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Formulation and Evaluation of Capecitabine Microspheres for Colorectal Cancer

Rabbani Sk*[1], Sujatha S[1], Kudipudi Harinadha Baba[2]

[1]Department of Pharmaceutics, Narayana Pharmacy College, Chinthareddy Palem, Nellore - 524003, Andhra Pradesh, India

[2]Department of Pharmaceutical Analysis, Narayana Pharmacy College, Chinthareddy Palem, Nellore - 524 003, Andhra Pradesh, India

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ABSTRACT

The present study aimed to formulate and evaluate Capecitabine microspheres for colorectal cancer, reduce dosing frequency, and improve patient compliance. Microspheres were prepared by emulsion solvent evaporation using polymers like ethyl cellulose (E.C.) and HPMC K-I00 in different ratios. The prepared microspheres were evaluated for flaw properties, percentage yield, drug entrapment efficiency, and *in vitro* dissolution studies. Results showed that as the concentration of polymer ratio increases, it affects the particle size, percentage yield, and drug release from the microspheres. The percentage yield of F6 microspheres was up to 95.13%. The release study was done with simulated intestinal fluid (SIF - pH 7.4) for 24 hours. It showed that the drug was protected from being released in the physiological environment of the intestine and efficiently released in the colon (95.85%). The optimized formulation F6 exhibited the drug release in a sustained manner arid following zero order, non-Fickian diffusion mechanism. An accelerated stability study was carried out for the optimized formulation. The results showed no significant changes in percentage drug entrapment efficiency, particle size, and *in vitro* controlled release of Capecitabine. The surface morphology analysis formulation F6 showed a spherical structure with smooth surface morphology. The prepared microspheres are promising drug delivery for sustained oral administration to target the colon and provide a better kinetic profile with improved bioavailability.

*Corresponding Author

Name: Rabbani Sk
Phone: 7842846913
Email: rabbanishaik733@gmail.com

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INTRODUCTION

Colorectal cancer has been the 2nd most frequent cancer killer as a whole, as well as 3rd most frequent cause of lung cancer-related mortality with in united states, both in females and males. Colorectal drug delivery, like a safe and effective therapeutic colorectal cancer, will provide effective concentration like an anti-cancer advisor at receptor sites but also spare the traditional cells for lowered dote and lowered duration of treatment [1]. Its effective active targeting of opioids towards the colorectal through the digestive tract (GIT) did require a shield of such an opioid from degeneration and discharge within the stomach and intestine and afterward makes sure sustained release inside the proximal intestines.

Minimize a dose intensity and mitigate adverse effects compared with conventional medicine. Capecitabine is an orally administered chemother-

apies agent used for the diagnosis of colon cancer and metastatic breast cancer. Capecitabine is just a prodrug that also proteolytic enzymes transformed about fluorouracil inside cancer, inhibiting DNA synthesis and slowing tumor cell expansion. However, it is quickly absorbed first from gastrointestinal trace its daily recommended dose has been huge [2]. Through being able to convert into the monitored, location-specific release dosage from 1st pass, various metabolic could be lessened bioavailability.

Methods of Preparation of Microspheres

Solvent Evaporation Method

Floating TNNHI particulate recommended dose FONN could be prepared by solvent dispersion and vaporization to create an empty internal structure. A polymer has been absorbed inside an organic phase, and also the opioid must be either absorbed or instead distributed within polymer concentration.

The solution containing the drug then is solubilized into such an aqueous medium usually contains ideal improver (surfactants/polymer) of about form oil-in-water emulsifiers. Just after the formation and stability of emulsifiers, an organic phase is vaporized by either raising the temperature under pressure or through constant stirring [Figure 1].

A solutes withdrawal results in polymer precipitation just at oil/water interaction like droplets, establishing cavity and therefore creating those porous of about conferring its hanging characteristics. Polymeric materials researched again for the advancement of specific processes encompass cellulose acetate, chitosan, eadragit, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide but also polycarbonate [3].

