Journal of Pharmacreations
PharmaCreations
ISSN: 2348-6295
Pharmacreations \ Vol 9 \ Issue 2 \ Apr - Jun - 2022
Jouranl Home page: www. pharmareations.com
Research article Open Access

DESIGN AND IN-VITRO CHARACTERIZATION OF LEVODOPA FLOTTING MICROSPHERES

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ABSTRACT

Levodopa, anti-Parkinson's drug has been chosen as a model drug in the formulation of floating drug delivery systems for the present work. It has been reported that bioavailability of Levodopa when given orally is (30%) and half-life of 1.5 hours. They can increase the bioavailability of drugs that are mainly absorbed in the upper gastrointestinal tract. For the formulation, three biocompatible polymers HPMC, Ethyl cellulose and Eudragit were chosen in varying proportions with the drug. The floating microspheres of drug with HPMC and Ethyl cellulose were buoyant while those with Eudragit S 100 showed greater buoyancy. The overall curve fitting into various mathematical models was found to be on average. The formulations F 5 best fitted into zero order and shows nonfiction diffusion mechanism. Thus, the formulated floating microspheres seem to be a potential candidate as an oral gastroprotective controlled drug delivery system in prolonging the drug retention stomach and increasing the bioavailability of drug.

Keywords: Levodopa, anti-Parkinson's drug, HPMC, gastrointestinal tract, zero order

1. INTRODUCTION

1.1 Oral Controlled Release Drug Delivery Systems

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

2. LITERATURE REVIEW

Mostafavi A *et, al.*,[3] have studied on prolonged release gastroprotective (GT) formulation of ciprofloxacin could be administered once daily with a conventional tablet (CT). A variety of polymers and effervescent properties were utilized to optimize the desired disposition profile. Tablets were prepared by the direct compression technique and evaluated for physical properties, swelling, floating and drug release.

Sauzet C *et al.*,[4] have formulated sustained release (SR)-gastroretentive dosage forms (GRDF) enabling prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. A new strategy was proposed for the development of gastroretentive dosage forms for ofloxacin preferably once daily.

Chavanpatil M *et al.*,[5] have developed a new intra-gastric floating in situ gelling system for controlled delivery of amoxicillin for the treatment of peptic ulcer disease caused by *Helicobacter pylori* (*H. pylori*). Gellan based amoxicillin floating in situ gelling systems (AFIG) were prepared by dissolving varying concentrations of gellan gum in

deionized water containing sodium citrate, to which varying concentrations of drug and calcium carbonate, as gas-forming agent, was added and dissolved by stirring.

Dave BS *et al.*,[26] have prepared gastroretentive drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum and hydroxypropyl methylcellulose were evaluated for gel-forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated.

Sauzet C *et al.*,[7] have develop an innovative floating gastro retentive dosage form (GRDF). The developed technology induced a low-density dosage form containing high active pharmaceutical ingredient (API) concentration by using a hydrophobic dusty powder excipient under specific conditions. The new dosage form was obtained by state of the art wet granulation manufacturing process.

3. AIM AND OBJECTIVE

The objective of the present work is to develop gastro retentive (floating) microsphere for Levodopa.

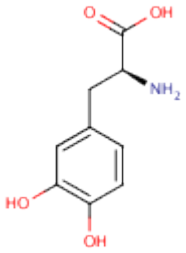
- Selection of right process for development of microspheres. A process like solvent evaporation is flexible and scalable.
- Selection of polymer to achieve controlled release for the required period of time.
- The characterization of microspheres in terms of encapsulation efficiency, particle size, release of drug from microspheres etc.

4. DRUG PROFILE

4.1 Levodopa

The naturally occurring form of dihydroxyphenylalanine and the immediate precursor of dopamine. Unlike dopamine itself, it can be taken orally and crosses the blood-brain barrier. It is rapidly taken up by dopaminergic neurons and converted to dopamine.

