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Entacapone microsponges in the treatment of acute Parkinson's disease: Design, development and evaluation

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***Abstract*---**Objective: The current study was based on the many different dose frequencies of entacapone, an anti-Parkinson's drug that was loaded with microsponges to change the dose frequency of the drug administration. Methods: Microsponges were made utilizing polymethacrylate polymers such as eudragit L100, eudragit S 100, and eudragit RS 100 in various ratios using a quasi-emulsion solvent diffusion, ratios such as (1:0.5, 1:1, 1:1.5 and 1:2). These polymers release the drug in a controlled manner. The polymer used for the preparation of microsponges was useful in forming sponges in which the drug was entrapped. By using the 3 polymers,12 formulations were prepared. Results: FT-IR and DSC tests were carried out and it was clear from the FT-IR and DSC spectra that there were no interactions between the entacapone and the polymer. out of 12 formulations 3 formulations were selected as optimized formulations based on the production yield (%), encapsulating efficiency, drug loading (%), and SEM analysis says that the produced microsponges formulation was extremely porous, indicating their potential for increased drug loading. In vitro dissolution profile revealed that from the three optimized formulations (RS2, S2, and L2) L2 formulation was more efficient, releasing 98.90% of the drug during a 12 h period and the results were evaluated kinetically. The best-fitted model was found to be the Higuchi model (R^2=0.9861) for L2 formulation. The 'n' value is 0.4487 which is indicative of quasi-fiction diffusion. Conclusions: It was proposed that entacapone microsponges having a porous structure and offering more extensive drug release are controlled by the predetermined rate in the treatment of acute Parkinsonism.

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Keywords---microsponges, eudragit S 100, eudragit L100, eudragit RS 100, Parkinsonism.

Introduction

Parkinson's disease (PD) is a progressive movement illness that affects 52.85 people out of every 100,000. The annual mortality rate was around 2.89/100,000, with an annual risk rate of 8.98 deaths[1]. Damage to dopaminergic neurons in the nigrostriatal pathway causes PD, which causes dementia, depression, and autonomic dysfunction. Non-motor symptoms generally take precedence in the later stages of the disease. The main signs of Parkinson's disease are the suppression of voluntary movements (hypokinesia), tremors at risk, usually starting in the hands that tend to reduce involuntary action, and muscle rigidness[2]. Levodopa (dopamine precursor), selegiline (monoamine oxidase inhibitor), tolcapone, and entacapone (catecholamine-o-methyl transferase inhibitors), amantadine (dopamine releasers), bromocriptine, lisuride, and ropinirole are the first-line medications used to treat PD (dopamine receptor agonists). Entacapone is a catecholamine-o-methyl transferase inhibitor with high lipophilicity that belongs to Biopharmaceutics Classification System (BCS) class IV[3]. It's a Tolcapone analog that's supposed to be less hepatotoxic. It has 98 % protein binding, a half-life of 0.4–0.7 h, a log p of 2.8, 35 % bioavailability, and hepatic metabolism. When compared to tolcapone, its activity is largely peripheral with a shorter duration of action. Because it does not cause dyskinesia, the main prescription for this drug is to treat early 'end-of-dose' deterioration[4]. The microsponge technology was developed by Won in 1987, and advanced polymer system, Inc was given the original patents. This company created other variants of the technology, which were applied to cosmetics as well as OTC and prescription pharmaceutical products[5]. Due to the minimal pore size of 0.25 µm, the microsponge drug delivery system offers unique qualities such as self-sterilization, which prevents bacteria from entering and contaminating the formulation[6]. Because of its porosity, a typical 25µm microsponge particle comprises about 25,000 pores and can have a 1 ft length and a storage capacity of up to 1 mL/g, it can entrap drugs up to three times its weight[7]. Due to its stability across a wide range of pH values and temperatures, this dosage form has a superior safety profile, and it is neither irritating, allergenic, or mutagenic in nature[8]. Entacapone's main drawbacks include its low solubility and a daily dose of 200 mg delivered up to 8 times. By increasing the solubility and bioavailability of entacapone, microsponge becomes an effective strategy for reducing the dose and frequency of entacapone administration**.** The goal of this work was to design and assess entacapone microsponges formulations using various polymethacrylate polymers for reduced dose frequency and long-term entacapone delivery.

