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Research Article

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

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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. Time-dependent polymer Eudragit RL100, RS100 separately and in combination (1:1) was used to formulate the microspheres by emulsion solvent diffusion technique using varying drug – polymer ratios (1:1 to 1:5). 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, almost spherical with somewhat folded and invaginated surface, and with good flow properties. CPB-loaded microspheres demonstrated good entrapment efficiency (of 55.43±1.54% to 84.08±1.62). 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 time based formulations showed lag time of 4hrs protect the drug from being released 4 hrs and efficiently released in colon (97.92%). Formulation RLRS4 gave most promising result among all formulations (3.62% release at end of 4 hrs and 94.10% at the end of the study). It is concluded from the present study that time dependent Eudragit microspheres are promising carriers for oral colon-targeted delivery of CPB for colorectal cancer.

KEYWORDS: *Capecitabine, Eudragit RL-100, Eudragit RS-100, microspheres, Time dependent, colon targeting, colorectal cancer.*

INTRODUCTION

Colorectal cancer (CRC) is a worldwide problem, with an annual incidence of approximately 1 million cases and an annual mortality of more than 500,000. The absolute number of cases will increase over the next two decades as a result of the aging and expansion of populations in both the developed and developing countries. CRC is the second most common cause of cancer mortality among men and women.[1]Colorectal cancer manifests as cancerous growths in the colon, rectum and appendix. Capecitabine is a pro-drug that is converted to fluorouracil in the body tissues following the oral administration.

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It is widely used in the treatment of metastatic colorectal cancer and breast cancer, since it is readily absorbed from the gastrointestinal tract. The recommended daily dose is large, i.e., 2.5 g/m2 and it has a short elimination half-life of 0.5–1 h.[2] Hence, formulating capecitabine as a oral colon targeted dosage form would provide greater or longer *in vitro* and *in vivo* antitumor activity, thereby reducing its toxic side effects. In particular, multi-particulate systems such as microspheres, beads, etc., exhibit specific advantages over other conventional dosage forms like tablets and capsule for oral colon-specific drug delivery. 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] A variety 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.[5]

Time-dependent delivery (pulsatile release, delayed or sigmoidal release system) has also been proposed as a means of targeting the colon. The transit time and rate of solid oral dosage forms through the GI tract is largely unpredictable due to the variability in gastric emptying time (residence time in the stomach), which can range from a few seconds to few hours depending on the size, shape, and density of the dosage form and the feed status of the individual [21] [(115-117)]. While small intestinal transit time is relatively constant (3 - 4 h) irrespective of formulation and dietary factors [21][118] and due to more viscous environment in the distal colonic region, it has long residence time of the contents (12 – 24 h) [21] [119, 120]. Time-dependent systems are designed to release their drug load after a pre-programmed lag time of 5 -6 hours equates to the time taken for the system to reach the colon. Most commonly used time-dependent polymers are copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups (Rohm Pharma, 2001).[22] The ammonium groups are present as salts and make the polymers permeable and act as channelling agents for the entrance of the dissolution medium through the microspheres wall causing its swelling. This gives an opportunity for the dissolved drug to diffuse out to the bulk medium. (Lehmann, 1997; Ro¨hm GmbH and Rohm America, 1999).[24, 23]

Eudragit RL and RS have the same chemical structure except that Eudragit RL100 has double the number of hydrophilic quaternary ammonium groups than Eudragit RS100. Hence Eudragit RL100 is more permeable than Eudragit RS100; formulations can be prepared with different combinations of Eudragit RL and RS to provide various degrees of sustained-release of the drug.[24]

The objective of the present investigation was to formulate and characterise the microspheres of capecitabine using time dependent polymers Eudragit RL 100 and RS100 separately and in combination for colon targeting.

MATERIALS AND METHODS

Chemicals

The capecitabine was a kind gift from Cipla Laboratories Ltd (Mumbai, India). eudragit RS100 and RL 100 were procured as a gift sample from E*vonik Degussa* India Pvt. Ltd., Mumbai, India. tween 80 and magnesium stearate 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 Eudragit S100 Microspheres[6]

CPB microspheres were prepared by o/o emulsification-solvent evaporation technique using two polymers i.e. Eudragit RL 100 and Eudragit RS 100. Polymers were used separately and in combination (1:1) to prepare microspheres.

To prepare microspheres polymer was dissolved in 10 ml acetone by using a magnetic stirrer. The CPB and magnesium stearate (100 mg) were added to the polymer solution and mixed for 15 minutes. The resulting dispersion was added slowly with the help of syringe to 70 ml light liquid paraffin containing tween 80 (1% w/v), while stirring at 700 rpm using a mechanical stirrer. Stirring was continued for 3 h until the acetone evaporated completely. The microspheres formed were filtered using Whatman no.1 filter paper. The residue was washed 4-5 times with 50 ml portions of n-hexane. The product was then dried at room temperature for 24 hours and kept in an airtight desiccator for further studies. All the formulation were prepared varying drug to polymer ratio (1:1, 1:2, 1:3, 1:4 and 1:5) using both the polymers Eudragit RL100 and RS100 separately and in combination.

Percentage yield[12]

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.

