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RESEARCH ARTICLE

FORMULATION AND CHARECTERISATION OF COLON TARGETED pH DEPENDENT MICROSPHERES OF CAPECITABINE FOR COLORECTAL CANCER

[*]Dilip Agrawal, M.S. Ranawat, C.S. Chauhan, Ravindra Kamble

Department of Pharmaceutics, Bhupal Nobles' College of pharmacy, Udaipur, India

**Corresponding Author's Email: dilip.kcp@gmail.com, Tel: 9928301430*

ABSTRACT

The aim of the present work was to prepare the colon-targeting microspheres of capecitabine (CPB) for the treatment of colorectal cancer to reduce dosing frequency and improve patient compliance. P^H-sensitive polymer Eudragit L100, S100 separately and in combination (1:2) was used to formulate the microspheres by emulsion solvent diffusion technique using varying drug – polymer ratios (1:2 to 1:6). Microspheres were evaluated for particle size, shape, flow properties, surface morphology by scanning electron microscopy, yield, drug content, and *in vitro* drug release behavior and found to be significantly affected by polymer concentration. The formulated microspheres were discrete, spherical with relatively smooth surface, and with good flow properties. CPB-loaded microspheres demonstrated good entrapment efficiency (53.28 to 93.76%). The release study was done in simulated gastrointestinal fluids for 2 hrs in SGF (pH 1.2), for 3 hrs in SIF (pH 6.8) and up to 24 hrs in SCF (pH 7.4) and have shown that the drug was protected from being released in the physiological environment of the stomach and small intestine and efficiently released in colon (99.39%). Formulation ELS2 gave the best result among all formulations (1.59% release at end of 2 hrs, 19.24% at the end of 5 hr, and 99.39% at the end of the study). It is concluded from the present study that p^H sensitive Eudragit microspheres are promising carriers for oral colon-targeted delivery of CPB for colorectal cancer.

Key Words: Capecitabine, Eudragit L-100, Eudragit S-100, microspheres, pH sensitive, colon targeting, colorectal cancer.

INTRODUCTION

Colorectal cancer manifests as cancerous growths in the colon, rectum and appendix. Colorectal cancer is the second most common cancer killer overall and third most common cause of cancer-related death in the United States in both males and females.[1] Oral colon-specific drug delivery system (CDDS) is more advantageous over conventional cancer chemotherapy as it is ineffective in delivering drugs to the colon due to absorption or degradation of the active ingredient in the upper gastrointestinal tract.[2] CDDS as an effective and safe therapy for colon cancer provides therapeutic concentrations of anticancer agent at the site of action and spare the normal tissues, with reduced dose and reduced duration of therapy.[3] The successful targeted delivery of drug to the colon via the gastrointestinal tract (GIT) requires the protection of a drug from degradation and release in the stomach and small intestine and then ensures abrupt or controlled release in the proximal colon.[4]

Capecitabine is an orally-administered chemotherapeutic agent used in the treatment of colorectal cancer and metastatic breast cancer. Capecitabine is a prodrug that is enzymatically converted to fluorouracil (antimetabolite) in the tumor, where it inhibits DNA synthesis and slows growth of tumor tissuesince it is readily absorbed from the gastrointestinal tract. The recommended daily dose is large, i.e., 2.5 g/m2 and it have a short elimination half-life of 0.5–1 h[5]. Varieties of approaches have been used and systems have been developed for the purpose of achieving colon targeting. These approaches are either drug-specific (prodrugs) or formulation-specific (coated or matrix preparations). The most commonly used targeting mechanisms are pH-dependent delivery; time-dependent delivery; pressure-dependent delivery; and bacteria-dependent delivery.[6]

