RESEARCH ARTICLE

Formulation and Evaluation of Docetaxel Floating Microspheres

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Received: 31st Mar 2023; Revised: 27th Oct, 2024; Accepted: 5th Nov, 2024; Available Online: 25th Dec, 2024

ABSTRACT
This study sought to create floating microspheres containing Docetaxel, a cutting-edge anti-mitotic chemotherapeutic medication frequently used in the treatment of breast, ovarian, and non-small cell lung malignancies. The experimental results demonstrated that FT-IR evaluation exhibited no significant peak shifts, suggesting that the drug within the microspheres is stable in the short term. Biocompatible polymers, that include chitosan and albumin, were incorporated for the development of microspheres, both of which generated a great deal of drug entrapment and sufficient yield. All formulations have acceptable flow characteristics to allow for simple capsule loading. Furthermore, raising its polymer concentration resulted in an enormous decrease in cumulative drug release percentage. The formulations D7 is best fitted in various kinetic models

Key Words : Docetaxel, FT-IR, Microspheres, Bioavailability, Anti-mitotic, Chitosan, Albumin, Gelatin.
How to cite this article: Arigela B, Talaparthi YD, Chanumolu K, Baratam A. Formulation and Evaluation of Docetaxel Floating Microspheres. International Journal of Drug Delivery Technology. 2024;14(4):2048-53.doi 10.25258/ijddt.14.4.15
Source of support: Nil.
Conflict of interest: None

INTRODUCTION

For many years, medicines have been delivered to patients in various forms that includes solid, liquid & semi solid dosage forms for the management of acute and chronic diseases[1]. In order to achieve and sustain therapeutic drug levels, Various medication delivery techniques might require to be frequently used throughout a given day, causing alterations to drug levels, eventually leading to toxicity and dropped efficacy[2]. This triggers fluctuations in drug concentrations, causing undesirable toxicity and diminished efficacy. Controlled delivery methods address issues which includes recurring doses and variable absorption. CRDDS are intended to provide precise control over the site and frequency of medicine release. Spatial targeting directs medication to a specific organ or tissue, whereas temporal delivery controls the pace at which the drug is delivered to the target site[3]. A controlled release system intends at distributing drugs at a rate that ensures a consistent blood level. This rate should be identical to continuous intravenous infusion, that delivers drug at a rate similar to its rate of elimination[4]. The rate of drug distribution should be consistent across time and irrespective of the amount of substance in the dosage form, leading to zero-order kinetics. Docetaxel is a chemotherapeutic drug used to treat multiple kinds of cancer. It interferes with microtubules in cells, which are components vital to cell division. It inhibits cancerous cell division and proliferation by stabilising microtubules[5]. Adverse effects include hair loss, nausea, tiredness, and reduced blood cell counts[6]. Docetaxel is poorly soluble in water, which limits its efficacy. Albumin binds to docetaxel, increasing its solubility and stability in the blood[7]. Chitosan assists in the maintenance of a consistent concentration of docetaxel in the circulation[8]. Combining albumin and chitosan in a single delivery method can improve the overall efficacy of docetaxel. Microspheres are solid, sphere-shaped particles having dimensions from 1 to 1000 µm. They receive protection by biodegradable polymers made from synthetic materials and modified natural ingredients Natural polymers as well as synthetic polymers also implemented[9]. Microsphere carrier systems based on naturally occurring biodegradable polymers have been attracting a lot of attention in the arena of sustained medication delivery for several years[10]

MATERIALS & METHODS

Materials

Gift sample of Docetaxel was acquired from Chandra labs, Hyderabad

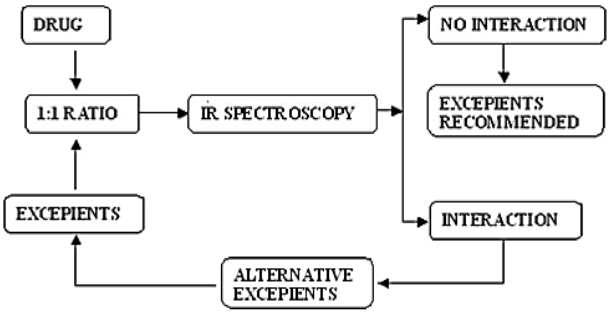

Figure 1 : FTIR Compatibility study

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Table 1: Prepared formulations of Floating Beads

