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Original Article

FORMULATION AND EVALUATION OF LEVODOPA EFFERVESCENT FLOATING TABLETS

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ABSTRACT

Objective: Levodopa is an immediate precursor of dopamine used in treatment of Parkinsonism disorders. The Levodopa effervescent floating tablets were prepared by direct compression technique, using different low density polymers (POLYOX different grades) in various drug polymer ratios.

Methods: The Levodopa effervescent floating tablets were prepared by direct compression method. The floating tablets were evaluated for friability, thickness, hardness, weight variation test, drug content, *in vitro* release and floating properties. The drug excipients compatibility was evaluated by DSC and FT-IR study.

Results: All the batches showed compliance with pharmacopoeia standards. Among all the formulation F4 containing PEO WSR 303 in 1:1 drug polymer ratio showed controlled drug release for 12h (99.15%) emerging as the best formulation and follow first order kinetics via, swelling, diffusion. An *in vitro* buoyancy study reveals that all batches showed good *in vitro* buoyancy. The DSC study revealed that there was no strong interaction between Levodopa and excipients. Stability studies were carried out for best formulation F4 (PEO WSR 303 in 1:1 drug polymer ratio) according to ICH guidelines. Stability studies (40±2oC/75±5% RH) for 3 month indicated that Levodopa was stable in floating tablets.

Conclusion: Hence different grades of low density polymer (PEO) in various drug polymer ratios can be used to prepare Levodopa floating tablets for prolongation of gastric residence time with enhanced patient compliance.

Keywords: Levodopa, Polyethylene oxide (PEO), Sodium bicarbonate, Floating drug delivery system, Effervescent floating tablets.

INTRODUCTION

Oral drug delivery is the most widely explored routes of administration among different routes that have been utilized for systemic delivery of drugs via the different dosage form. Oral route is considered most natural, suitable and most widely accepted one by the patients due to its ease of administration, patient acceptance, and cost effective manufacturing process [1]. An oral drug delivery system providing a uniform drug delivery can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn't take into account the site specific absorption rates within the gastrointestinal tract (GIT) [2]. Therefore, there is a need of developing a drug delivery system that releases the drug at the right time, at the specific site and with the desired rate. Invariably, conventional dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time. The concept of gastro retentive drug delivery system came from the need to localize the drug at a certain site in the body [3]. It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of these drugs. Especially the site of drug absorption is mainly stomach or upper part of the small intestine, then it is necessary to retain the dosage form at the site of absorption, but the gastrointestinal transit is the limitation for such type of dosage forms [4].

Controlling the residence time of drug delivery system in a particular region of the gastrointestinal (GI) tract can be made via several approaches: Intragastric floating system, high density system, muco adhesive system, unfolding, extendable and expandable system and porous Hydrogels [5, 6]. On contact with the gastric fluid form a water impermeable colloidal gel barrier and bulk density<1 and thus remain buoyant in the stomach, for a prolonged period of time, without affecting the gastric emptying rate [7, 8].

Levodopa is clinically used for the treatment of Parkinsonism disorders and is the naturally occurring form of di hydroxy phenylalanine and the immediate precursor of dopamine. Levodopa is a metabolic precursor of dopamine [9]. It restores dopamine levels in extrapyramidal centers (substantianiagra) that atrophy in Parkinsonism. Levodopa is readily transported into the CNS and converted to dopamine in the brain. Large doses of Levodopa are required, because much of the drug is decarboxylated by dopamine decarboxylase to dopamine in the periphery [10]. The main limitation to the therapeutic effectiveness of Levodopa is having a short plasma half-life of 1 to 3 hours, low bioavailability and has a high solubility in the acidic pH [11, 12]. Levodopa uptake mainly takes place in an upper part of small intestine. It appears more plausible that slower delivery to the absorption area in the upper small intestine promotes the uptake of Levodopa. The gastroretentive drug delivery is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the levodopa by releasing before absorption area. The aim of the present investigation is to develop floating drug delivery system for Levodopa, which increases the gastric residence time, minimizes the problems associated with conventional dosage forms.