The pH-dependent approach is based on the pH gradient of GIT that increases progressively from the stomach (pH 1.5-3.5) and small intestine (pH 5.5-6.8) to the colon (6.4-7.0). The most commonly used pH-dependent polymers are derivatives of acrylic acid and cellulose. By combining the knowledge of polymers and their solubility at different pH environments, delivery systems have been designed to deliver drugs at the target site. Most commonly used pH-dependent polymers are methacrylic acid copolymer (i.e., Eudragit L100 and Eudragit S100), which dissolve at pH 6.0, and 7.0, respectively. [7, 8] These polymers do not dissolve in stomach and intestinal pH due to hydrogen bonding between the hydroxyl groups of the carboxylic moiety and the carbonyl oxygen of ester groups in the polymer molecules. However, they dissolves in the colon because of the ionization of their carboxyl functional groups and releases the drug in the colon.[9] It is possible to modify the polymer characteristics, by using the combination of Eudragit S100 and L100 in varying ratio.[10] The addition of Eudragit L100 to Eudragit S100 in varying ratios altered the pH at which the polymer solubilised to produce formulations with high accuracy.

The objective of the present investigation was to formulate and characterise the microspheres of capecitabine using pH sensitive polymers Eudragit S 100 and L 100 separately and in combination for colon targeting.

MATERIALS AND METHODS

The capecitabine was a kind gift from Cipla Laboratories Ltd (Mumbai, India). Eudragit S100 and L 100 were procured as a gift sample from E*vonik Degussa* India Pvt. Ltd., Mumbai, India. Tween 80 and dichloromethane were purchased from *Central Drug* House (P) Ltd. New Delhi. All other chemicals and reagents used in the study were of analytical grade.

Preparation of Capecitabine Loaded pH Sensitive Microspheres[11, 12]

Microspheres were prepared by a method based on the o/w emulsification-solvent evaporation technique using two polymers i.e. Eudragit L 100 and Eudragit S 100 reported by Lamprecht et al with some modifications. Polymers were used separately and in combination (1:2 respectively) to prepare microspheres.

To prepare microspheres polymer and capecitabine were dissolved in 5 ml DCM (organic solvent) and ultrasonicated for 5 minutes. The resultant solution was dispersed drop-wise in aqueous medium containing 0.1% w/v Tween 80 (stabilizer), while stirring at 700 rpm using mechanical stirrer. This system was maintained under mechanical agitation at room temperature for 45 minutes to allow the complete solvent evaporation. The microspheres were decanted, filtered and washed with distilled water for 3 times. The microspheres were air dried and kept in an airtight desiccator for further studies. All the formulation were prepared varying drug to polymer ratio (1:2, 1:3, 1:4, 1:5 and 1:6) using both the polymers Eudragit L100 and S100 separately and in combination. . The detailed Parameters for all the preparations are summarized in Table 1.

Table: 1. Formulation Details of pH Sensitive Microspheres

Formulation Code	CPB (mg)	Polymer(mg)		Drug : polymer	DCM (ml)
		Eudragit L	Eudragit L		
EL1	100	200	-	1:2	5
EL2	100	300	-	1:3	5
EL3	100	400	-	1:4	5
EL4	100	500	-	1:5	5
EL5	100	600	-	1:6	5
ES1	100	-	200	1:2	5
ES2	100	-	300	1:3	5
ES3	100	-	400	1:4	5
ES4	100	-	500	1:5	5
ES5	100	-	600	1:6	5
ELS1	100	67	133	1:2	5
ELS2	100	100	200	1:3	5
ELS3	100	133	267	1:4	5
ELS4	100	167	333	1:5	5
ELS5	100	200	400	1:6	5

Percentage yield[13]

The prepared microspheres were collected and weighted. The actual weight of obtained microspheres divided by the total amount of all material that was used for the preparation of the microspheres using following equation:

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipients and drug}} \times 100$$

Characterization of the Microspheres

Particle size of microspheres

The particle size of the microspheres was determined by using optical microscopy method.[13]

A small amount of dry microspheres was suspended in distilled water. A small drop of suspension was placed on a clean glass slide. The slide containing suspended microspheres was mounted on the stage of the microscope and 300 particles were measured using a calibrated ocular micrometer. The process was repeated three times for each batch prepared.

Morphology

Shape and surface morphology was studied with projection microscope and photographs were taken and the selected formulations were further investigated using Environmental Scanning Electron Microscopy (ESEM, XL30, Philips, Netherlands). The samples were randomly scanned and photomicrographs were taken with ESEM.