S.No	Docetaxel Formulations	Drug: Polymer Ratio		Glutaraldehyde (ml)	Tween 80 (ml)
		Docetaxel (mg)	(Albumin: Chitosan) (mg)		
			40:40	20	1
1	D_1	80			
2	D_2	80	40:80	20	1
3	D_3	80	40:120	20	1
4	D_4	80	80:40	20	1
5	D_5	80	80:80	20	1
6	D_6	80	80:120	20	1
7	D_7	80	120:40	20	1
8	D_8	80	120:80	20	1
9	D9	80	120:120	20	1

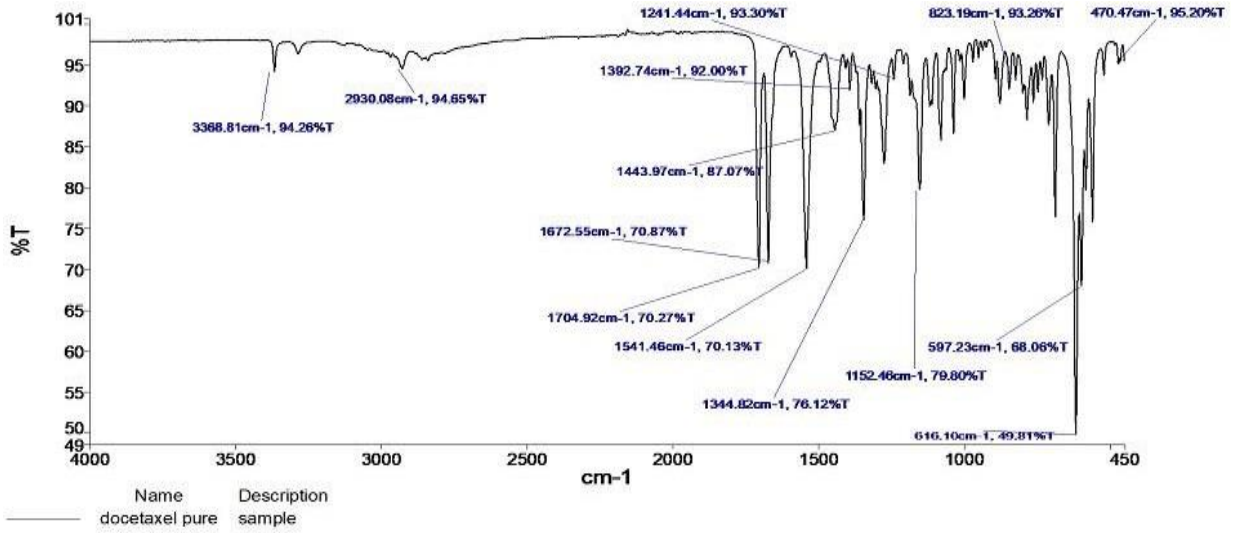

Figure 2: FT-IR spectra of docetaxel pure drug

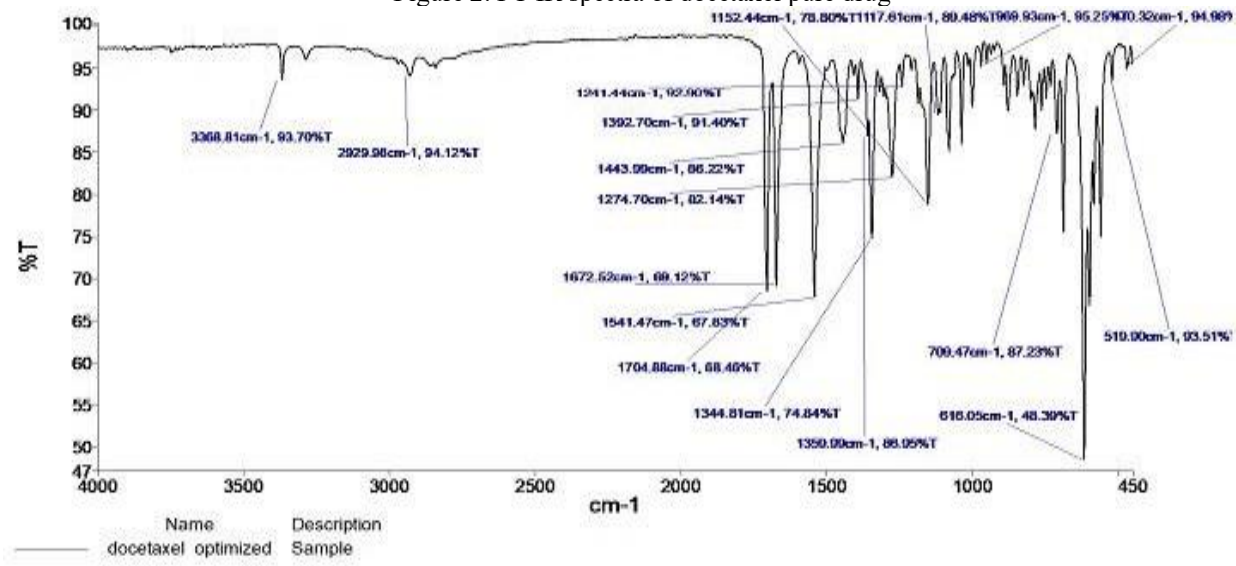

Figure 3: FT-IR spectra of docetaxel formualation

Chitosan, Gelatin, CaCo3 procured from Mylan chemicals Albumin, Span 80 used were of Pharmacopeial grade

Methods

Docetaxel's pre-formulation investigations included the following[11]

Solubility: Exploratory the extent to which Docetaxel dissolves in various solvents to find the optimal formulations methods and conditions.

Melting Point

Docetaxel's melting point is determined to gain insight into its thermal properties and stability, which may impact

Table 2: Physical Parameters related to Docetaxel Formulations

S.No.	Docetaxel Formulations	Percentage yield	Docetaxel Drug Amount (mg)	%Drug entrapment efficiency	Swelling index
1	D1	82.2	74.2	62.41	30.41
2	D2	82.41	78.68	65.16	33.68
3	D3	84.17	77.47	67.62	39.94
4	D4	84.62	79.2	70.18	41.3
5	D5	83.29	75.6	76.21	34.18
6	D6	84.61	77.4	78.17	35.18
7	D7	87.19	82.9	88.24	45.68
8	D8	86.42	80.7	86.19	46.62
9	D9	84.16	79.14	83.48	42.75

Table 3 : Coefficient of Regression (R^2) Values in the Analysis of Release Data of Docetaxel Microspheres

Docetaxel Formulations	Zero Order	First order	Higuchi Plot	Peppas-Plot
D1	0.926	0.986	0.994	0.994
D2	0.893	0.987	0.998	0.992
D3	0.894	0.978	0.996	0.991
D4	0.897	0.987	0.998	0.994