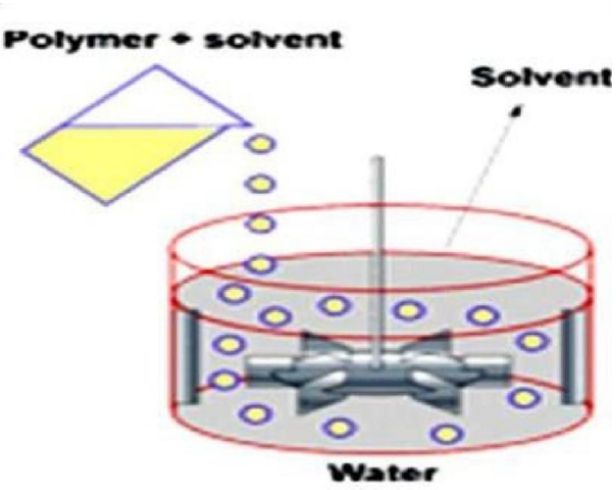

Figure 1: Solvent Evaporation

Ionotropic Gelation Method

Ionotropic Gelation relies upon that capacity like poly electrolyte balance of about cross-link inside the existence of refute ions to make beads. Until its use of alginates. Gellan gum, chitosan, and carboxymethyl cellulose, again for encapsulation like a thug or even cellular, ionic gelation method, have already been broadly used for this purpose [4]. Its natural poly electrolyte supplements through spite, possessing property like covering upon that opioid core but also behaves as controlled release retardants including definite anions through with their chemical nature, such ions present shapes meshwork configuration through trying to also combine with polyvalent cations and stimulate gelatinization through directly binds primarily towards the anion slabs. Hydrogel beads have been generated by attempting to drop a drug-loaded polymeric solution into an aqueous phase like polyvalent ionic compounds. A schematic representation of the ionotropic gelling technique can be seen in Figure 2.

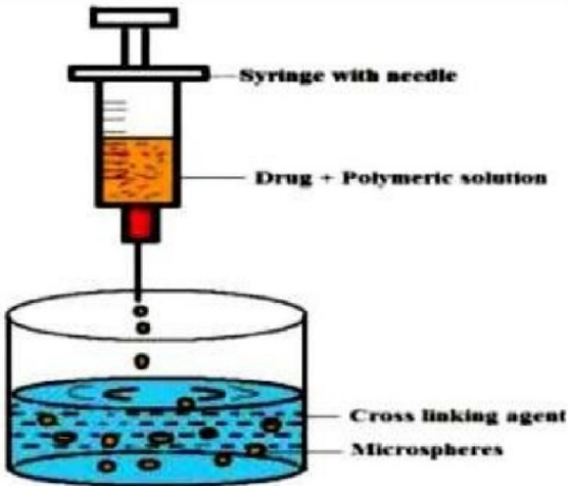

Figure 2: Ionotropic Gelation

Emulsion Solvent Diffusion Method

Within an emulsion solvent evaporation technique, an attachment between both the opioid and also organic phase has been greater than those of the organic phase but rather appropriate solvent [5]. An opioid has been disintegrated within the organic phase, but also the solution has been distributed with an aqueous system generating emulsifiers droplets, although the organic phase has been miscible (Figure 2). An organic phase dispersion progressively out from the emulsified raindrops more into the encompassing aqueous solution, and the aqueous medium dispersed in with the droplets through which opioid solidifies.

MATERIALS AND METHODS

HPMC: Aqualon. usa, Coloroon Asia Pvt Ltd, Cellulose: Colorcon Asia Pvt. Ltd; Goa, Dichloromethane: Avantor performance, India (RFCL Ltd), Polyethylene Glycol: Alpha Chemika, Mumbai, PVA: Alpha Chenfika, Mumbai, HCI: Merck Specialties Pvt. Ltd; Mumbai, Sodium Hydroxide: Merck Specialties Pvt Ltd: Mumbai, Potassium di-hydrogen Phosphate: Merck Specialties Pvt. Ltd; Mumbai. The above materials, the best possible Pharma grade available, were supplied by the manufacturer for this research. All the reagents and chemicals used are of analytical grade.