Flow Properties[13]

The flow properties of microspheres were investigated by determining the angle of repose, bulk density, tapped density, Carr's and Hausner's ratio. Each parameter was calculated three times for each batch prepared and results were averaged.

(i) Angle of Repose

Angle of repose (θ) was measured according to the fixed funnel of Banker and Anderson. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip at a given height of 1cm (H), above graph paper placed on a flat horizontal surface. The microspheres were carefully poured through the funnel until the apex of the conical pile so formed just reached

the tip of the funnel. Thus, the R being the radius of the base of the microspheres conical pile:

$$\tan\theta = \frac{H}{R}$$

$$\theta = \tan^{-1}\left(\frac{H}{R}\right)$$

Where, θ = Angle of repose

H = Height of pile

R = Radius of pile.

(ii) Carr's Index and Hausner's Ratio

Poured density was determined by placing exact quantity 'M ' of microsphere into a graduated cylinder and measuring the volume' V ' occupied by the microspheres.

$$\text{Poured Density} = \frac{M}{V}$$

Tapped density was determined by placing a graduated cylinder containing a known quantity (M) of the prepared microspheres on a mechanical tapping apparatus, which was operated for a fixed number of taps until the bed volume reached to a minimum.

$$\text{Tapped Density} = \frac{M}{V}$$

The Carr's Index and Hausner's ratio were calculated using formula:

$$\text{Carr`s index (\%)} = \frac{\text{Tapped} - \text{Poured density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Poured density}}$$

Percentage drug entrapment

To determine the drug entrapment, an accurately weighed amount (100 mg) of microspheres was dispersed in 100 mL of PBS (pH 7.4) in volumetric flask and shaken vigorously for 24 hrs using rotary shaker. Supernatant was filtered using a Whattman filter (0.45-µm pore size) and analyzed for drug content by measuring absorbance in UV-spectrophotometer (ShimadzuUV-1800, Japan) at 239.6 nm.

The drug content of each sample was determined in triplicate, and results were averaged. Drug entrapment efficiency was calculated by using the following formula: [13]

$$\%\text{Drug Entrapment} = \frac{\text{Practical content}}{\text{Theoretical content}} \times 100$$

In Vitro Drug Release Studies[15, 16]

The in vitro drug release study of colon targeting CPB loaded microspheres was carried out in pH progression medium. The pH progression medium was attained by using simulated gastrointestinal fluids i.e. SGF, SIF, SCF pH in sequence, to mimic mouth-to-colon transit. Simulated gastric fluid (SGF) pH 1.2 consisted of NaCl (2.0 g), 0.1N HCl (7 mL), simulated intestinal fluid (SIF) of pH 6.8 consisted of Na_2HPO_4 (28.80 gm), KH_2PO_4 (11.45 gm), simulated colonic fluid (SCF) of pH 7.4 consisted of KH_2PO_4 (6.8 g), 0.2N NaOH (190 mL) in 1000 mL distilled water. For first 2 hours, the dissolution study was conducted in SGF (pH 1.2) as the average gastric emptying time is about 2h. Then the dissolution medium was replaced with SIF (pH 6.8) study was continued for next 3 hours as the average small intestinal transit time is about 3h. After 5 hours, the dissolution medium was replaced with SCF (pH 7.4) and the study was continued till the end of release study.

The drug dissolution test of microspheres was performed by the paddle method using USP XXIII paddle type dissolution apparatus (TDT-08L, Electro lab India, Mumbai) at 100 rpm and 37°C ± 0.5°C. Microspheres (100 mg) were weighed accurately and filled in tea bags. The tea bags were tied using thread with paddle and loaded into the basket of dissolution apparatus containing 900mL of dissolution medium. The samples (5mL) were withdrawn from the dissolution medium at time interval of 1 hr using a pipette fitted with a microfilter at its tips and analyzed for drug by UV spectrophotometer against a standard curve($R^2 > 0.99$) obtained at λ = 239.60 nm. Perfect sink condition was maintained during the drug dissolution study period with the addition of an equal volume of fresh release medium at the same temperature. All the readings were taken in triplicate and results were averaged.