D5	0.878	0.966	0.990	0.988
D6	0.908	0.976	0.993	0.993
D7	0.909	0.976	0.998	0.9931
D8	0.929	0.986	0.995	0.994
D9	0.890	0.983	0.998	0.9934

Table 4 : Release Parameters From Docetaxel Microspheres

Docetaxel	Release Rate		Release Exponent
F.CODE	K_0 (mg/hr)	K_1 (h^{-1})	'n' Values
D1	5.72	0.110	0.659
D2	5.90	0.121	0.672
D3	5.67	0.112	0.665
D4	5.81	0.114	0.668
D5	5.39	0.103	0.659
D6	5.78	0.116	0.665
D7	6.53	0.160	0.685
D8	6.12	0.129	0.670
D9	5.76	0.115	0.668

formulation.

Drug-Polymer Compatibility Studies

Analysing whether Docetaxel interacts with the various polymers used in its formulation to assure product compatibility and stability.

Method of preparation

Heat Stabilization Technique

To evenly distribute 80mg of drug, mix 5ml of 1%w/v albumin solution, 5ml of 2%w/v chitosan in 2% acetic acid, and 5ml of 15% w/v gelatin solution (water) with 1.5% w/v CaCO3. Add 25ml of Glutaraldehyde and 20ml of Tween 80 to a syringe and gently stir for a period of 10 minutes at 60-70°C and 1000 RPM (without forming an emulsion). Cool to 50°C for 30 minutes and wash.[12]

Characterization of Formulated Docetaxel Microspheres

The mass of dried out microspheres retrieved from every batch was assessed in relation against the initial mass of starting materials to figure out the percentage yield of microspheres. The efficacy of drug entrapment was investigated by crushing microspheres containing 80mg of Docetaxel. The powder was dissolved in methanol and 0.1N HCl, filtered, and spectrophotometrically analysed[13]. Microspheres were identified by their micromeritic attributes, which included Size, Density, The Carr's compressibility index, Hausner's ratio, and Critical angle of repose[14].

