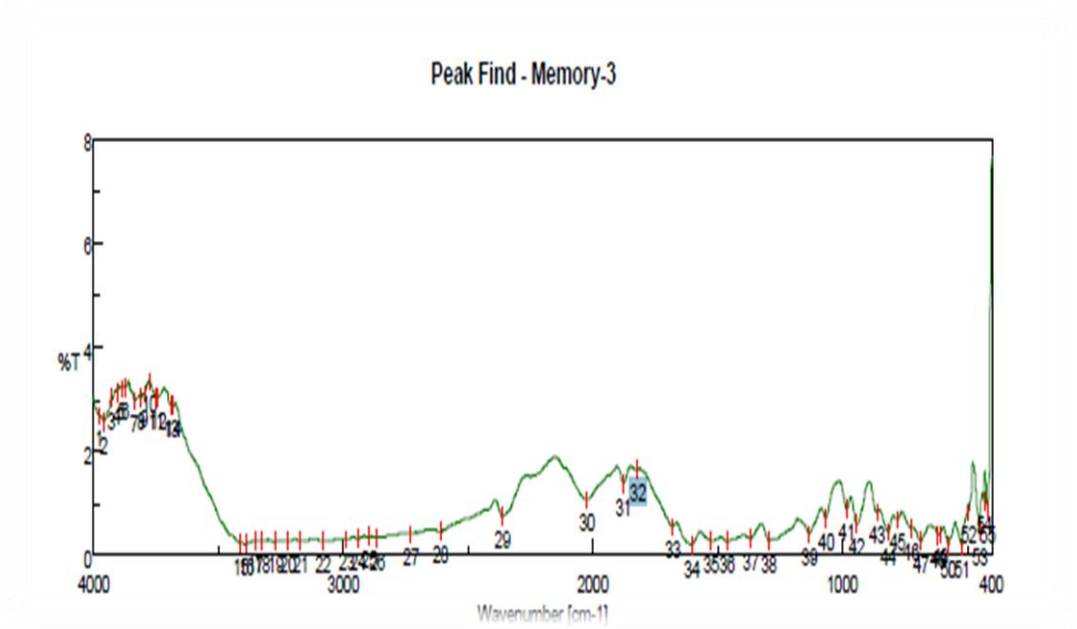

Fig. 1: FTIR spectra of pure Levodopa

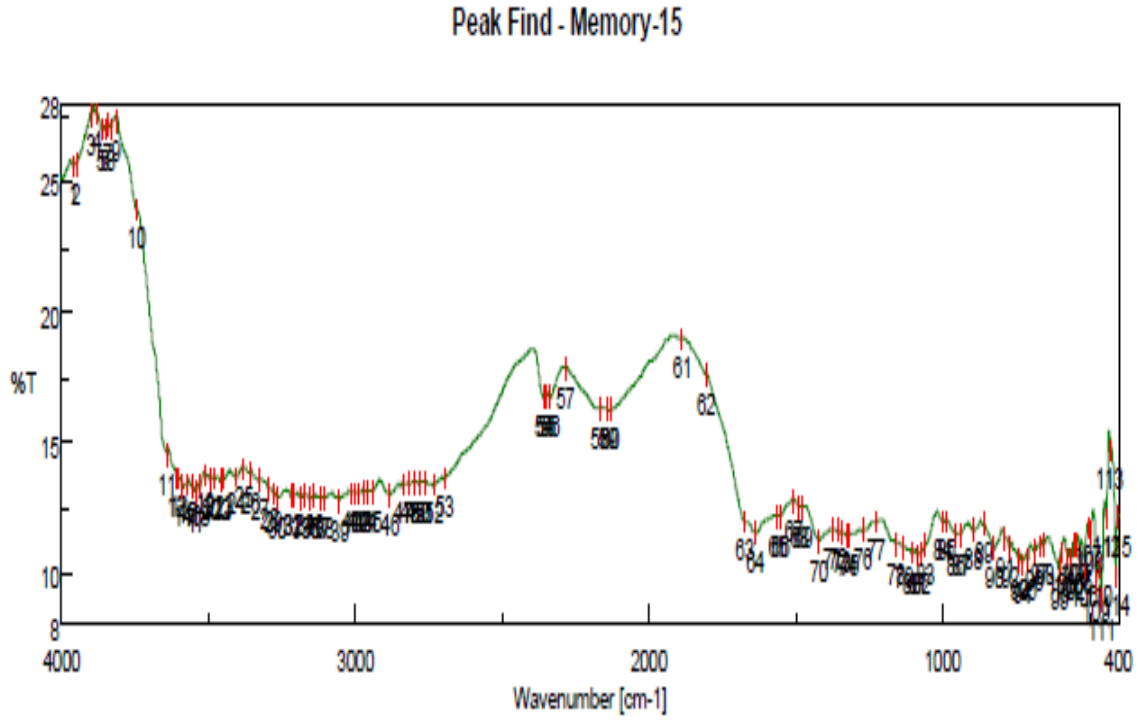

Fig. 2: FTIR spectra of Sodium Alginate

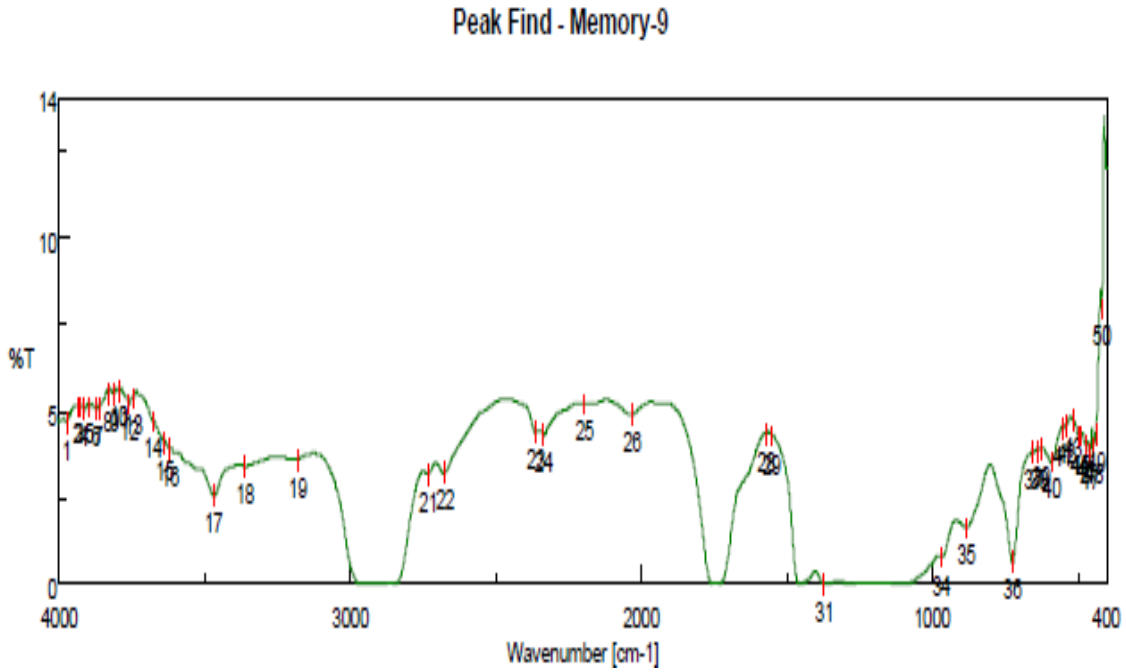

Fig. 3: FTIR spectra of Coconut oil

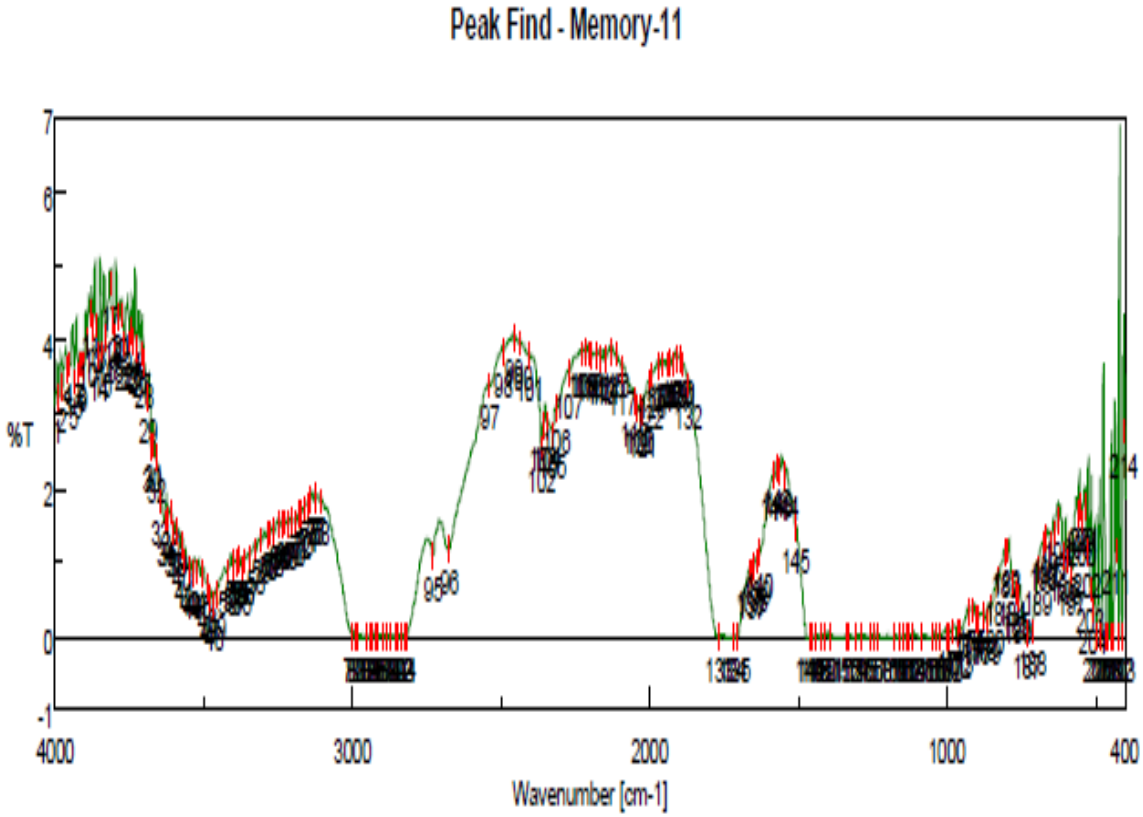

Fig. 4: FTIR spectra of Levodopa and coconut oil

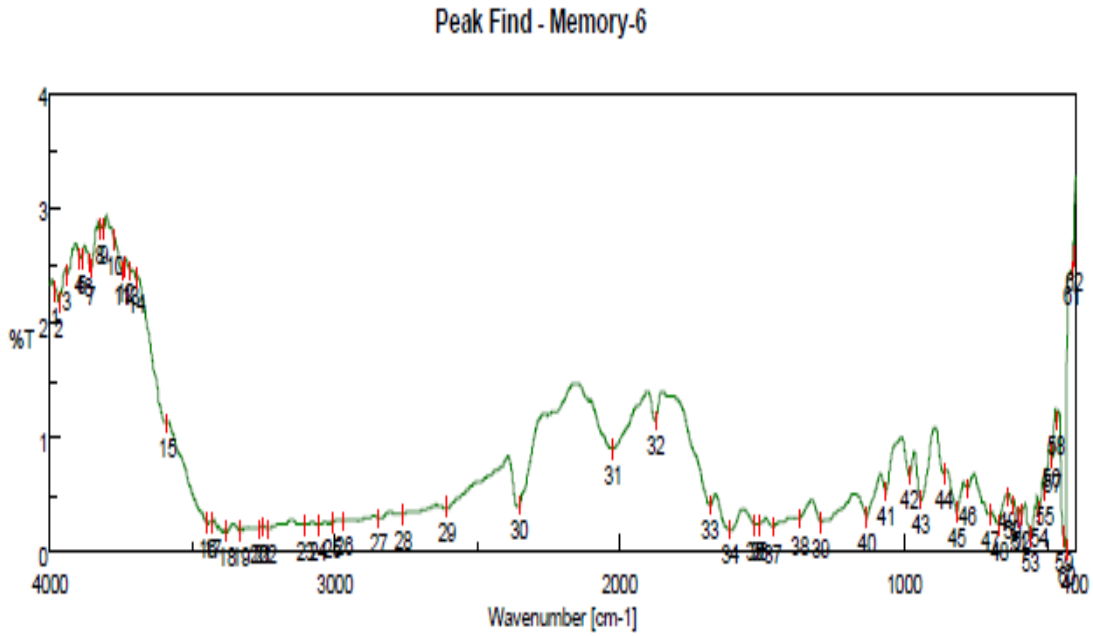

Fig. 5: FTIR spectra of Levodopa and Sodium Alginate

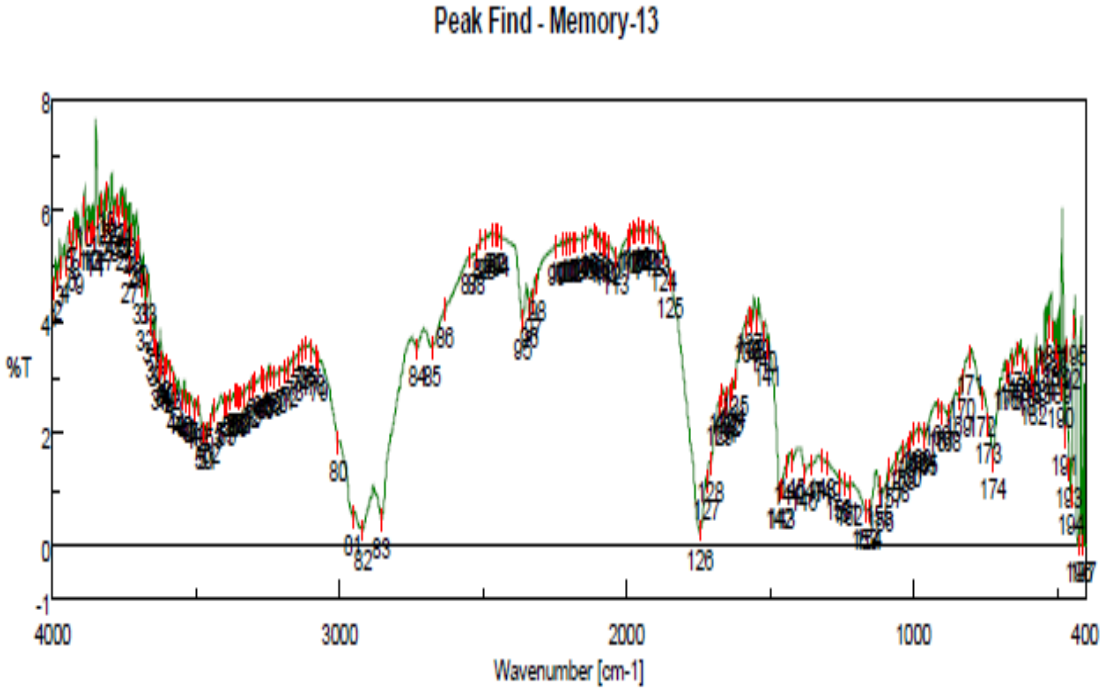

Fig. 6: FTIR spectra of prepared Floating Alginate gel beads

Table 3: Drug excipients compatibility studies using FTIR