MATERIALS AND METHODS

Materials

Levodopa was a gift sample from Hetero Pharma Ltd, Hyderabad. PEO WSR coagulant, PEO WSR 303 and PEO N 750 other polymers were received as the gift sample from Aurobindo Pharma, Hyderabad. Sodium bicarbonate, Talc and magnesium Stearate from SD fine chemicals Pvt. Ltd, Mumbai. Hydrochloric acid is from Merck specialties Pvt Ltd, Mumbai.

Methods

Levodopa floating tablet preparation

Levodopa floating tablets were prepared by direct compression method. The different formulation composition is shown in table 1. All the powders passed through 40 mesh sieve. The required quantity of Levodopa, various PEO grades and sodium bicarbonate was mixed thoroughly. Talc and magnesium stearate were finally added as a glidant and lubricant respectively. The blend was directly compressed (6 mm and 7.5 mm diameter, circular flat faced punches) on a sixteen station rotary tablet punching machine (Cadmach Machinery Ltd., Ahmedabad, India). Each tablet contained 50 mg of Levodopa. All the tablets were stored in airtight containers for further study.

Table 1: Composition of Levodopa floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levodopa	50	50	50	50	50	50	50	50	50
PEO WSR coagulant	50	75	100	-	-	-	-	-	-
PEO WSR 303	-	-	-	50	75	100	-	-	-
PEO N 750	-	-	-	-	-	-	50	75	100
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Total weight	123	148	173	123	148	173	123	148	173

Evaluation of floating tablets

Thickness

The thickness in millimeter (mm) was measured individually for 10 pre weighed Levodopa floating tablets of each formulation by using Digital Vernier caliper. The average thickness and standard deviation were reported [13].

Tablet hardness

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 5 Levodopa floating tablets with known weight and thickness of each formulation was recorded in kg/cm^2 and the average hardness and standard deviation were reported [14].

Friability

Ten Levodopa floating tablets were selected from each batch and weighed. Each batch of tablets was rotated at 25 rpm for 4 min (100 revolutions) in the Roche friabilator. The Levodopa tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets [15].

$$Percentage friability = (Initial weight - Final weight)100/Initial weight$$

Weight variation test

All prepared Levodopa floating tablets were evaluated for weight variati on as per USP monograph. Ten (10) Levodopa tablets from each batch were individually weighed in grams (g) on an analytical balance. The average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits [16].

Drug content

The formulated Levodopa effervescent floating tablets were assayed for drug content. From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one Levodopa tablet was transferred into a 100 ml volumetric flask, to this 100 ml of 0.1N HCL was added and then the solution was subjected to sonication for about 2 hs. The solution was filtered and suitably diluted with preheated fresh 0.1N HCL buffer. The drug content was estimated by recording the absorbance at 280 nm by using UV-Visible spectrophotometer [17].

***In-vitro* drug release**

In vitro Levodopa release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 37±0.5ºC. The study was performed with rotation speed of 100 rpm using 900 ml dissolution medium of 0.1N HCl buffer. The samples were withdrawn at predetermined intervals and replaced with an equal volume of buffer. The Levodopa release at different time intervals was measured using an ultraviolet visible spectrophotometer (Elico, Ahmedabad, India) at 280 nm after suitable dilution. The study was performed in triplicate [18].

Release kinetic studies

To find out the mechanism of drug release from Levodopa floating tablets, the *in vitro* release data was treated with different kinetic models, namely zero order, first order, Higuchi and Korsmeyer-Peppas. A criterion for selecting the most appropriate model was based on goodness of fit, high regression coefficient value [19].

***In vitro* buoyancy test**

The prepared Levodopa floating tablets were subjected to *in vitro* buoyancy test by placing them in 250 ml beaker containing 200 ml 0.1N HCl (pH 1.2, temp. 37±0.5 ^{0}C). The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which the dosage form remains buoyant is called Total Floating Time (TFT) [20].

DSC studies

Thermal properties of Levodopa and best formulations were evaluated by differential scanning Calorimetry (DSC) using a diamond (DSC) (Mettler star sw8. 10). The analysis was performed at a rate 5 ^{0}C min^{-1} to 350 ^{0}C temperature range under nitrogen flow of 25 ml min^{-1} [21].

FTIR studies

The pure Levodopa drug and best formulations powders were mixed separately with IR grade KBr and pellets were prepared by applying a pressure of 10 tons in a hydraulic press. The pellets were analyzed in the frequency range between wave numbers 4000 to 400 cm^{-1}at 4 cm^{-1} resolution.