Examination of Formulated Docetaxel Microspheres

An optical microscope with a magnification of 45x was used for examining the size of microsphere samples[15]. The diameters of the microsphere were measured at this magnification. Furthermore, the swelling ratio of several dry microspheres was measured gravimetrically after immersing them in 0.1N Hydrochloric acid for half day[16]. Within this period, the microspheres were frequently extracted from the solution, gently wiped to eliminate any excess moisture, and weighed with the aid of a balance.

***In-vitro* dissolution study**

Dissolution studies were performed employing an eight-station apparatus at 37 ± 0.5°C . Rotating basket is employed and maintained at 100 RPM. Baskets containing microspheres were immersed in 900 ml of 0.1N HCl. Microspheres equivalent to 80 mg of Docetaxel per formulation were used. At designated intervals, aliquots were withdrawn and examined for drug release using absorbance values. In order to maintain the sink conditions constant the withdrawn volume was refilled with fresh, pre-heated 0.1N Hydrochloric Acid.[17]

RESULTS & DISCUSSION

Docetaxel is freely soluble in CH_3OH & C_2H_5OH , Soluble in $CHCl_3$, Practically insoluble in H_20. M.P of Drug is within the limit (232°C). FTIR investigations were utilised in determining drug and excipient compatibility. The spectral studies shows no chemical interaction between drug and excipient. The values for percent compressibility, Carr's Index, and Critical angle of repose were less than 16, 1.25, and 30, respectively. The outcomes show that Docetaxel formulations have excellent flow properties. The % Yield was in the range of 80-88% for microspheres containing albumin, chitosan. The Drug Entrapment efficacy was in the range of 62.66-88.66% for microspheres containing albumin, chitosan. The swelling index of the formulations ranged from 30% to 47% after two hours of interaction with the simulated gastric media.