Description	Reported Frequency	Pure Drug(cm^{-1})	Coconut oil	Sodium Alginate	Drug+all excipients
NH_2	3500-3300	3411.46	3470.28	3460.63	3495.35
O-H	3600-3200	3274.54	3621.66	3212.83	3230.18
C=C	1600-1400	1462.74	1459.85	1475.28	1644.27
C=O	1640-1690	1680.66	1753.94	1637.27	1638.2

All the characteristic IR peaks related to pure drug Levodopa also appeared in the FTIR spectrum of drug mixed with polymer, so there was no chemical incompatibility between drug and polymer.

Particle Size:

Table 4: Average particle size of the Levodopa loaded floating Alginate gel beads

S. No.	Formulation Code	Particle size(mm)
1.	F1	2.80±0.01
2.	F2	2.65±0.02
3.	F3	2.43±0.01
4.	F4	2.64±0.01
5.	F5	2.43±0.03
6.	F6	2.01±0.01

Particle size of the gel beads ranges from 2.01±0.01mm to 2.80±0.01 mm. As the concentration of polymer increases its particle size increases.

Drug content:

Table 5: Drug content of the prepared Alginate gel beads

S. No	Formulation code	Drug content(mg)
1.	F1	56.00±0.05
2.	F2	62.00±0.023
3.	F3	68.00±0.040
4.	F4	61.00±0.05
5.	F5	58.00±0.020
6.	F6	55.00±0.028

The obtained results are reported in Table 13. The drug content was found to be in the range of 55±0.028mg-68±0.040mg.

Shape and Surface morphology:

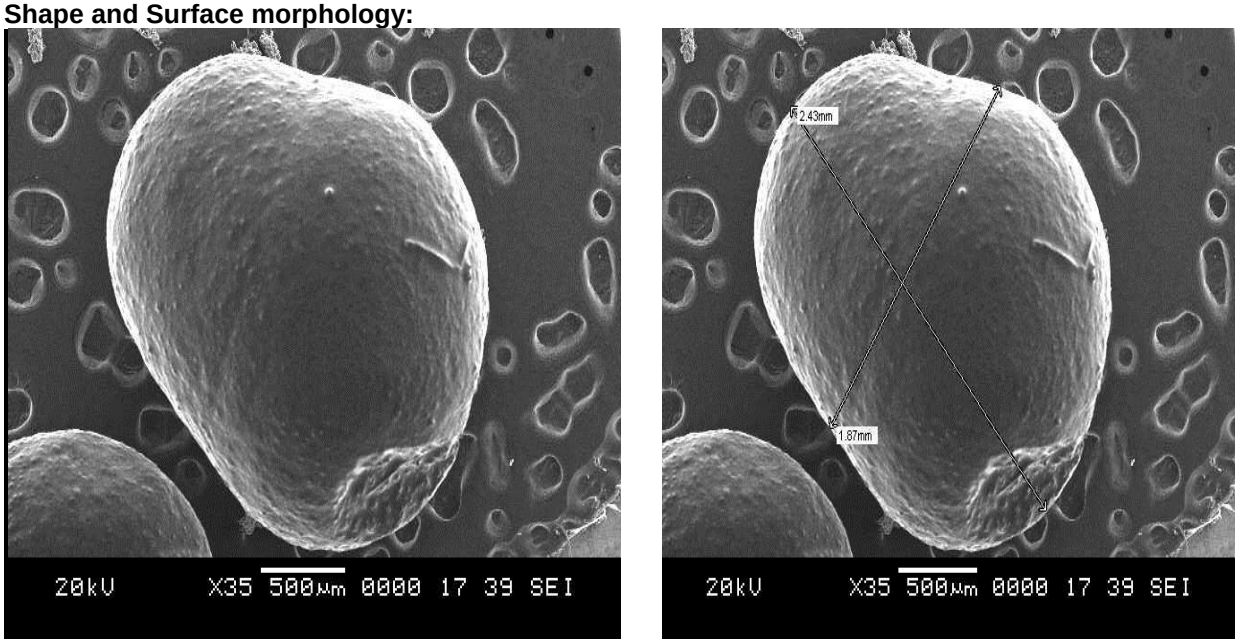

Fig. 7: SEM of Levodopa Floating gel beads (F3)

The shape and surface morphology of the prepared gel beads were observed by scanning electron microscopy. SEM photographs of formulations F3 revealed that gel beads were spherical, discrete with smooth surface.

***In-vitro* Buoyancy**

Table 6: *In- vitro* buoyancy percentage of Levodopa floating alginate gel beads

Sl. No	Formulation Code	Percentage Buoyancy (%)
1.	F1	30.15
2.	F2	82.35
3.	F3	85.70
4.	F4	81.25
5.	F5	82.35
6.	F6	70.58

The In-vitro buoyancy test was performed for all the formulations and the result was found to be 30.15%-85.70%.

***In-vitro* drug release:**

***In-vitro* drug release study of floating gel beads of Levodopa**

Table 7*: In-vitro* drug release data of all formulations (F1-F6)

S. No.	Time (hours)	Percentage Cumulative Drug Release					
		F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	1	20.21	15.92	17.82	10.13	20.97	25.98
3.	2	25.36	17.83	18.78	17.86	25.13	32.15
4.	3	35.82	28.89	27.63	20.81	30.67	36.51
5.	4	39.16	32.21	31.8	25.9	40.36	42.84
6.	5	45.15	37.47	35.43	30.18	45.95	50.48
7.	6	52.50	47.21	45.32	35.12	55.37	57.82
8.	7	58.18	53.05	51.1	45.91	62.95	63.91
9.	8	66.28	62.13	54.1	48.73	70.92	75.93
10.	9	72.84	66.04	61.89	52.71	80.38	82.75
11.	10	79.31	71.53	74.32	68.42	85.32	90.16
12.	11	84.02	80.03	82.65	72.95	90.94	93.76
13.	12	85.14	84.94	84.13	84.76	95.54	97.18

All the formulations were subjected for *in vitro* dissolution studies using USP type II dissolution apparatus in 900 ml of 0.1N HCl dissolution medium at 50 rpm at 37^{o}C ± 0.5^{o}C. The percentage of Levodopa released as a function of time for F6 is 97.18 for 12 hours. The percentage of Levodopa released as a function of time for formulation F3 was found to be 84.13 for 12 hours.