Stability studies

The stability was carried out according to ICH guidelines. The best formulation was subjected to stability study at 40°C/75% RH for 90 d. The samples were evaluated for hardness, friability and drug content during stability studies [22].

RESULTS AND DISCUSSION

The physical attributes of the Levodopa floating tablet were found to be satisfactory. Typical tablet defects, such as capping, chipping and picking, were not observed. The physicochemical characterizations of different batches of Levodopa floating tablets are given in (table 2). The thicknesses of the Levodopa tablets were ranged between 3.31±0.20 to 3.88±0.02 mm. All the batches of Levodopa showed uniform thickness.

Weight variations for different formulations of Levodopa tablets were found to be 122.47±0.71 to 173.13±0.54 mg. The average percentage deviation of all Levodopa floating tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement [23].

The hardness of all the Levodopa floating tablet formulations were ranged from 4.49±0.51 to 4.86±0.36 kg/cm^2 indicated good mechanical strength with physical and mechanical stress condition, this may be referred to increasing the concentration of PEO polymer that present in formulas, tablet hardness was significantly increased with increased polymer concentration, viscosity and compression force [24].

The percentage friability of all the formulations ranged from 0.300 to 0.594 %. In the present study, the percentage friability for all Levodopa floating tablet formulations was less than 1% which ensure that formulated tablets are mechanically stable; friability was unaffected with polymer concentration and viscosity, however was significantly decreased with increased compression force [24].

The percentage of drug content for F1 to F9 was found to be in between 99.60±0.17% to 100.76±0.94% of Levodopa, which indicates that the prepared dosage form (floating tablets) had uniform distribution and proper dose of levodopa, which may be attributed to the effect of PEO polymer and sustained drug release [25].

Table 2: Physicochemical properties of levodopa floating tablets

Formulation code	Hardness (kg/cm²)	Thickness (mm)	% Friability	Weight variation	Drug content	Floating lag time (Sec)	Floating time (hrs)
F1	4.53±0.28	3.42±0.04	0.374	122.97±0.55	99.60±0.17	46	10
F2	4.69±0.31	3.64±0.17	0.352	147.71±0.69	100.16±0.06	69	12
F3	4.77±0.41	3.81±0.17	0.502	173.04±0.56	99.90±0.19	95	>12
F4	4.49±0.51	3.51±0.03	0.545	122.81±0.57	99.63±0.23	32	>12
F5	4.62±0.22	3.69±0.11	0.594	147.93±0.42	99.90±0.29	54	>12
F6	4.71±0.26	3.88±0.02	0.300	173.13±0.54	100.76±0.94	67	>12
F7	4.61±0.26	3.31±0.20	0.536	122.47±0.71	101.03±0.11	68	7
F8	4.70±0.30	3.64±0.06	0.593	147.40±0.38	100.50±0.45	97	10
F9	4.86±0.36	3.69±0.07	0.514	172.85±0.47	100.65±0.36	131	10

All the batches of Levodopa floating tablets were found to exhibit short floating lag times due to the presence of a gas generating agent, sodium bicarbonate. The buoyancy properties of various Levodopa floating tablets were given in table 2. The floating lag time of all formulations was less than 3 min and floating duration was more than 12 h.

This can be explained by that a high polymer content result in the formulation of a strong gel, as a PEO polymer content is increased, the resulting gelatinous diffusion layer becomes stronger and more resistant to diffusion [26].

The Levodopa release from the floating tablets prepared using PEO polymers was slow release up to 16 h, depending upon the concentration and type of PEO polymer used. The order of increasing release retarding effect observed with various PEO polymers was polyox WSR 303<polyox coagulant<polyox N 750. As increase in the polymer concentration increases the viscosity of the gel as well as the formation of gel layer with longer diffusional path. This could cause a decrease in the effective diffusion co-efficient of drug and therefore reduction in drug release rate. The comparative dissolution profile is presented in fig. 1.

Based on the results of all formulations, F4 was selected as best formulation because it showed 99 % cumulative drug release at the end of 12 h. F4 formulations follow first order release kinetics with the diffusion mechanism. Korsmeyer-Peppas plots, 'n' value 0.917 indicating that the Levodopa releases mechanism followed anomalous transport mechanism.