Methodology

Preparation of Capecitabine-Loaded Microspheres

Microspheres have been prepared through the emulsion solvent diffusion technique until capecitabine is mildly soluble in water opioids. Polymeric materials ethyl cellulose and t-1pmc disintegrated through 20 ml like DCM [6]. Such polymeric materials but also opioids were also mixed thoroughly of about create a clear solution, after which 0.1% of polyethylene glycol was added, which functions as an emulsifier. Therefore, the previous section solution has been solubilized by adding a drop at a time into the aqueous phase containing 160 ml of 0.4% water, like PVA, as just an emulsifying agent. Dichloromethane has been excluded there at 35°c through vaporization. Even as solutes were just being deleted, an emulsifying agent consistently maintained droplets of their globular setup but avoided through accumulating till the solutes were obliterated and the microspheres solidified just like secretive particulate. Eventually, solidified microspheres are cleaned of deionized water [7]. The obtained microspheres have been kept at room temperature and consequently held through desiccators. A similar procedure has been reproduced, such as all six formulations [Table 1].

Evaluation of Prepared Floating Microspheres

The prepared floating microspheres were evaluated for size analysis, Scanning electron microscopy (SEM), Bulk Density, Tapped Density, Carr's Index, and Hausner's ratio. Angle of Repose, Drug Content, Drug Entrapment Efficiency, buoyancy, and *In* vitro dissolution studies [8].

Scanning Electron Microscopy

Microsphere morphology has been researched using a scanning electron microscope (SEM). Specimens such as sem have been able to prepare by gently spattering on the double adhesive tape trapped to such an aluminum stub. Stubs were also painted for platinum to a width of about ten the under a kind of argon atmosphere using just a gold sputter component inside a high-vacuum evaporator. A scratch usually contains a film deposited and positioned within a scanning electron microscopy compartment. Specimens were also randomized searched, and photomicrographs were begun taking just at acceleration wattage like 20 kv, an initial depth of focus of 30' to enquire about the interior morphological characteristics microspheres were split into two parts items using a cutting [9].

Size Analysis of Microspheres

The size of a microsphere's particles was resolute through optical microscopy [10]. A slight drop-like suspension has been positioned on such a glass beaker slide. Slide usually contains suspension microspheres has been assembled upon that phase of a magnifying glass, but also 300 particulate have been assessed, increasing an adjusted ocular micrometric. The method has been replicated three times for every batch able to prepare.

Bulk Density and True Density

Bulk density and tapped density have been assessed using high-density equipment. Specimens were put inside a 100 ml measuring cylinder. A cylinder has been corrected upon that bulk density equipment, and a timer "mob has been arranged, such as 100 toppings. High density and tapped density have been determined by calculating from the following formulae [11]. A tapped density has been selected by calculating, through gm per ml.

$$Bulk\ density = \frac{Bulk\ volume\ of\ microcapsules}{Weight\ of\ microcapsules}$$

$$Tapped\ Density = \frac{Tapped\ mass\ of\ microcapsules}{Tapped\ volume\ of\ microcapsules}$$

The Measure of Powder Compressibility

Using high-density equipment, Carr's index and Hausner's ratio have been ascertained from the tapped and bulk densities of such recognized poundage-like specimens. The following equations were used to determine carr's index and Hausner's ratio.

$$Carr's\ Index = \frac{Tapped\ Density}{Tapped\ density - bulk\ density}$$

$$Hausner's\ Ratio = \frac{Bulk\ density}{Tapped\ density}$$

The Angle of Repose

The flow characteristics of microcapsules were studied by measuring the angle of Repose employing the fixed funnel method. Such as suitable allowing components after which the tip of Repose will be less than 30° [12]. The rise of Repose has been determined by calculating using the given equations.