Structure



MolecularWeight:197.1879

Chemical Formula: $C_9H_{11}NO_4$

IUPAC Name: (2S)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid

5. MATERIALS AND METHODS

5.1 MATERIALS

Materials used for the formulation development

1	LEVODOPA	Chandra labs Hyderabad	Pharmaceutical grade
2	HPMC	SD Fine Chemicals Ltd., Mumbai	Pharmaceutical grade
3	ETHYL CELLULOSE	SD Fine Chemicals Ltd., Mumbai	Pharmaceutical grade
4	POLY VINYL ALCOHOL	SD Fine Chemicals Ltd., Mumbai	Pharmaceutical grade
5	EUDRAGIT S100	SD Fine Chemicals Ltd., Mumbai	Pharmaceutical grade

Equipment used for the process

S. No	Name of the Equipment	Manufactured by
1	Dissolution apparatus	Lab India
2	Glass ware	Cad mach
3	U.V. Spectrophotometer	Shimadzu
4	Analytical Balance	Adair Dutt Instruments Pvt. Ltd., AD50B
5	Thermostatic Hot Plate with Magnetic Stirrer	Remi Motor Mumbai

5.3 ESTIMATION OF LEVODOPA

5.3.1 Standard Graph Of Levodopa

Standard Stock solution: 100 mg of levodopa was dissolved in small quantity of ethanol and make up to 100 ml 0.1N HCL to give a concentration of (1000 µg/ml)

5.3.2 Calibration curve of Levodopa in 0.1 N HCL:

The standard solutions were prepared by proper dilutions of the primary stock solution with buffer to obtain working standards in the concentration range of 10-50µg/ml of pure sample of levodopa.

5.3.3 Drug-Excipients Compatibility study

Levodopa was mixed with all excipients, used in the formulation in different ratios and subjected to Physical observation/FTIR.

5.4 EXPERMENTAL METHODS

5.4.1 Preparation of Floating Microspheres Of Levodopa

Floating microspheres were prepared by the solvent evaporation method. Various concentration of polymer in suitable solvents were mixed well with the levodopa with different ratios of polymer as shown in Table and this pasty.

5.4.2 Formulation Design

Table 1: Formulation of Levodopa Floating Microspheres

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levodopa	200	200	200	200	200	200	200	200	200
HPMC	200	400	600	-	-	-	-	-	-
Eudragit S100	-	-	-	200	400	600	-	-	-
Ethyl cellulose	-	-	-	-	-	-	200	400	600
$NaHCO_3$	200	400	600	200	400	600	200	400	600
Water (ml)	q.s	q.s	q.s	-	-	-	-	-	-
Dichloromethane:Ethanol (2:1) (ml)	-	-	-	q.s	q.s	q.s	-	-	-
Ethanol (ml)	-	-	-	-	-	-	q.s	q.s	q.s

q.s – Quantity sufficient

5.5 Evaluation Of Microspheres

5.5.1 In vitro Buoyancy studies

The in vitro buoyancy was determined by floating lag time, and total floating time. The microspheres were placed in a 100ml beaker containing 0.1N HCl. The time required for the microspheres to rise to the surface and float was determined as floating lag time.

$$\% \text{ Buoyancy} = Q_f / (Q_f + Q_s) \times 100$$

Where,

Q_f and Q_s are the weight of the floating and settled microspheres respectively.

5.5.2 Drug Entrapment Efficiency

Microspheres equivalent to 200 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl (pH-1.2) repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using 0.1N HCl (pH-1.2).

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

5.5.3 Determination of percentage yield

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula[37].

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

5.5.4 In-vitro Release Study

The drug release study was performed for microsphere containing quantity equivalent to 200mg of Levodopa by using USP dissolution apparatus Type I in 900 ml of 0.1N HCl dissolution media (pH-1.2) at 100 rpm and 37^0C temperature. 10 ml of sample was withdrawn at predetermined time interval for 12 hours and same volume of fresh medium was replaced to maintained sink condition. Details of dissolution testing: • Apparatus: Electrolab USP TDT 08L, • Dissolution media: 0.1 N HCl (pH-1.2) , • Speed: 50 rpm, • Volume of medium: 900 ml, • Aliquots taken at each time interval: 5ml

6. RESULTS AND DISCUSSION

6.1 PREFORMULATION STUDIES

SPECTROSCOPIC STUDIES

6.1.1 Determination of λ max

A solution of 10µg/ml of levodopa was scanned in the range of 200 to 400nm. The drug exhibited a λmax at 280nm in simulated gastric fluid pH 1.2 and had good reproducibility. Correlation between the concentration and absorbance was found to be near to 0.9995, with a slope of 0.0349 and intercept of 0.0097.