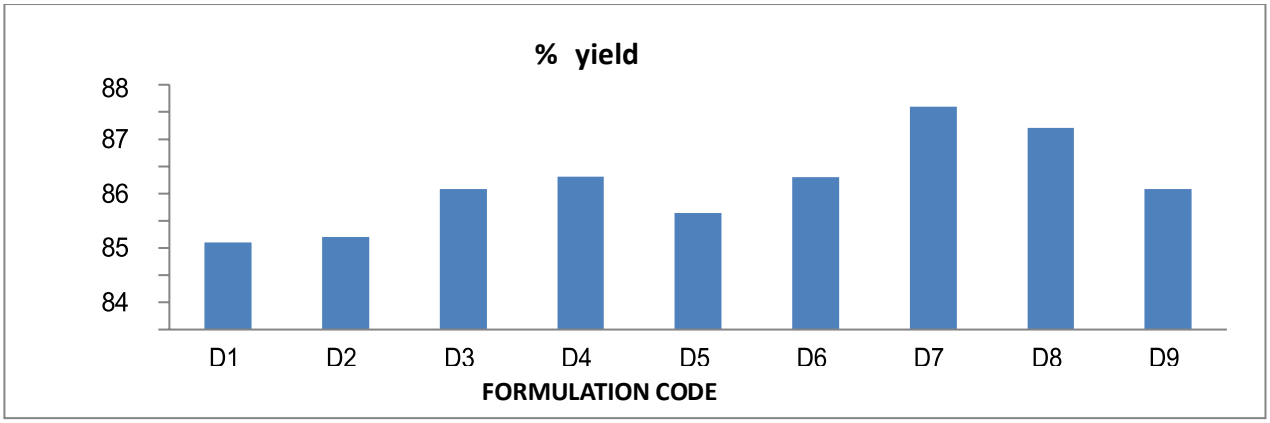

Figure 4: Percentage Yield graph for D1-D9 formulations

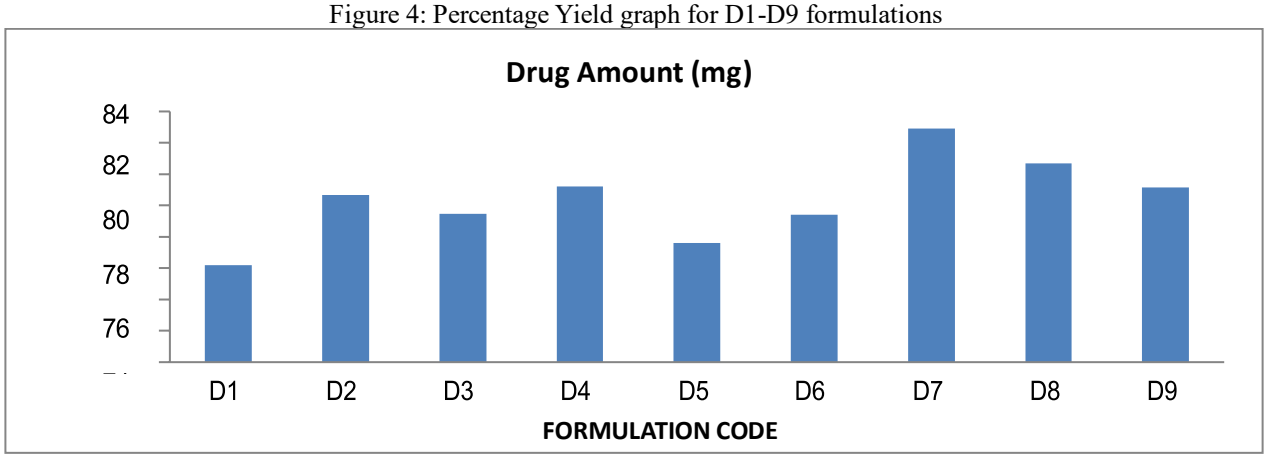

Figure 5: Drug amount graph for D1-D9 formulations

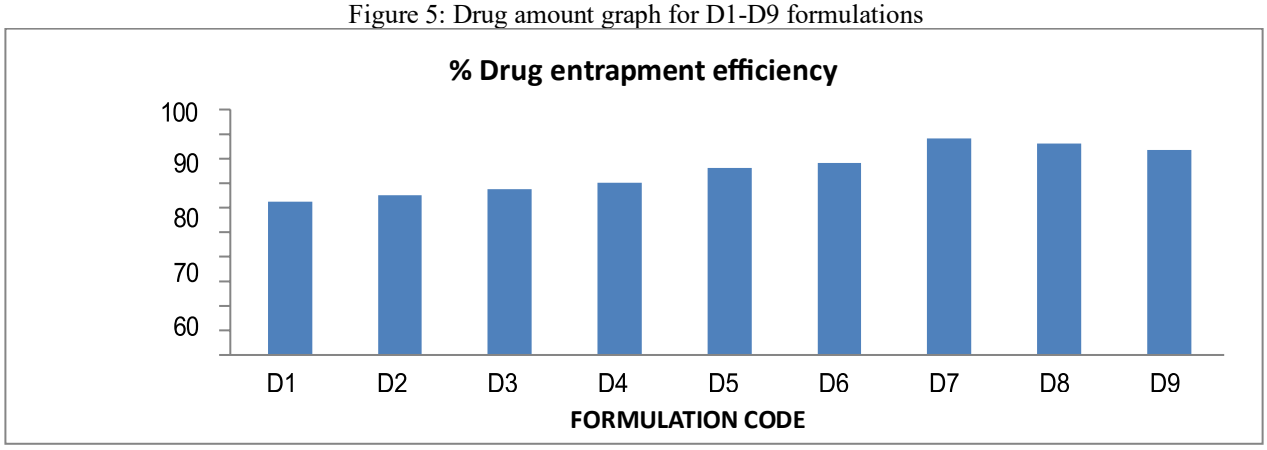

Figure 6: % Drug entrapment efficiency graph for D1-D9 formulations

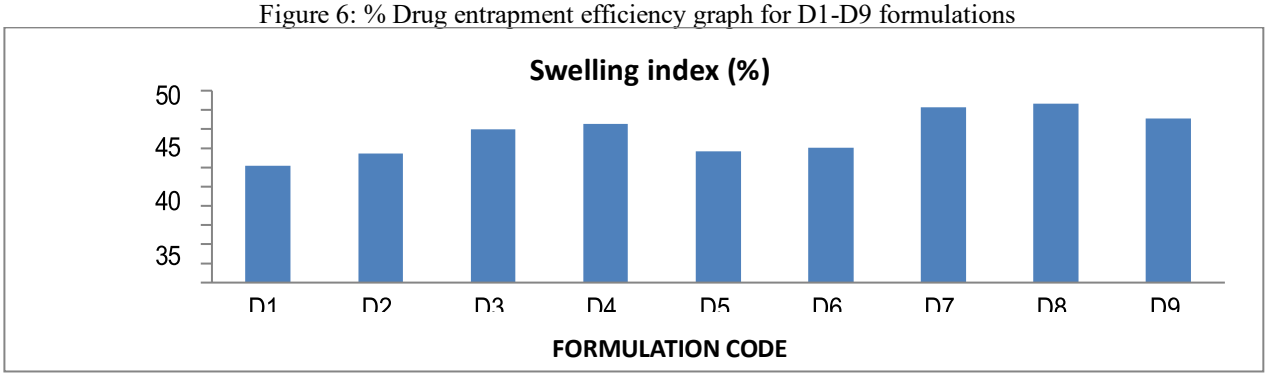

Figure 7: Swelling index % graph for formulations F1-F9

SUMMARY & CONCLUSION

The FT-IR investigation verifies the drug's short-term stability in the beads, as there is no substantial movement

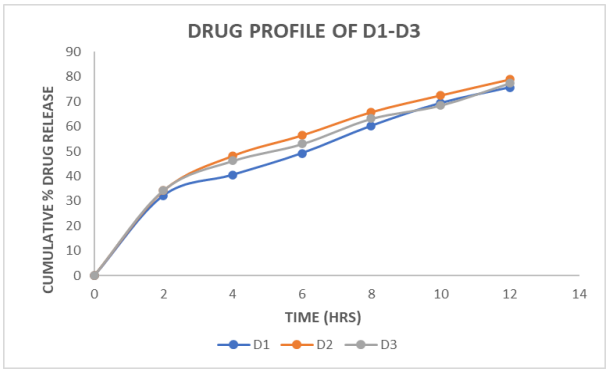

Figure 8: Dissolution Profile of Docetaxel Microspheres (D1, D2, D3) formulations.

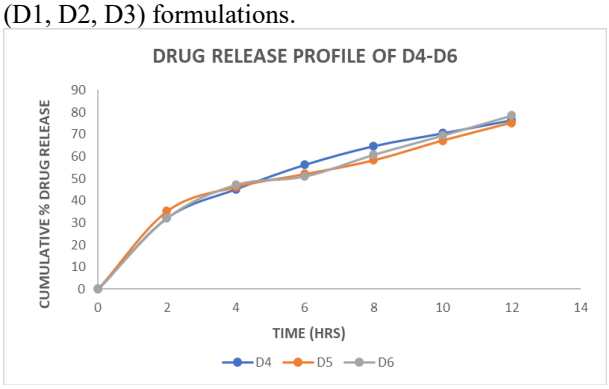

Figure 9 : Dissolution Profile of Docetaxel Microspheres (D4, D5, D6) formulations.