Materials and Methods

Entacapone is gifted by Aurobindo pharma, Hyderabad India. Eudragit S100, Eudragit L100, and Eudragit RS 100 were gift samples from Hetero labs, Hyderabad India. Loba Chemie and qualigens fine chemicals in Mumbai, India,

provided polyvinyl alcohol and ethanol. All other ingredients used were of analytic grade and purchased from authentic suppliers.

Construction of Calibration Curve for Entacapone

Preparation of Stock Solution

Weigh 25 mg of the drug, dissolve in pH of 5.5 phosphate buffer, then makeup with buffer up to 25 mL. The above one is noted as stock I. From stock I, 10 mL of solution was taken and made up to 100 mL with buffer this was noted as stock II. To obtain 5µg, 10 µg, 15 µg, 20 µg, and 25 µg concentrations, take 0.5 mL, 1.0 mL, 1.5 mL, 2.0 mL, and 2.5 mL solutions from stock II and made up with 5.5 buffer up to 10 mL. The sample absorbance was seen at 314 nm in a UV spectrophotometer. The entacapone calibration curve was constructed by plotting the absorbance against the concentration. From the plot, we get a regression equation.

Fourier Transform Infrared (FTIR) Spectroscopy

Fourier transform infrared analysis (FTIR) was performed by FTIR instrument (Spectrum one, PerkinElmer, USA) over the range of wave number 4000-450 cm^{-1}.

Differential Scanning Calorimetry

DSC characterization was performed to determine the physical characterization of pure Entacapone and the prepared entacapone microsponge. DSC scans were performed on a differential scanning calorimeter (DSC1, Mettler Toledo, Switzerland). The samples were scanned at a rate of 10°C/min from 30°C to 320°C under a nitrogen environment[9].

Surface Morphology

Scanning electron microscopy (SEM) was used to examine the microsponge's surface morphology (Hitachi S-250, Japan). The microsponges were put on aluminum stubs, vacuum-coated with gold, and examined under a scanning electron microscope[9].

Microsponge Preparation

The entacapone microsponges were prepared by a quasi-emulsion solvent diffusion process with various polymer concentrations. Internal phase containing polymer such as Eudragit dissolved in ethyl alcohol in this, the drug is then gently dissolved in the polymer solution. After that, the internal phase is poured into the external phase, which contains polyvinyl alcohol and distilled water, and stirred continuously at 1000 rpm for 6 h. The microsponges were then separated by filtering the mixture. The product (microsponges) was dried for 12 hours in an air-heated oven at 40°C[10].

Table 1: Composition of Microsponges Formulations

Sl. No	Formulation code	Qty of the drug (mg)	PVA in (mg)	Eudragit (mg)			Ethanol (ml)	Distilled water (ml)
				RS	S	L		
1	RS-1	200	50	100	-	-	5	100
2	RS-2	200	50	200	-	-	5	100
3	RS-3	200	50	300	-	-	5	100
4	RS-4	200	50	400	-	-	5	100
5	S-1	200	50	-	100	-	5	100
6	S-2	200	50	-	200	-	5	100
7	S-3	200	50	-	300	-	5	100
8	S-4	200	50	-	400	-	5	100
9	L-1	200	50	-	-	100	5	100
10	L-2	200	50	-	-	200	5	100
11	L-3	200	50	-	-	300	5	100
12	L-4	200	50	-	-	400	5	100

Evaluation of Microsponge

The Production yield, Actual drug content, and encapsulating efficiency of the produced microsponges were determined.

Production Yield (%)

Microsponges production yield was determined by the formula mentioned below[11].

$$\text{Production yield (PY)} = \frac{practicle\ mass\ of\ microsponges}{theoreticle\ mass\ (polymer+drug)} x100$$

Actual Drug Content and Encapsulation Efficiency (%)

In 100 ml of pH 5.5 buffer, the weighed amount of drug-loaded microsponges (100 mg) was stored and stirred for 4 h. Using a UV spectrophotometer, filtered samples (using a 0.45 µm membrane filter) were compared to a blank at 314 nm (Elico, double beam spectrophotometer). The following equation was used to calculate drug content and encapsulation efficiency for all batches[11-13].

$$\text{Actual drug content (\%)}: \frac{actual\ content\ in\ weighed\ quantity\ of\ microsponges}{weighed\ quantity\ of\ microsponges} \text{x } 100$$

$$\text{Encapsulation efficiency} = \frac{actual\ content\ in\ weighed\ quantiyty\ of\ microsponges}{theoretical\ content\ in\ microsponges} \text{x } 100$$