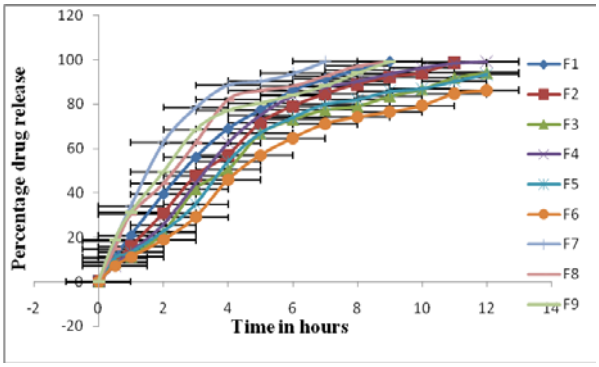

Fig. 1: Comparative release profile of formulation F1 to F9

The *in vitro* dissolution data was fitted in different kinetic models viz. Zero order, first order, Higuchi and Korsmeyer-Peppas equation (table 3). The release kinetics shows that the prepared Levodopa floating tablets with different grades of PEO in various ratios follow first order kinetics with the diffusion mechanism. The release exponent of the Peppas equation n value was between 0.515 to 0.983 suggests the drug release mechanism was non Fickian diffusion transport mechanism.

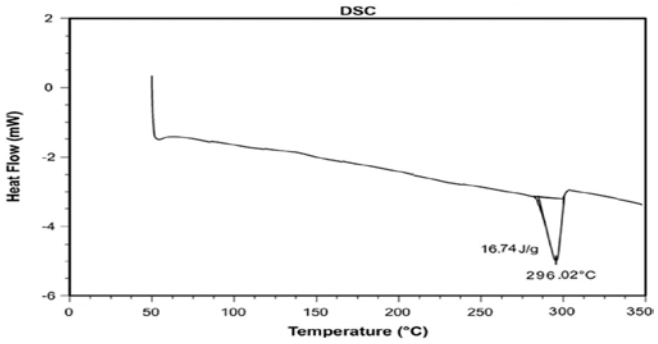

Fig. 2: DSC Thermo grams of pure Levodopa

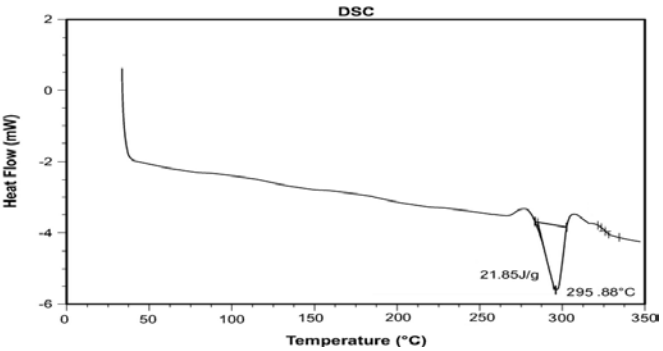

Fig. 3: DSC Thermo grams of best formulation F4

Table 3: Kinetic parameter of levodopa floating tablets

Formulation code	Zero order	First order	Higuchi	Korsmeyer peppas (n)	Korsmeyer peppas (r^2)
F1	0.972	0.980	0.986	0.734	0.980
F2	0.983	0.992	0.987	0.844	0.974
F3	0.973	0.981	0.985	0.949	0.974
F4	0.975	0.989	0.992	0.917	0.867
F5	0.975	0.986	0.982	0.943	0.935
F6	0.981	0.987	0.985	0.983	0.931
F7	0.891	0.896	0.948	0.527	0.922
F8	0.928	0.966	0.977	0.584	0.963
F9	0.908	0.972	0.972	0.515	0.957

DSC study was conducted on the selected formulations. A DSC thermo gram of pure Levodopa shows sharp endothermic peak at 296.02˚C. Similar endothermic peaks were obtained at 295.88^{0}C for the best formulation F4. The presence of all peaks indicates that all ingredients are compatible with Levodopa and no incompatibility between the selected ingredients. A thermo gram of F4 formulation and drug are shown in fig. 2-3.