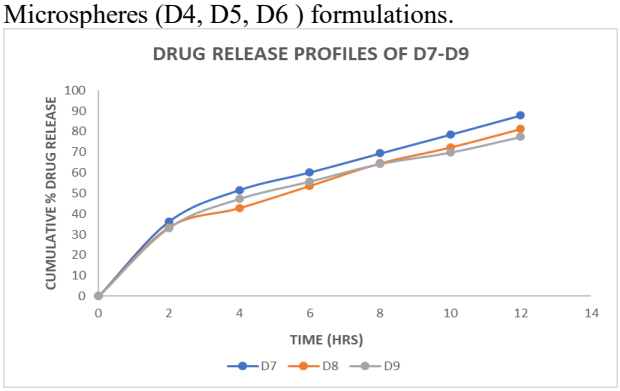

Figure 10 : Dissolution Profile of Docetaxel Microspheres (D7, D8, D9) formulations.

in peaks. Chitosan and albumin are biocompatible polymers that may be utilised to create microspheres. Both polymers have high drug entrapment rates and yields. All formulations had acceptable flow qualities, making them suitable for capsule filling. The formulation D7 performed best in the first order kinetic and Higuchi models. The formulation D7 follows Non-Ficikian Diffusion

Acknowledgements

Authors are thankful to the Management and principal of KVSR Siddhartha College of Pharmaceutical Sciences for providing the necessary facilities.

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