In order to determine the mechanism & kinetics of drug release from the microspheres and to compare the release profile various formulations, the in-vitro release data were fitted to mathematical models. The kinetic models included zero order, first order, Higuch and Korsmeyer-Peppas model.

RESULTS AND DISCUSSION

Preparation of Capecitabine Loaded p^H sensitive Microspheres

P^H sensitive microspheres of capecitabine were successfully prepared by o/w emulsification-solvent evaporation technique. This method is used for microsphere preparation because of its simplicity, reproducibility, and fast processing with minimum controllable process variables that can be easily implemented at the industrial level.[11] Eudragit L100, Eudragit S100 and their combination (1:2) were used to prepare p^H sensitive microspheres. Eudragit L100 and Eudragit S100 dissolve at pH 6.0, and 7.0, respectively. These polymers do not dissolve at stomach and intestinal pH but dissolve in the colon and release the drug in the colon. It was evident that the pH in the proximal colon ranges from 6.6 to 7.0 and then reaches up to neutral in distal colon. Therefore, The Eudragit L-100 and S-100 were combined in different ratios and solubility of these combinations was checked in different pH solutions. From the solubility parameters, it was found that

Eudragit L-100 and S-100 in the ratios 1:2 was soluble in pH range of 6.6–7.0.[17] Hence, this combination was selected for preparation of microspheres. DCM was used as organic solvent as it is an effective solvent for the polymer (Eudragit S100 and L 100) and drug at each of its selected levels. Tween 80 was used as stabilizer and necessary for microsphere formation with superior topographical characteristics.

The percentage yield of different formulations was calculated and the results were shown in Table: 2 the yield was found in the range of 89.45% to 97.67% for all the formulations (EL1 to ELS5). The results indicated that the method o/w emulsification-solvent evaporation yields better percentage of CPB microspheres.

As shown in Table: 2 the results demonstrated that drug/polymer ratios affected the microshperes characteristics while keeping the other variables constant. Particle size analysis of capecitabine microspheres showed that the mean microsphere diameter was affected by drug/polymer ratio. The mean diameter of all the formulations of pH sensitive polymers varied from 84.58±7.29 µm to 124.41±9.25µm with varying drug/polymer ratio. The average particle size of microspheres increased with increasing polymer concentration, as higher concentration of polymer produced a more viscous dispersion, which formed larger droplets and consequently larger microspheres were formed.

Table 2: Physical Characteristics of pH Sensitive Microspheres

Serial no.	Formulation code	Average Particle Size (µm)	Yield (%)	Entrapment Efficiency (%)
1.	EL1	103.42±7.31	89.45	75.52
2.	EL2	107.51±5.52	92.08	76.21
3.	EL3	110.64±.8.23	94.78	80.65
4.	EL4	117.24±4.42	95.50	82.32
5.	EL5	124.41±9.25	96.45	83.46
6.	ES1	95.20±6.12	87.46	53.28
7.	ES2	101.54±8.11	88.24	68.06
8.	ES3	107.10±4.21	93.51	70.09
9.	ES4	114.56±10.14	97.67	72.64
10.	ES5	119.02±8.12	94.36	72.03
11.	ELS1	84.58±7.29	95.50	84.01
12.	ELS2	99.74±12.74	90.78	86.88
13.	ELS3	102.97±7.65	97.25	89.81
14.	ELS4	105.75±6.41	94.48	93.76
15.	ELS5	109.32±4.54	95.64	91.93

Results shown are average of three readings ±SD,(n=3)