FT-IR studies were carried out to know the compatibility. FT-IR results revealed no interaction between levodopa and excipients, since similar peaks of specific functional groups were observed as shown in fig. 4-5. It was found that there was no interference to the Levodopa with excipients and PEO polymer used in the formulations.

F4 formulation was selected for the stability studies. The results of the stability study were shown in table 4. The Levodopa floating tablets did not show any significant change in physicochemical parameters and other tests. Thus, it was found that the floating tablets of Levodopa (F4) were stable under short term storage conditions for at least 3 months.

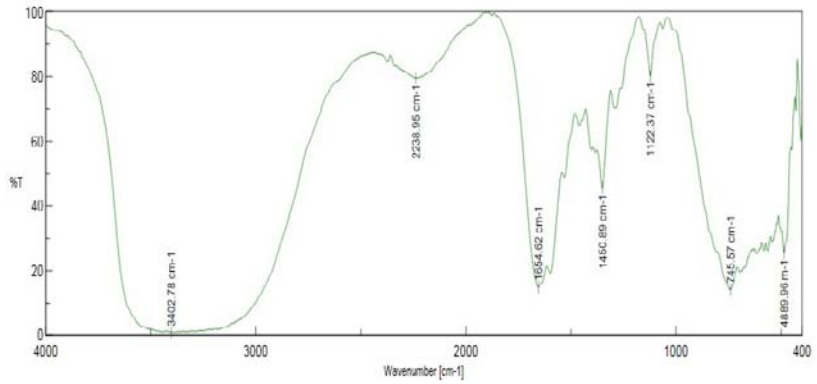

Fig. 4: FTIR thermo grams of thermo grams of pure levodopa

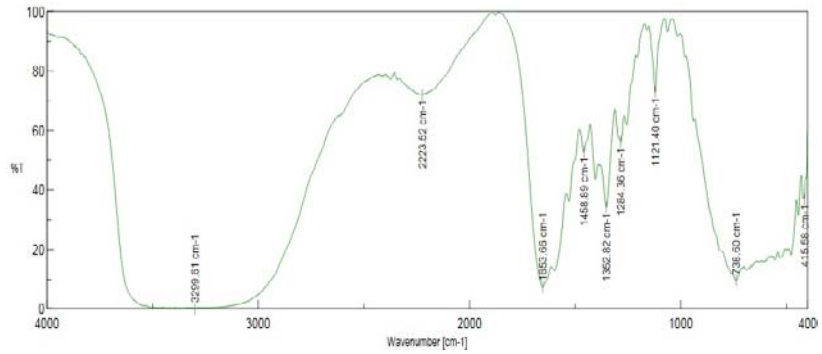

Fig. 5: FTIR thermo grams of best formulation F4

Table 4: Stability study results of formulation F4

Formulation code	Stability period	Hardness (Kg/cm^2)	Friability	Drug content %
F4	0	4.5±0.51	0.55	99.63±0.23
	30 Days	4.4±0.61	0.59	99.13±0.46
	60 Days	4.2±0.54	0.67	98.21±0.65
	90 Days	4.0±0.73	0.77	97.35±0.37

CONCLUSION

The present work was to study the effect of various low density PEO polymers on *in vitro* release rate from a floating tablet of Levodopa. The floating drug delivery was a promising approach to achieve a prolongation of gastric residence time of the Levodopa. Different types of low density matrix forming polymers PEO were studied. Sodium bicarbonate was added as a gas generating agent to improve

the floating capacity of the tablet. Formulation F4 containing PEO 303 showed sustained drug release for 12h (99.15%) emerging as best formulation. The cumulative percentage drug was decreased with increase in polymer concentration. Mechanism of drug release of best formulation F4 found to be first order non-Fickian diffusion. IR and DSC studies proved that no chemical interaction in Levodopa and the polymer of the developed floating tablets. The stability studies were carried out according to ICH guidelines and selected F4 formulation was stable at 40°C/75% RH up to 3 months. Thus, the results of the current study clearly indicate, a promising potential of the Levodopa floating system as an alternative to the conventional dosage form. The prepared formulations can be successfully commercialized after establishing the safety and efficacy in healthy human volunteers.

CONFLICT OF INTERESTS

Declared None

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