6.1.2 Calibration curve of levodopa in 0.1 N HCL

the calibration curve data of levodopa in 0.1NHCL at 280nm. Fig.1 shows the standard calibration curve with a regression value of 0.993, slope of 0.0292 and intercept of 0.0021. The curve was found to be linear in the concentration range of 2-12µg/ml.

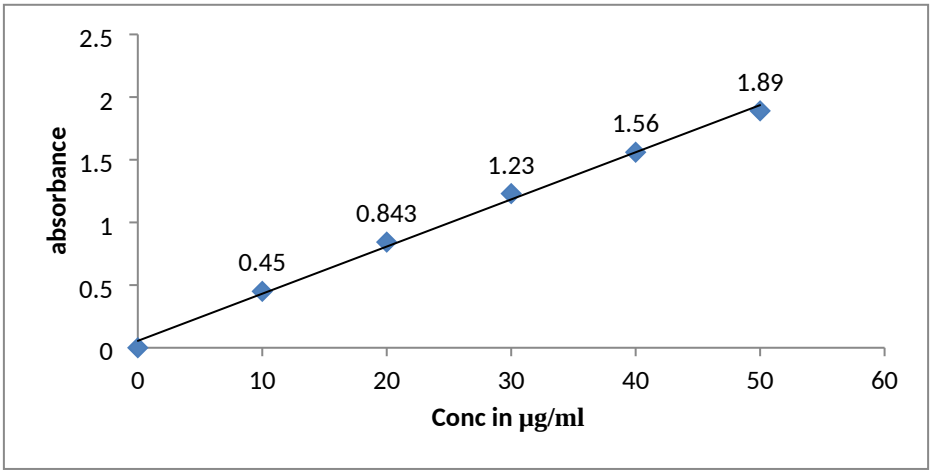


Fig 1: Standard graph of levodopa in 0.1 N HCL

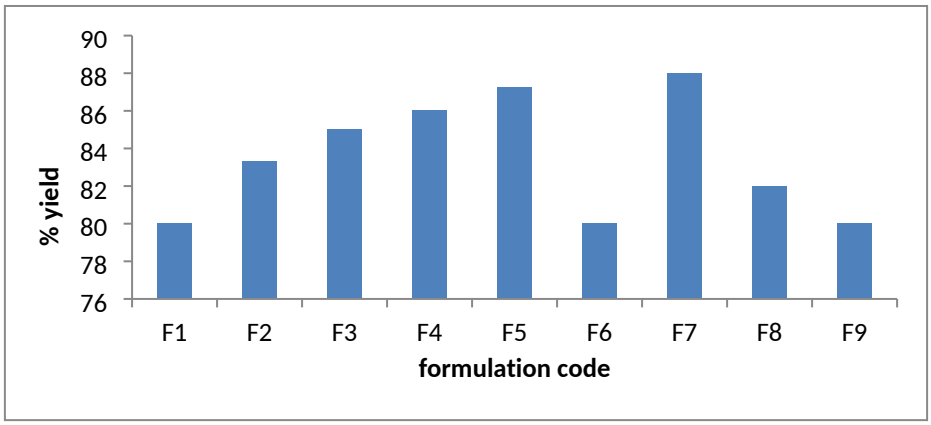


Fig 2: % yield vs Formulation code

Table 2: Microparticulate Analysis

Formulation	Bulk density	Tapped density	Carr's Index	Hausner	Angle of
F1	0.45±0.045	0.52 ± 0.09	15.60±0.2	1.15±0.02	28.06⌖ 0.31
F2	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	27.58⌖ 0.15
F3	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08	28.44⌖ 0.11
F4	0.45±0.045	0.52 ± 0.04	15.19±0.1	1.15±0.06	28.36⌖ 0.13
F5	0.44±0.044	0.52± 0.01	15.48±0.6	1.18±0.08	28.52⌖ 0.19
F6	0.45±0.045	0.51 ± 0.04	13.48±0.8	1.13±0.09	29.32⌖ 0.19
F7	0.51±0.045	0.59 ± 0.04	14.48±0.8	1.15±0.09	29.69⌖ 0.19
F8	0.45±0.041	0.52 ± 0.10	15.60±0.21	1.15±0.04	28.06⌖ 0.41
F9	0.44±0.041	0.52± 0.11	15.48±0.54	1.18±0.12	28.52⌖ 0.15