Table 3: Flow Properties of pH Sensitive Microspheres

Serial no.	Formulation code	Angle of Repose (°)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner's Ratio
1.	EL1	25.45±1.15	0.219±0.017	0.253±0.008	13.44	1.16
2.	EL2	24.30±1.01	0.315±0.014	0.363±0.007	13.22	1.15
3.	EL3	24.10±0.75	0.247±0.012	0.289±0.006	14.53	1.17
4.	EL4	22.80±0.52	0.224±0.015	0.271±0.006	17.34	1.21
5.	EL5	18.92±0.74	0.297±0.014	0.357±0.007	16.81	1.20
6.	ES1	24.25±0.63	0.314±0.009	0.364±0.008	13.74	1.16
7.	ES2	23.70±0.42	0.278±0.011	0.327±0.005	14.98	1.18
8.	ES3	21.55±1.35	0.303±0.013	0.368±0.007	17.66	1.21
9.	ES4	20.83±0.79	0.329±0.011	0.391±0.006	15.86	1.19
10.	ES5	19.34±0.88	0.352±0.014	0.412±0.004	14.56	1.17
11.	ELS1	24.41±1.45	0.249±0.020	0.293±0.008	15.02	1.18
12.	ELS2	22.60±0.64	0.226±0.018	0.264±0.006	14.39	1.17
13.	ELS3	22.32±1.34	0.256±0.010	0.287±0.007	10.80	1.12
14.	ELS4	20.50±0.42	0.283±0.015	0.329±0.006	13.98	1.16
15.	ELS5	20.22±1.16	0.197±0.013	0.225±0.004	12.44	1.14

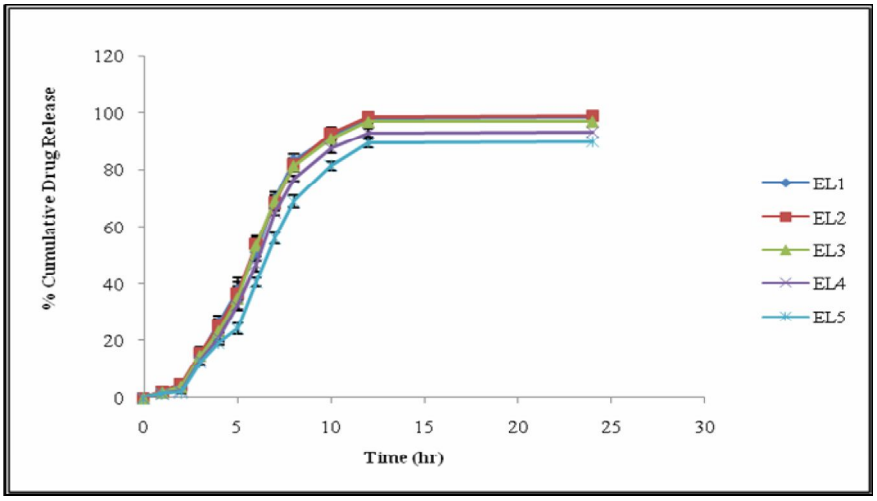
Results shown are average of three readings ±SD,(n=3)

It can be clearly observed from the photographs (Fig.4) of the microspheres prepared by solvent evaporation technique, that the microspheres are small, spherical and discrete. The shape and surface morphology was further confirmed with the SEM photograph (Fig.5). The microspheres were spherical and have almost smooth surface.

The values of angles of repose were in the range of 18.92° ± 0.74 to 25.45° ± 1.15, the values of Carr's index were in the range of 10.80% to 17.66% and the values of Hausner ratio were ranged from 1.12 to 1.21 for all the formulations (Table 3). Comparison of calculated results with standard values indicates an overall good free flowing nature of microspheres of all batches. Values of angle of repose ≤ 30° usually indicate a free flowing material, while values of compressibility index below 20 % give rise to good flow characteristics.

Percent entrapment efficiency of the formulations was found in the range of 53.28% to 93.76 in all the formulations given in Table:2. All the formulations show good entrapment efficiency. The entrapment efficiency of Eudragit L100 microspheres was found better than that of Eudragit S100 microspheres. But it was found excellent for the formulations prepared with the combinations of these two polymers. Overall a similar pattern was found in three categories (EL1-EL5, ES1-ES5 and ELS1-ELS5) that the percentage entrapment increased by increasing the polymer ratio. It was reported in the literature that the encapsulation efficiency depends on the solubility of the drug in the solvent and continuous phase. An increase in the concentration of polymer in a fixed volume of organic solvent resulted in an increase in encapsulation efficiency.[17] Hence capecitabine being aqueous soluble drug required high concentration of polymer in dosage form for better formulation development.