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

Table 1: Formulation of Capecitabine Microspheres

Formulation	Drug (mg)	Ethyl Cellulose (mg)	HPMC K-100 (mg)	Polymer Ratio
F1	500	300	300	1:1
F2	500	600	600	1:1
F3	500	900	900	1:1
F4	500	200	200	2:1
F5	500	400	400	2:1
F6	500	600	600	2:1

Table 2: Kinetic Release Models with Their Equations

Model	Equation
Zero-order kinetics	Q - Q0-Kot
First order kinetics	Q=QO(1-e^{-klt})
Higuchi square root model	Qt=KH t1/2
Hixson-Crowell's cube root model	$3\sqrt{Qo} - 3\sqrt{Qt}$=vKHCt
Korsmeyer-peppas model	$\frac{Qt}{Q\infty}$=Kktn

Table 3: Size Analysis

S. No	Formulation	Arithmetic Mean of Particle Size
1.	Fl	93 = 0.24
2.	F2	64+ 0.78
3.	F3	45±0.05
4.	F4	97+ 0.53
5.	F5	70±0.79
6.	F6	11 0 ± 0.25

Mean ± S.D. of Three Determinations

Table 4: Carr's Index and Hausner's Ratio

S. No	Formulation	Carr's Index	Hausner's ratio
1.	Fl	14.13±0.31	1.16±0.25
2.	F2	11.36±0.37	1.12±0.26
3.	F3	14.07±0.41	1.16±0.24
4.	F4	10.89±0.27	1.23±0.26
5.	F5	14.85±0/6	1.17±0.13
6.	F6	12.24±0.27	1.14±0.16

Mean ± S.D. of Three Determinations

Table 5: Angle of Repose Mean ± S.D. of Three Determinations

S. No	Formulation	Angle of Repose
1.	Fl	22.80±0.14
2.	F2	20.48±0.26
3.	r3	22.20±0.23
4.	F4	23.56±0.25
5.	F5	20.75±0.42
6.	F6	21.72±0.18

Mean ± S.D. of Three Determinations

Table 6: Drug Entrapment Efficiency

S. No	Formulation	Drug Content (mg)	Entrapment Efficiency (%)
1.	Fl	40.55 ±0.79	81.10±0.01
2.	F2	41.10 ± 1.09	82.20 ± 1.03
3.	F3	43.60 ± 1.08	87.20 ± 0.05
4.	F4	42.20 ± 0.40	84.40 ± 0.07
5.	F5	43.70 ± 1.05	87.40 ±. 0.01
6.	F6	44.95± 1.20	89.30 ± 0.05

Mean ± S.D. of Three Determinations

Table 7: Percentage Yield

S. No	Formulation	Percentage Yield
1.	Fl	79.24 ± 1.24
2.	F2	86.78 ± 1.56
3.	F3	94.88 ± 1.31
4.	F4	86.25± 1.21
5.	F5	18.29 ± 1.30
6.	F6	95.13 ± 1.37

Mean ± S.D. of Three Determinations

Table 8: Kinetic Modeling of Drug Release from F6

S.No	(min) Time Log T	Square rout of Time	% C.R.	% Drug Remaining	Lug % C.R.	Log % Drug Remaining	Square root Drug Remaining
1	0	0	0	100	0	2	4.641
2	2	0.30 I 0	1.4142	09.56	90.44	0.9804	1.95636	4.4886
3	4	0.6020	2.0	19.25	80.75	1.2844	1.9074	4.32229
4	6	0.7781	2.4494	25.43	74.57	1.4053	1.87256	4.20908
5	8	0.9030	2.8284	3I.34	68.66	1.4960	1.83670	4.09481
6	10	1.0434	3.1622	36.72	63.28	1.5649	1.80126	3.98494
7	12	1.0791	3.4241	44.11	55.89	1.6445	1.74733	3.82335
8	14	1.1461	3.741	52.09	47.91	1.7167	1.68042	3.61196
9	16	12041	4.9423	6123	39.77	1.7798	1.59955	3.41338
10	18	1.2552	4.2426	68.75	31.25	1.8372	L49485	3.14930
11	20	1.3010	4.4721	77.56	22.44	1.8896	1.35102	2.82059
12	22	1.3424	4.6904	86.45	11.97	1.9367	1.13193	2.38403
13	24	1.3302	4.8989	95.85	4.15	1.9815	0.618048	1.60700

Table 9: Regression Coefficients or Kinetic Release Model

Order of Kinetics	Regression Coefficient (r^2)
Zero-order	0.9541
First order	0.8027
Higuchi release	0.9541
Korsmeyer Peppas	0.7604
Hixson Crowel	0.9081

Table 10: Accelerated Stability Studies or Optimized Formulations F6

Parameters	0 Days	30 Days	60 Days	90 Days
Particle size	110.2 ± 0.25	110.2 ± 0.31	111.2 ± 0.25	112.2 ± 0.23
Entrapment Efficiency	89.30 ± 0.05	89.32 ± 0.06	89.32 ± 0.05	90.30 ± 0.03
In-Vitro Drug Release	95.85 ± 0.41	95.92 ± 0.46	95.95 ± 0.41	96.85 ± 0.42

Where, H is the height; R is the radius of the cone.