***In Vitro* Drug Release Study**

The dissolution of entacapone microsponges *in vitro* was investigated using a USP II dissolution Apparatus (Lab India) rotating at 50 rpm. For 12 h, 900 mL of standard buffer pH 5.5 was used. The temperature of the dissolution media was kept constant at 37°C. At predetermined intervals, samples of dissolving medium (5mL) were extracted with a syringe fitted with a prefilter and tested for drug release by measuring the absorbance at 314 nm. At each time interval, the volume extracted was replaced with a new batch of dissolving medium. The

dissolving tests were performed three times. The percentage of drug released over time was calculated and shown.

***In Vitro* Release Kinetics:** [14-16]

Dissolution data of the above formulations were fitted in Zero order, First order equations. Zero-Order Kinetics: Zero-order is the cumulative amount of drug released vs. time,

$$C = K_0 t$$

$$\text{Log } C = \text{Log } C_0 - k_t / 2.303$$

Where K_O is the zero-order rate constant in concentration/time units, and t is the time in hours. A straight line with a slope equal to K_O would intercept the origin of the axes on a graph of concentration vs. time. Kinetics of first order. First-order as a log cumulative proportion of remaining drug vs. time, The initial drug concentration is C_O, the first order constant is k, and the time is t.

Higuchi Model

Higuchi's model as a square root of time vs. cumulative percentage of drug released

$$Q = K_t {}^1/_2$$

Where K represents the constant reflecting the design variables and t represents the time in hours. As a result, the rate of drug release is proportional to the square root of time reciprocal.

Hixson-Crowell Release Equation

A linear plot of the cube root of the initial concentration minus the cube root of percent remaining versus time in hours.

Korsmeyer Peppas Equations

Data for the first 60% of drug release were plotted in the Korsmeyer equation log cumulative percentage of drug released vs. log time, and the exponent n was determined using the slope of the straight line.

$$M_t / M_\infty = Kt^n$$

Where M_t/M_∞ denotes fractional solute release, t denotes release time, K denotes a kinetic constant specific to the drug/polymer system, and n denotes an exponent describing the tracer release mechanism. If the exponent $n = 0.45$, the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, the drug release mechanism is non-Fickian or anomalous diffusion. Case-II Transport or typical zero-order release is indicated by an exponent value of 0.89.

Results and Discussion

Calibration Curve of Entacapone

The calibration of entacapone was done in this study utilizing UV-spectrophotometry and detecting the absorbance at 314 nm. The calibration curve and the absorbance vs. concentration values are provided in Table. In the range of 5-25 µg/mL, the absorbance vs. concentration obeyed Beer's law. The absorbance and concentration had a good correlation, and the coefficient of determination R^2 was found to be 0.9947.

Table 2: Absorbance of Entacapone in pH 5.5 phosphate buffer

Concentration µg/ml	Absorbance
5	0.0397±0.0015
10	0.0998±0.0034
15	0.1669±0.0023
20	0.2248±0.0045
25	0.2944±0.0019

*All values are expressed in mean±SD (n=3)

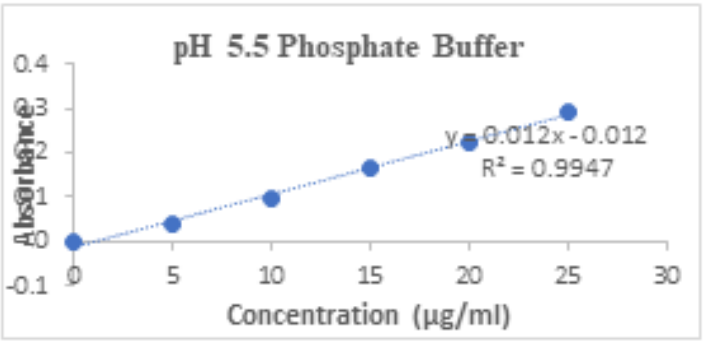


Fig 1: Calibration curve for Entacapone

FT-IR Studies

The IR spectra were captured on Spectrum one FT-IR spectrophotometer and the wavenumbers were recorded in cm^{-1}. The spectrum of entacapone shown on fig 2 and observed peak at 3334.4 cm^{-1}(OH), 2732.4 cm^{-1} (CH aliphatic), 2217 cm^{-1} (C≡N), 1754.6 cm^{-1} (C=O), 1632.7 cm^{-1} (NO_2), 1440 cm^{-1} (CH_3 bend), 600-1100 cm^{-1} (OOP, Aromatic). The spectrum of entacapone mixed with Eudragit L100 and optimized formulation showed similar characteristics with minor shifts. This indicates that there is no interaction between the drug and polymer used in the study.