In vitro drug release study of pH dependent CPB microspheres was performed in pH progression medium and the in vitro drug release data of CPB in simulated gastrointestinal fluids (SGF, SIF and SCF) for all the formulations are given in Fig:1 to Fig: 3. The drug release was found to be 1.97 to 10.97% for EL1 to EL5, 1.81 to 5.53% for ES1 to ES5 and 0.84 to2.98% for ELS1 to ELS5 at the end of 2 hrs in SGF (pH 1.2). In SIF (pH 6.8) for next 3 hrs, the drug release was found in the range of 39.24 to 67.88% for EL1 to EL5, 6.08 to 9.45% for ES1 to ES5 and 7.09 to 25.89% for ELS1 to ELS5 at the end of 5 hrs. At the end of the study (24 hrs) the cumulative drug release was found to be 89.73 to 98.29% for EL1 to EL5, 71.91 to 92.13% for ES1 to ES5 and 84.55 to 99.39% for ELS1 to ELS5. The result shows that the cumulative drug release deceased as the polymer concentration increased. It may be due to the fact that the increase in polymer concentration increases the density of polymer matrix and the diffusion path length that the drug has to traverse.



Results shown are average of three readings ±SD,(n=3)

Figure 1: Zero order plots for Release Profile of Formulations EL1 to EL5

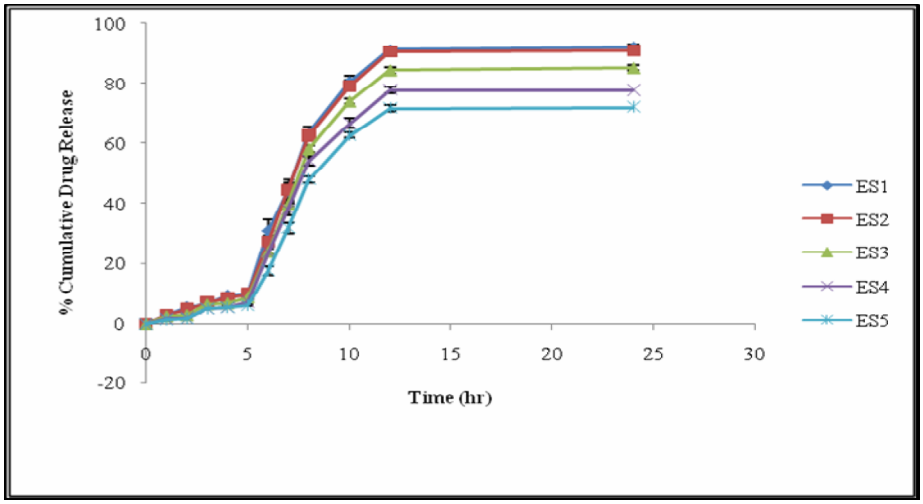
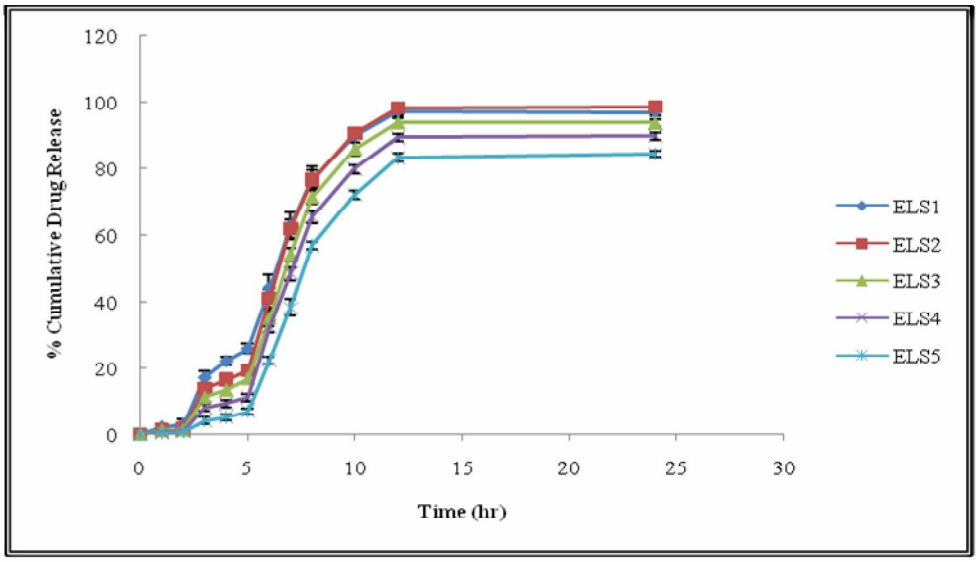