Table 3: Average particle size of Levodopa microspheres

S.No	Batches	Mean Particle Size(µm)
1	F_1	540 µm
2	F_2	602 µm
3	F_3	644 µm
4	F4	612 µm
5	F5	528 µm
6	F6	624 µm
7	F7	588 µm
8	F8	598 µm
9	F9	626 µm

In-Vitro Drug Release Studies

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, pH 1.2. The results of the in-vitro dissolution studies of formulations F_1 to F_9 are shown in table no.25 The plots of Cumulative percentage drug release Vs Time. Table shows the comparison of % CDR for formulations F_1 to F9.

Table 4: Percentage cummulative drug release for all formulations

TIME(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	23	18	16	28.4	16.25	14	25.3	23	11.30
2	32	27.2	24	40.3	21.3	20	37.2	38	19.6
3	41.5	36	31	49.7	28.6	26	44.3	45	25.4
4	57.6	45	42	55.3	30.4	28	52.4	50	28.2
5	68.2	53	49	62.4	38.2	38	57.8	54	36.3
6	79.7	67	54	68.3	44.3	42	65.2	63	40.4
7	86.4	72	58.7	76.9	51.6	48	70.8	69	46.8
8	-	84	70.4	83.2	57.2	54	79.2	78	59.3
10	-	-	-	86.9	78.3	63	85.2	83	62.4
12	-	-	-	-	86.2	76	-	-	71.2

In-Vitro Drug Release Kinetics

For understanding the mechanism of drug release and releas e rate kinetics of the drug from dosage form, the in-vitro drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer- Peppas model. The values are compiled. The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered.

Table 5: R^2 values for release kinetics

RELEASE KINEITCS				
	ZERO	HIGUCHI	PEPPAS	FIRST
	1	2	3	4
	Q Vs T	Q Vs √T	Log C Vs Log T	Log % Remain Vs T
Slope	6.85	24.73	1.18	-0.06
Intercept	4.99	10.45	0.73	2.06
Correlation	0.99	0.95	0.83	-0.95
R 2	0.9850	0.9365	0.69	0.91

Stability Studies of Levodopa Optimized Formulation

The optimized formulation of Levodopa (F5) were subjected to short-term stability testing by storing the microspheres at room temperature 25°C/60%RH.

Table 6: Stability studies of optimized formulation at room temperature

Time	Colour	Drug entrapment efficiency ± St.D. at Room Temperature	Cumulative % drug release ± St.D.
First day	White	92.00± 0.91	86.20±0.55
30 days	White	91.84 ± 0.23	86.01±0.72
60 days	White	91. 06 ± 0.62	85.62±0.65
90 days	White	90. 92 ± 0.31	85.20±0.98

7. SUMMARY

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired plasma concentration of the drug for a particular period of time. However, incomplete release of the drug, shorter residence times of dosage forms in the upper GIT leads to lower oral bioavailability. Such limitations of the conventional dosage forms have paved way to an era of controlled and novel drug delivery systems.

8. CONCLUSION

The present study has been a satisfactory attempt to formulate a floating Microspheres of Levodopa with a view of improving its oral bioavailability and giving a controlled release of the drug. From the experimental results it can be concluded that, FT-IR study shows no significant shifting of the peaks therefore it confirms the short term stability of the drug in the microspheres. Biocompatible polymers like can be HPMC, Ethyl cellulose and Eudragit used to formulate a floating Microspheres. Good percentage drug entrapment and practical yields were obtained with the polymers. The flow properties of all formulations were within the acceptable range and therefore they could be easily filled into capsules. The floating microspheres of drug with HPMC and Ethyl cellulose were buoyant while those with Eudragit S 100 showed greater buoyancy. Cumulative percentage drug release significantly decreased with increase in polymer concentration.

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