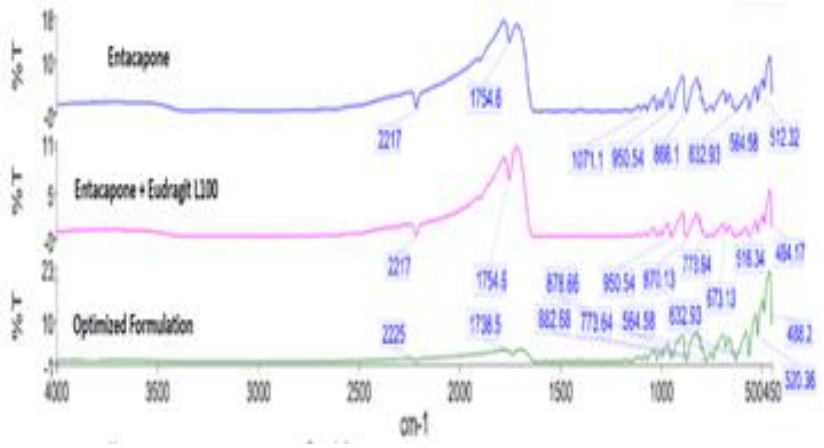


Fig 2: FTIR Overlay of Entacapone pure drug, Eudragit L100, and Optimized Formulation L2