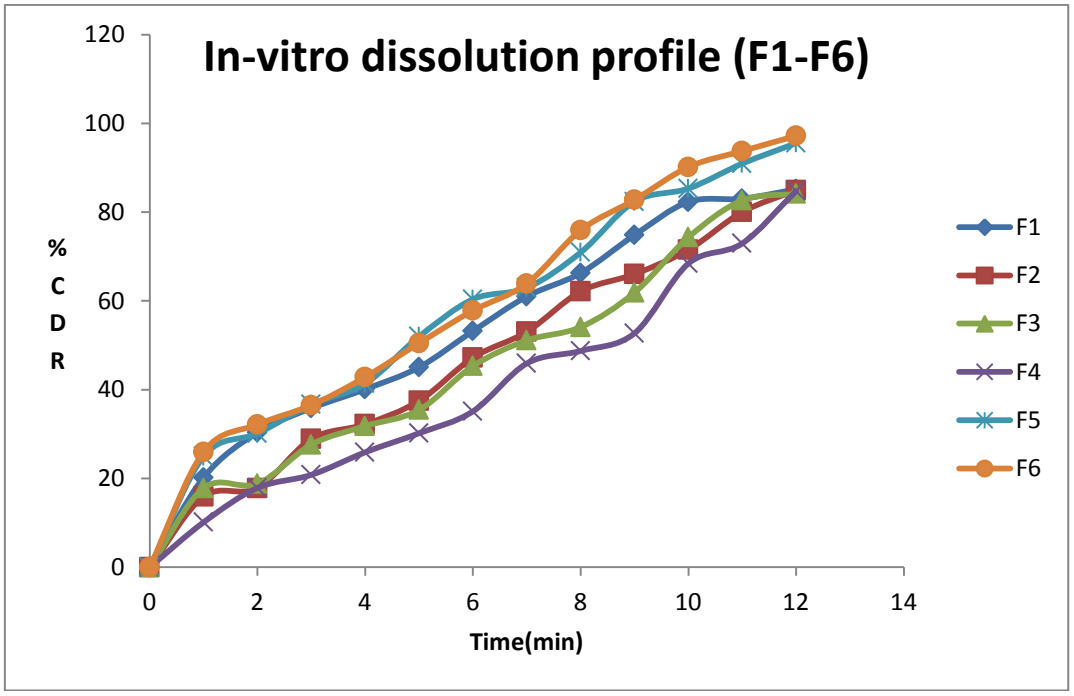

Fig. 8: *In-vitro* release profile Levodopa floating gel beads (F1-F6)

In-vitro drug release kinetics:

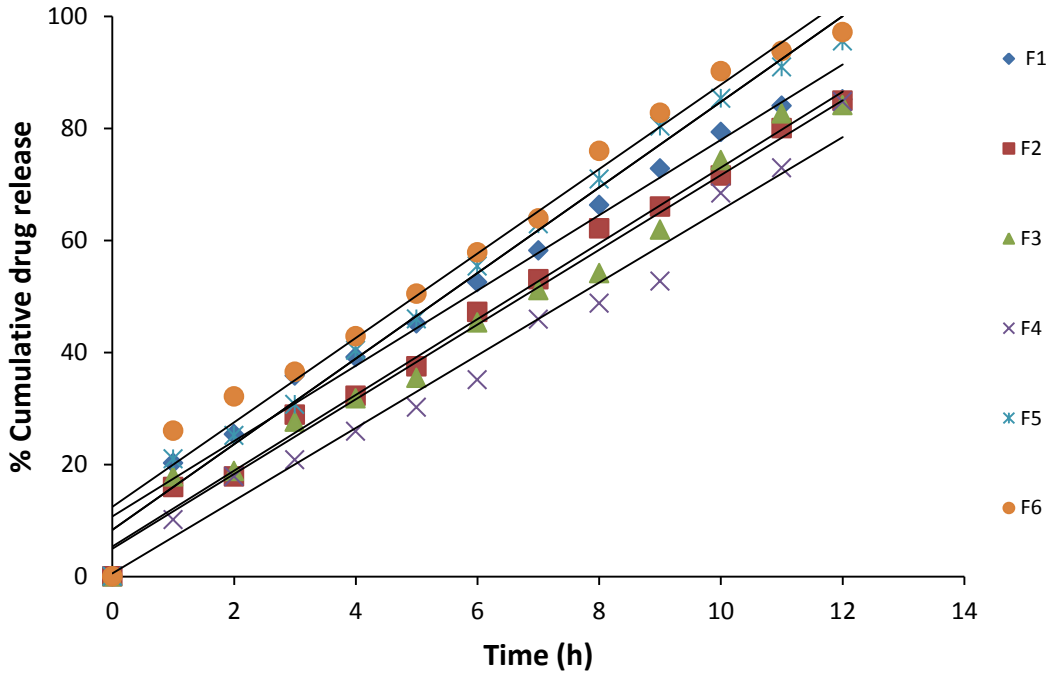

Fig. 9: Zero order kinetics

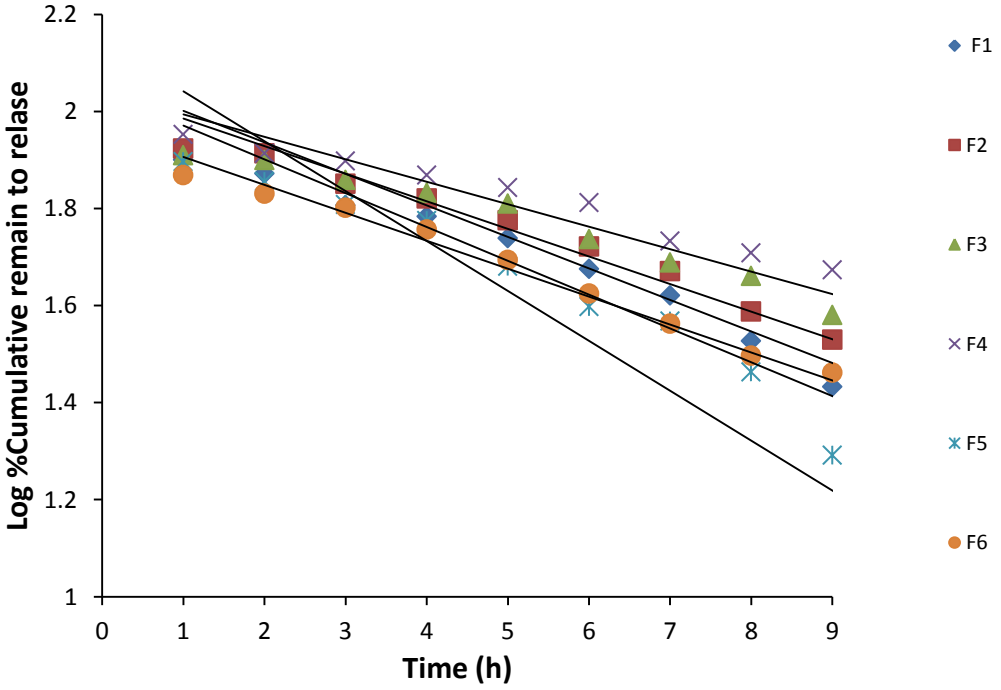

Fig. 10: First order kinetics

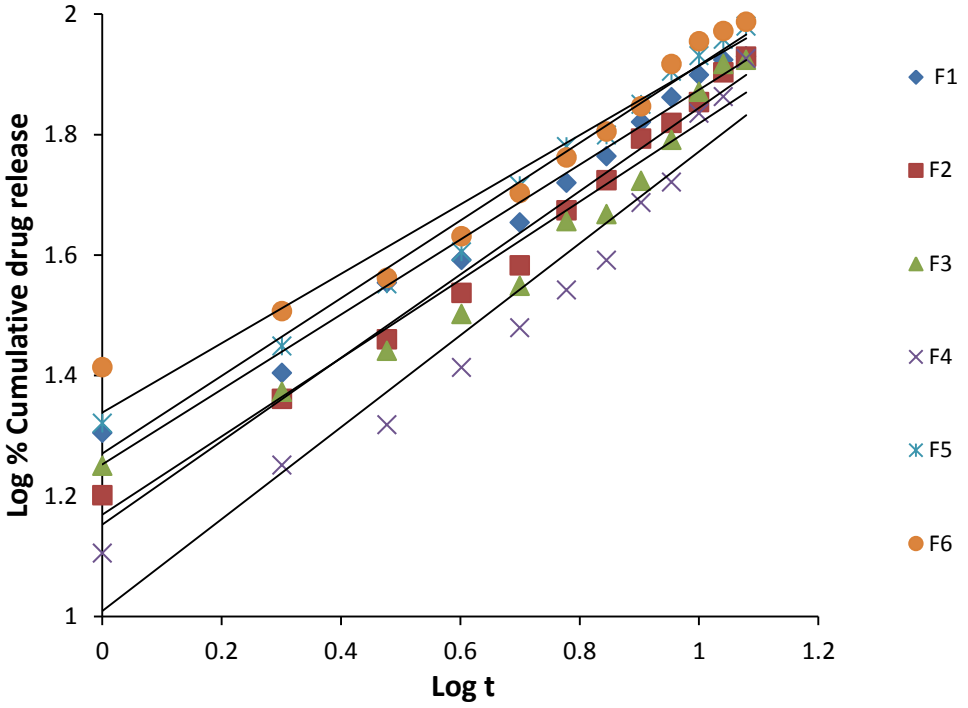

Fig. 11: Peppas model

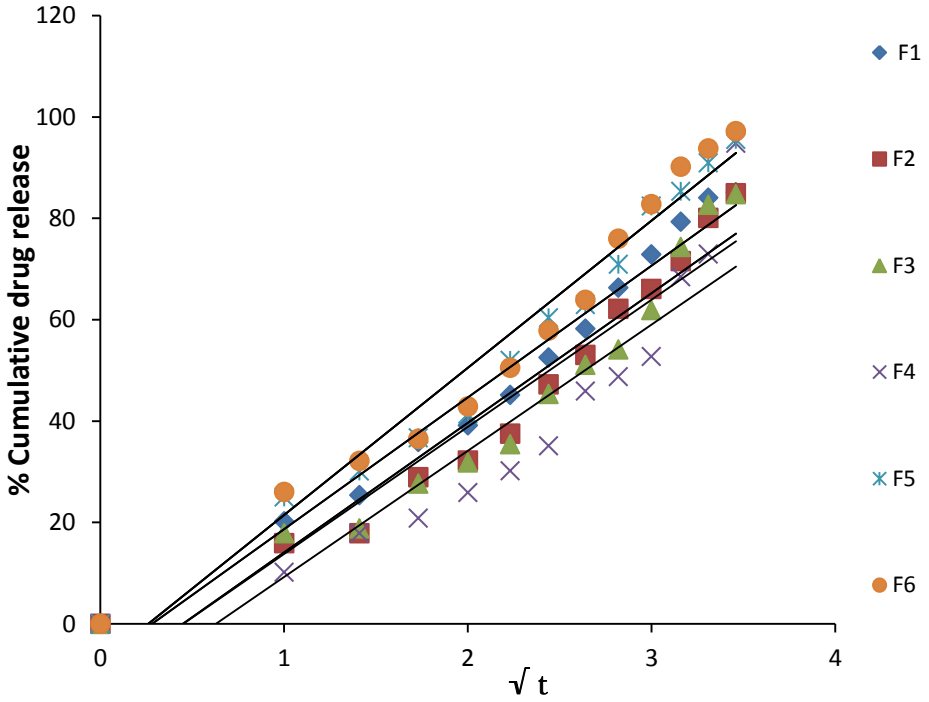

Fig.12: Higuchi model

Table 8: Kinetics release study of various floating gel beads of Levodopa formulations

Formulation code	Zero Order	First Order	Higuchi Matrix	Peppas Plot	
				R^2 values	n values
F1	0.9764	0.9642	0.9737	0.9748	0.6223
F2	0.9915	0.9466	0.9457	0.9837	0.6921
F3	0.9839	0.9376	0.9236	0.9404	0.6497
F4	0.9796	0.9420	0.8857	0.9403	0.7632
F5	0.9872	0.9056	0.9564	0.9844	0.6448
F6	0.9843	0.9807	0.9650	0.9555	0.5759

Stability Studies of the optimized formulations:

Table 9: Drug Content, Percentage Buoyancy and *In-vitro* drug release of floating gel beads of Levodopa formulation (F3) after Stability Studies

Time(Days)		Drug Content (mg)	Buoyancy (%)	% cumulative drug release
0		68.00	84	84.13
30	At 25 ± 2 °C/ 60 ± 5 % RH	67.80	83.8	84.12
	At 40 ± 2 °C/ 70 ± 5 % RH	67.12	83.2	84.00
60	At 25 ± 2 °C/ 60 ± 5 % RH	66.94	83.1	83.94
	At 40 ± 2 °C/ 70 ± 5 % RH	66.53	82	83.92