Drug Content and Entrapment Efficiency

Microspheres similar to 50 mg of an opioid have been begun taking such as assessment. The quantity of opioids entrapped has been approximated by smashing microparticles and trying to extract aliquots like ph 7.4 PBS repetitively. An extricate transmitted to a 50 ml volumetric flask, and the volume was made using ph 7.4 PBS [13]. The solution has been filtrated, and the absorbance was recorded since appropriate dispersion spectrophotometrically about 239 nm against a suitable blank. The quantity of opioids encapsulated within microspheres has been determined by calculating even by following equations.

$$DEE = \frac{Amount\ of\ the\ drug\ actually\ present}{Theoretical\ drug\ load\ expected} \times 100$$

Percentage Yield

The prepared microspheres were collected and weighed. The measured Weight was divided by the total amount deli non-volatile components which were used for the preparation of the microspheres.

$$Percentage\ Yield\ (\%) = \frac{W1}{W2} \times 100$$

Where, W1 = Weight of microspheres; W2 = Total Weight of drug and polymer used in the formulation.

***In-Vitro* Release Study**

Invitro drug release was investigated in simulated intestinal fluid (SIF -pH 7.4 phosphate buffer) until complete degradation [14]. A drug dissolution test like microspheres has been conducted using USP XXIII paddle kind of dissociation equipment (TDT-08L, electro lab India, Mumbai) at about 100 rpm 37°c ± 0.5°c_ microspheres (100 mg) have been weighed precisely but also packed through tea bags. Tea bags have been linked utilizing thread for a paddle and loaded into the dissociation equipment, usually containing a 900 ml-like dissolution medium.

A specimen (10 ml) was forced to withdraw from the dissolution medium at intervals like 1 hr using just a pipette equipped with such a micro filter now at tips but also evaluated such as opioid through LTV spectrometer against a standard curve (r2 > 0_99) acquired at = 239 nit!.

Flawless sink affliction has been preserved during the dissolution rates period of study also with added of such an equal amount like fresh discharge moderate around the same temp [15].

The cumulative amount of drug release = C x D.F. x D.M.

Where, C = concentration of drug at each time interval (pg/m1); D.F. = Dilution Factor is 100; DM = Dissolution Medium (900 ml).

Kinetics of Drug Release (Model Dependent Methods)

To investigate the mechanism of release of drugs from the prepared microspheres [16], the release data were analyzed with the following mathematical release models [Table 2].

1. Cumulative percentage drug release Vs. $^{-}4$ (Higuchi's classical diffusion equation)

2. Time Vs. Cube root of Percentage drug remaining (Hixson - Crowell)

3. Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

Stability Studies

Accelerated stability studies were performed for the final optimized formulation [17]. The prepared microspheres were selected for stability studies, which showed an appropriate balance between the drug content and the percentage release. The ready formulation was packed in aluminum foil and stored at 40 'Ct2T/75%R.E1±55^{1}0RH temperatures per ICH guidelines [18]. As per the standard protocol, the samples must be analyzed at 0, 1. 2, 3, and 6 months' time points.

RESULTS AND DISCUSSION

Drug Excipients Compatibility Studies

The interaction studies [Table 3] were to determine whether any interactions between drugs and the excipients used in the production of microspheres [Figure 3 and Figure 4].