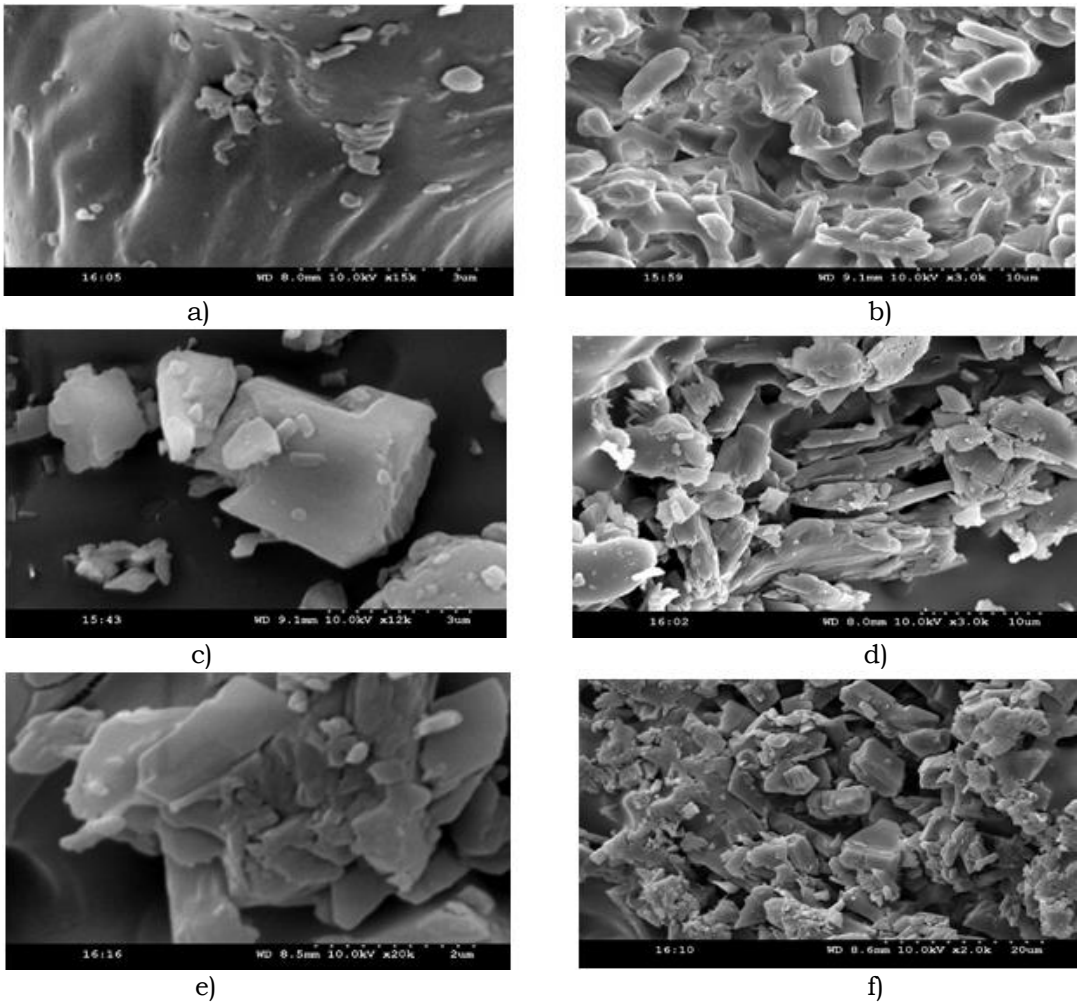
DSC Studies

DSC was recorded using DSC1, Mettler Toledo, Switzerland, spectra were shown in fig 3 by observing the graph the transition temperature which is an endothermic reaction was observed at 165.22°C for entacapone and 158.20°C for optimized formulation. Thus, there is no or less interaction between drug and polymer

Fig 3: DSC Overlay of Entacapone and Optimized formulation L2

Surface Morphology

The Eudragit L100 prepared microsponges had a surface that was completely smooth. The shape of the sponges was found to be uneven, and it was observed that there were sharp edges. The nature of the surface was such that it was porous, and it was observed that the drug was entrapped inside the polymer. This substance gives the polymer a cushioning effect. The microsponges that were made with Eudragit S100 and RS100 had a smooth appearance but were not porous in their natural state. In addition to this, the particles have an asymmetrical form, as shown in fig 4.



a) b)

c) d)

e) f)

Fig 4: (a-f) SEM photographs of optimized entacapone microsponges. a and b represent Entacapone with Eudragit L100, c and d represent Entacapone with Eudragit S100 and e and f represent Entacapone with Eudragit RS 100

Evaluation of Entacapone Microsponges

The microsponges were prepared in drug-polymer ratios of RS1(1:0.5), RS2 (1:1), RS3 (1:1.50), RS4 (1:2), S1 (1:0.5), S2 (1:1), S3 (1:1.50), S4 (1:2), L1 (1:0.50), L2 (1:1), L3 (1:1.50) and L4 (1:2) using eudragit RS100, eudragit S100, and eudragit L100.

Production Yield (%)

The production yield of all the formulations was found to be in the range of 45±0.47 to 80.50±0.59% for formulation with Eudragit RS100, 40±0.52 to 70.67±0.29% for Eudragit S100, and 38.33±0.40 to 74.8±0.30% for Eudragit L100

Actual Drug Content (%) and Encapsulating Efficiency (%)

Different formulations showed Actual drug content values that varied between 65±0.45 and 22.4±0.41% and Encapsulation efficiency values varied between 66.40±0.28 to 52.45±0.09% because the polymer concentration increases the encapsulation efficiency is decreased as shown in table 3.

Table 3: Product yield (%), drug loading (%), entrapment efficiency (%)

Formulation code	Product yield (%)	Actual drug content (%)	Encapsulation efficiency (%)
RS-1	45.33±0.35	50±0.33	66.22±0.23
RS-2	80.50±0.59	35±0.37	63.30±0.32
RS-3	45±0.47	25±0.23	59.25±0.17
RS-4	75.16±0.23	25±0.28	55.13±0.19
S-1	40±0.52	50±0.28	66.40±0.28
S-2	64±0.30	55±0.36	62.63±0.60
S-3	68±0.37	65±0.45	58.44±0.55
S-4	70.67±0.29	35±0.43	54.21±0.57
L-1	38.33±0.40	65±0.53	64.35±0.09
L-2	61.25±0.25	22.4±0.41	60.76±0.15
L-3	74.8±0.30	60±0.42	57.51±0.17
L-4	43.5±0.46	30±0.32	52.45±0.09

*all values are expressed in mean±SD (n=3)

Drug Release Profiles of Microsponges:

Drug release studies indicated that microsponge formulations RS1, RS2, RS3, RS4, S1, S2, S3, S4 L1, L2, L3, and L4 released drug for about 12hrs. Among these 12 formulations, the drug release by RS2 is 98.72% at 8h, S2 is 96.36% at 10 h, L2 is 98.90% at 12 h; shows the maximum release for about 12 h among these three L2 formulation gives best drug release at 12h shown on table 4. so kinetically evaluated the data suggest that L2 formulation follows Higuchi kinetics and based on n value 0.44 from korsmeyer peppas shown that drug release follows quasi fiction diffusion mechanism as shown on table 5.