The stability studies were carried out for all the formulation at 25±2^{o}C with 60±5% RH and 40±2^{o}C with 70±5% RH for two month. The results indicated that the gel beads did not show any physical changes during the study period and the drug content was found of the formulation F3 around 66.53mg at the end of two month. There were no significant differences found in the percentage cumulative drug release after stability study.

CONCLUSION

Floating Gel beads of Levodopa were prepared successfully by emulsion gelation method by using polymer Sodium Alginate and coconut oil.

The following conclusions were drawn from the present investigation:

- Preformulation studies like Melting point, Solubility and UV analysis were carried out and they comply with the standards.
- The FTIR spectral data indicates that there was no interaction between drug and the utilized polymers. All the polymers are compatible with the drug.
- Six preliminary formulations were prepared by Emulsion Gelation method and were evaluated. All the prepared floating gel beads were subjected to various evaluation parameters like preformulation studies, spectroscopic studies, particle size analysis, micromeritic studies, drug content, entrapment efficiency, *in-vitro* buoyancy test, *in-vitro* drug release study.
- Micromeritic studies revealed that the prepared gel beads exhibited good flow property.
- The average particle size of the Levodopa floating gel beads has increased with an increase in its drug to polymer ratio.
- SEM analysis of the gel beads revealed that all the prepared gel beads were discrete spherical in shape with satisfactory surface morphology. The outer surface was of the gel beads smooth and dense.
- Buoyancy time increases with increase in polymer concentration. All the prepared formulation showed good percentage buoyancy in the range 30.15% to 85.70%.
- *In-vitro* release studies showed that gel beads containing higher concentration of polymer (4%) showed a larger degree of sustained release. The *in-vitro* drug release was found to be in the range of 84.13% to 97.18%.
- Drug release kinetics studies revealed that the release data was best fitted with zero order kinetics. The diffusion exponent ‘n’ value of the Koesemeyer-Peppas model was found to be in the range of 0.5-1 indicating Non-Fickian diffusion of drug through Levodopa floating gel beads.
- Short-term stability studies of the formulations indicate that there are no significant changes in the appearance, drug content, percentage buoyancy and dissolution parameter values after 60 days of storage at 25±2^{0}C with 60±5% RH and 40±2 ºC with 70±5% RH.

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