Differential Scanning Calorimetry (DSC)

Medication excipient interactions are essential for, among other things, the release of the drug from

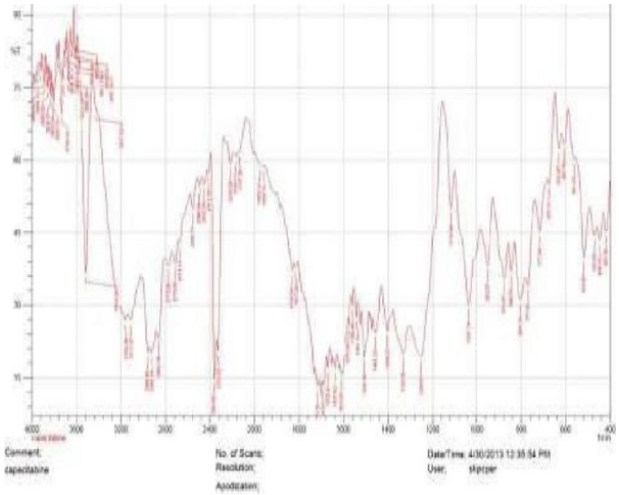

Figure 3: FTIR Spectrum of Capecitabine

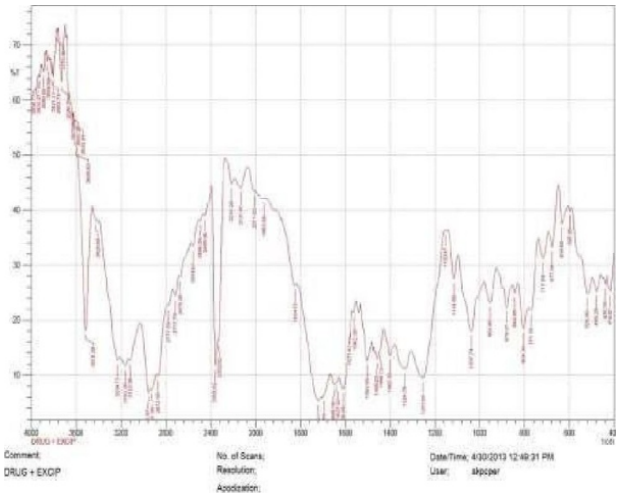

Figure 4: FTIR Spectrum of Drug and Polymer Mixture

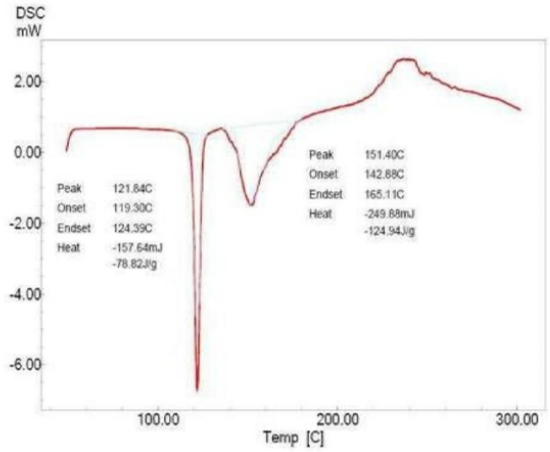

Figure 5: DSC Thermograms of (A) Pure Capecitabine and (B) Drug-Loaded Microspheres (F6)

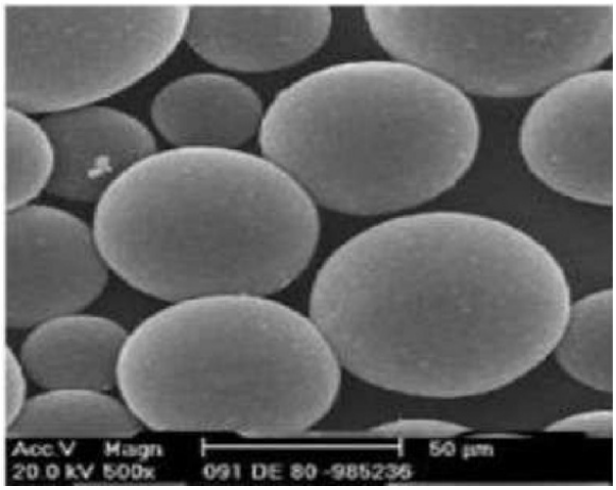

Figure 6: Scanning Electron Micrographs of Microsphere Formulation F6 Size Analysis

the formulation. The physical and chemical interactions between the medication and the excipients utilized have been studied using DSC. Figure 5 shows the obtained DSC thermograms. It demonstrates that the drug's breakdown temperature was 121.84^{o}C and the formulation mixture was 122.20 °C. It indicates there is no chemical interaction between Capecitabine and the polymer used.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy of optimized formulation F6 is shown in Figure 6. The view of the microspheres showed a spherical structure with a smooth surface morphology and discrete. The outer surface of the microspheres was smooth and showed some porous structure.