Figure 2: Zero order plots for Release Profile of Formulations ES1 to ES5



Results shown are average of three readings ±SD,(n=3)

Figure 3: Zero order plots for Release Profile of Formulations ELS1 to ELS5

It is observed that all the formulations gave the drug release less than 6±5% in first two hrs in SGF (pH 1.2) and this may be due to initial dissolution of drug particles adsorbed at the surface. Hence, all the formulations can prevent the drug from being released in the physiological environment of the stomach. Formulations EL1 to EL5 released 50±15% of drug in SIF (pH 6.8) and rest of the drug was released in SCF (pH7.4), as the polymer Eudragit L100 get dissolved at pH 6.0. Formulations ES1 to ES5 gave only 8±2% of the drug release in SIF may be due to swelling of polymer and significant drug release was observed in SCF (pH 7.4). These formulations of Eudragit S 100 did not release complete drug in SCF. ELS1 to ELS5 released 16±7% drug in SIF due to faster solubilisation of Eudragit L 100 than Eudragit S100 at the pH 6.8, because L100 polymer is soluble at pH 6.0. These formulations delivered their drug load in a controlled manner in SCF and gave the maximum drug release at the end of the study as compare to ES1 to ES5.

Overall the formulation ELS2 showed more promising results amongst all the formulations (1.59% release at end of 2 hrs, 19.24% at the end of 5 hr, and 99.39% at the end of the study).

Drug release mechanisms were determined by fitting *in vitro* drug release data to various kinetic models. The kinetic model showing highest regression coefficient was considered as the most appropriate model for the dissolution data. By comparing regression values (R^2) for Zero order, First order, Higuchi model, and Korsmeyer–Peppas model, it is concluded that all formulations gave good fit to the Korsmeyer–Peppas model. The diffusion exponent (n) values were found to be greater than 1, so the drug release follows super case II transport. This model will help to analyze the release of formulations, when the release mechanism is not well known or when more than one type of release phenomenon could be involved.[19]

Table 4: Kinetic Parameters of pH sensitive microspheres of Different Models

Formulation	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	K (mg/h)	R^2	K (h^{-1})	R^2	K ($mg/h^{1/2}$)	R^2	R^2	n
EL1	5.0012	0.696	-0.094	0.8382	27.993	0.8206	0.9001	1.5703
EL2	5.0126	0.6997	-0.0979	0.8368	28.022	0.823	0.9011	1.5638
EL3	4.9618	0.6917	-0.0979	0.8153	27.744	0.814	0.9015	1.5866
EL4	4.8093	0.699	-0.0618	0.7964	26.716	0.8119	0.9021	1.6647
EL5	4.6327	0.7286	-0.0515	0.8053	25.304	0.8181	0.9067	1.6549
ES1	4.8545	0.748	-0.0573	0.8123	25.466	0.7748	0.9045	1.4848
ES2	4.8144	0.746	-0.0549	0.8001	25.203	0.7695	0.9031	1.4798
ES3	4.5274	0.7475	-0.0436	0.7969	23.607	0.7649	0.9043	1.5228
ES4	4.1549	0.741	-0.0346	0.7814	21.719	0.7621	0.9011	1.5874
ES5	3.8531	0.7456	-0.0294	0.7758	19.981	0.7547	0.91	1.5798
ELS1	4.9931	0.7172	-0.0803	0.7958	27.414	0.8137	0.9015	1.5771
ELS2	5.1906	0.7187	-0.0974	0.8214	28.104	0.793	0.9024	1.7247
ELS3	4.9671	0.7251	-0.0636	0.791	26.653	0.7858	0.9065	1.731
ELS4	4.8018	0.7338	-0.0524	0.7995	25.449	0.7757	0.904	1.8315
ELS5	4.5596	0.7492	-0.0428	0.8022	23.649	0.7586	0.9049	1.8633