Table 4: *In vitro* Drug Release Studies Results for Optimized Formulations

Time (h)	RS2	S2	L2
0.5	26.08±0.09	19.09±0.24	27.06±0.09
1	31.96±0.23	35.45±0.14	30.05±0.12
2	36.45±0.25	38.18±0.23	36.53±0.13
3	42.44±0.36	43.63±0.35	43.36±0.25
4	53.43±0.45	46.36±0.38	51.43±0.32
5	62.36±0.12	50±0.42	59.63±0.06
6	75.33±0.24	58.18±0.36	66.73±0.17
7	89.16±0.15	65.45±0.23	72.33±0.24
8	98.72±0.09	72.72±0.12	80.19±0.36
9		81.81±0.29	86.14±0.07
10		96.36±0.27	92.24±0.45
11			96.10±0.25
12			98.90±0.23

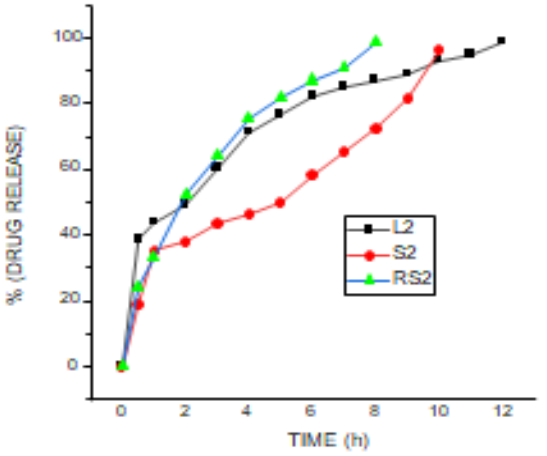


Fig 5: Drug Release profile for optimized formulations

Table 5: Mechanism of Drug Release Studies on Optimized Formulations Entacapone-Loaded Microsponges

Tablet	Zero-order		First-order		Higuchi	Hixon	Korsmeyer peppas	
	R^2	K_o(%h)	R^2	K_1(hr^{-1})	R^2	R^2	R^2	n
L2	0.9445	7.2659	0.8622	0.2963	0.9861	0.9539	0.9563	0.4487
S2	0.9300	7.5304	0.7446	0.2224	0.9431	0.9300	0.9260	0.4529
RS2	0.9600	10.608	0.7389	0.3700	0.9436	0.9600	0.9078	0.4740

*all values are expressed in mean±SD (n=3)