The average particle size of microspheres as determined by optical microscopy using a stage micrometer and ocular micrometer is shown in Table 4, and the units were analyzed in triplicate. All batches of microspheres were prepared by keeping the drug amount and solvent volume constant The particle size of floating microspheres varied between 45+0.05 to 110+0.25 tine. The results indicate that the mean particle size increases with increased concentration of polymers as the viscosity increases particle size increases. The formulation F6 showed a maximum particle size of I I 0±0.25 um compared to other formulations.

Bulk Density and Tapped Density

The prepared microspheres for all the formulations were evaluated for bulk density and tapped density by using bulk density apparatus, and the results are shown in Table 5.

The bulk density was found in the range of 0.933-0.984 gm/cm^{3}. The tapped density ranged between 0.941- 0.99 gm/cm^{3}.

Size Analysis

The average particle size of microspheres, as determined by optical microscopy using a stage micrometer and an ocular micrometer, is shown in Table 3. The units were analyzed in triplicate. All batches of microspheres were prepared by keeping the drug amount and solvent volume constant. The particle size of floating microspheres varied between 45±0.05 to 110=0.25. The results indicate that the mean particle size increases with increased concentration of polymers; as the viscosity increases, particle size increases. The formulation F6 showed a maximum particle size of 110±0.25 μm compared to other formulations.

The Angle of Repose

All formulations Fl to F6 of microspheres were evaluated for angle of Repose (Table 5); the rise of Repose of all the formulations was within the range of 20'-25°; these values indicate that the prepared microspheres exhibited excellent flow properties.

Drug Content and Entrapment Efficiency

The values of drug loading and entrapment efficiency % are shown in Table 6. Drug content of the prepared formulations ranged between 40.55 ± 10.79 to 44.95 ± 24 mg, and drug entrapment efficiency varied from 81.10 ± 0.01 to 89.30=0.05%. This result indicated that the drug content and entrapment efficiency increased with the concentration of Ethylcellulose with the combination of HPMC K-100. Polymer concentration increases the viscosity of the solution. This was due to the ethyl cellulose showing good entrapment efficiency and the rank order of entrapment efficiency F6> F5> F3>F4> F2> Fl.

Percentage Yield

The percentage yield for the microspheres prepared by emulsion solvent evaporation was recorded in Table 8, and it was determined by collected the microspheres and weighed. The measured Weight was divided by the total amount of all polymer components used to prepare the microspheres [Table 9]. The percentage yields of microspheres of all formulations were in the range of 79.24± 1.24 to 95.13±1.37% [Table 7]. The formulation F6 showed a maximum percentage yield of 95.13 1.37% compared to other formulations.

Accelerated Stability Studies

The most influential formulation's drug entrapment efficiency, particle size, and in vitro release research were assessed, and the results revealed no appreciable changes during storage. In the improved formulas, a foil made of aluminum wraps and seals F6. Table 10 displays the findings from stability studies.

CONCLUSION

The formulation of colon-targeted microspheres of the chemotherapeutic compound capecitabine utilizing the polymers E.C. and HPMC in combination was successful. The emulsion solvent evaporation method created spherical and freely flowing microspheres. The efficient formulations were found to have a strong recovery yield and percent drug entrapment due to the microspheres' good flow ability, which suggests that they may be handled and either filled into a capsule or crushed to tablet dose FCPMI. According to the study, the polymer concentration impacted the microspheres' release profile, and microspheres could delay the release of Capecitabine until it reached the colon. The produced microspheres provide potential as a colon-targeted delivery system since they have a higher kinetic profile and bioavailability.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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