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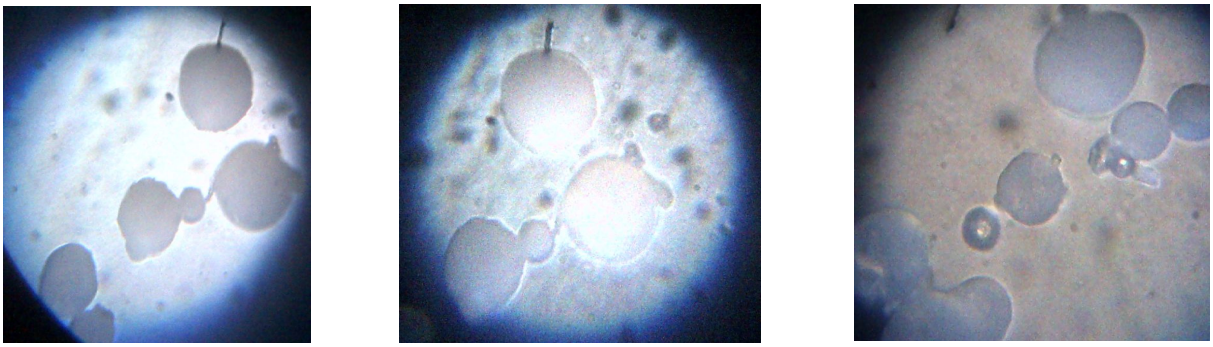

(a) (b) (c)

Figure 4: (a) Photograph of microspheres (EL2) (b)Photograph of microspheres (ES3) (c) Photograph of microspheres (ELS3)

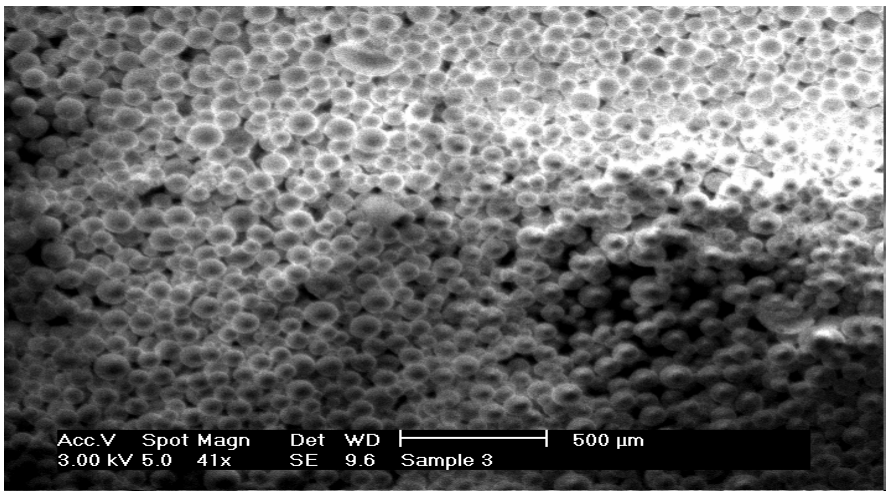

Figure 5: Sem photograph of microspheres (ELS2)

CONCLUSION

In this study, colon targeted microspheres of anticancer drug Capecitabine were formulated successfully using pH sensitive polymers Eudragit L100, S100 separately and in combination (1:2) for colonic delivery of drug. Spherical and free-flowing microspheres were prepared by emulsion solvent evaporation method. The good flowability and packability of microspheres, indicates that they can be successfully handled and either filled into a capsule or compressed to tablet dosage form. All the formulations were found to be efficient with good recovery yield and percent drug entrapment. The study revealed that the release profile of microspheres was affected by polymer concentration and microspheres were capable to retard the release of CPB until it reaches the colon. This shows that pH sensitive colon targeting micro particulate drug delivery system can be used to treat the colorectal cancer by minimising the wastage of drug and undue toxic effect on the normal cells.

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