Fig 6: Zero-order plot of optimized formulation L2

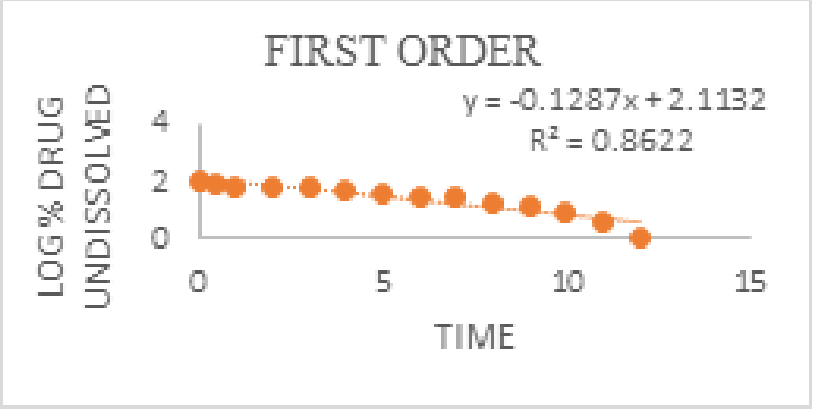


Fig 7: First order plot of optimized formulation L2

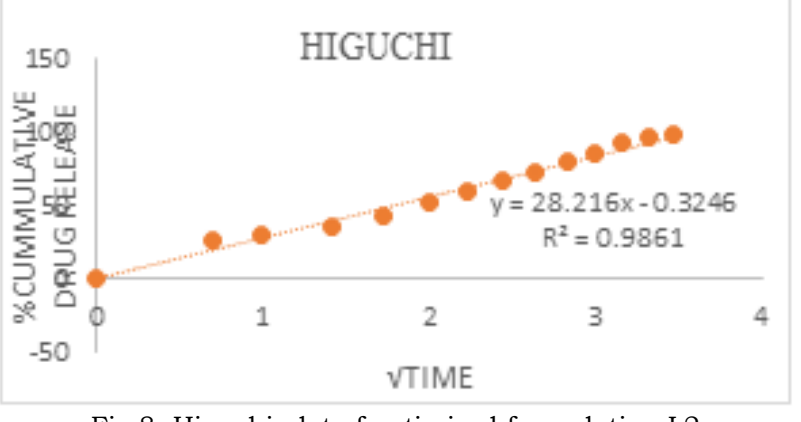


Fig 8: Higuchi plot of optimized formulation L2

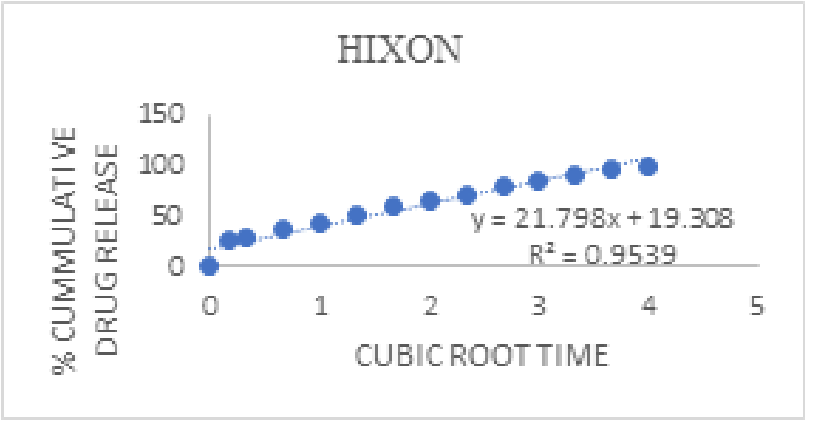


Fig 9: Hixon plot of optimized formulation L2

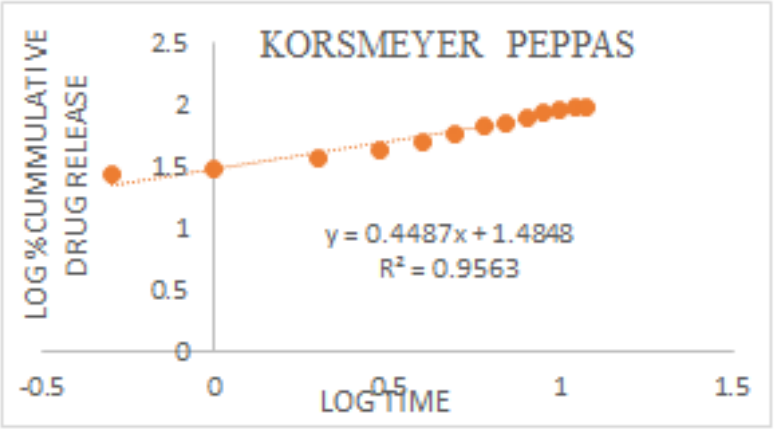


Fig 10: Korsmeyer Peppas plot of optimized formulation L2

Conclusions

The current work used Ethanol and Eudragits as the internal phase and 5% w/v of PVA as the external phase to generate a sustained release of entacapone-loaded microsponges for the goal of boosting drug release. Twelve formulations were made with three polymers, and three of them, RS2, S2, and L2, were chosen and their drug release characteristics compared. Out of the three formulations, L2 produced acceptable results, with drug release at 12 h of 98.90%. Further drug kinetic results revealed that the formulation L2 follows the Higuchi model, and the drug release mechanism as determined by the 'n' value of Korsmeyer Peppas was 0.4487, indicating quasi-fickian diffusion not only drug release studies and also based on morphological studies, entacapone-loaded microsponges having a porous structure and it can release the drug in a controlled rate, is an alternative route of delivery in the treatment of acute Parkinsonism.

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