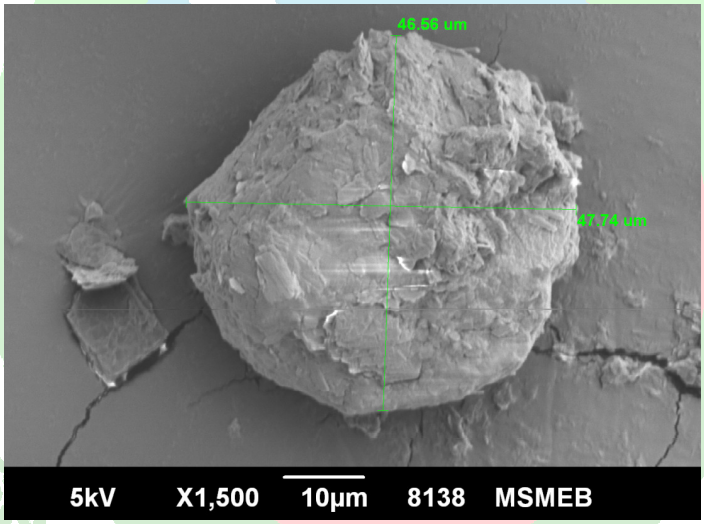

Fig:1. Sem Photograph of Formulation RLRS 4

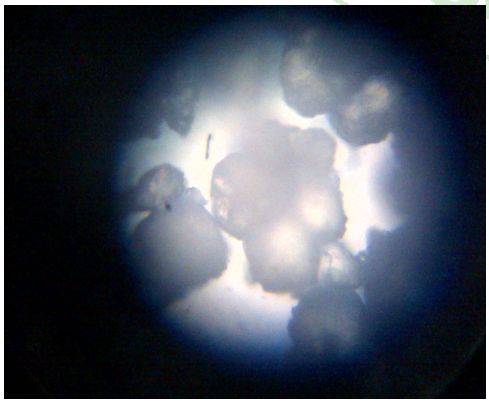

Fig: 2. Photograph of formulation RL2

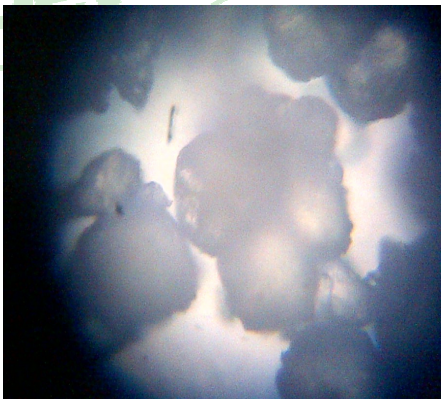

Fig: 3. Photograph of Formulation RS 3

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:

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

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

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: [12]

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

In Vitro Drug Release Studies[14, 15]

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 time dependent Microspheres

Time dependent microspheres of the highly water soluble drug CPB was successfully prepared by emulsion solvent evaporation method. In this method, drug polymer mixtures were dispersed into an immiscible vehicle to form an emulsion. As the solvent is evaporated, the droplets become gradually concentrated and the nucleation takes place to produce microspheres. Eudragit RL100 and Eudragit RS100 and their combination (1:1) were used to prepare time dependent microspheres.

Table: 1. Formulation Details of Time dependent microspheres Microspheres

Formulation code	CPB (mg)	Polymer(mg)		Drug : polymer	Magnesium stearate (mg)	Tween 80
		Eudragit RL 100	Eudragit RS 100			
RL1	100	100	-	1:1	100	1 %
RL2	100	200	-	1:2	100	1 %
RL3	100	300	-	1:3	100	1 %
RL4	100	400	-	1:4	100	1 %
RL5	100	500	-	1:5	100	1 %
RS1	100	-	100	1:1	100	1 %
RS2	100	-	200	1:2	100	1 %
RS3	100	-	300	1:3	100	1 %
RS4	100	-	400	1:4	100	1 %
RS5	100	-	500	1:5	100	1 %
RLRS1	100	50	50	1:1	100	1 %
RLRS2	100	100	100	1:2	100	1 %
RLRS3	100	150	150	1:3	100	1 %
RLRS4	100	200	200	1:4	100	1 %
RLRS5	100	250	250	1:5	100	1 %

The percentage yield of different formulations was calculated and the results were shown in Table: 2. The yield was found in the range of 87.21% to 98.62 % for all the formulations (RL1 to RLRS5). The results indicated that the method o/w emulsification-solvent evaporation yields better percentage of CPB microspheres.

Table: 2. Physical Characteristics of Time Dependent Microspheres

Serial no.	Formulation code	Yield (%)	Entrapment Efficiency (%)	Average Particle Size (µm)
1.	RL1	87.21	55.43±1.54	118.20±3.52
2.	RL2	89.25	64.76±1.75	127.41±5.15
3.	RL3	92.53	67.85±0.98	139.52±12.91
4.	RL4	94.60	69.04±1.61	147.10±9.45
5.	RL5	93.85	72.81±1.05	154.03±12.46
6.	RS1	91.57	58.18±1.90	125.65±5.20
7.	RS2	93.25	65.80±2.13	134.15±7.50
8.	RS3	94.75	68.88±1.48	145.43±9.40
9.	RS4	98.62	71.99±.65	160.42±7.65
10.	RS5	97.80	73.39±1.21	167.05±11.20
11.	RLRS1	94.56	70.17±1.89	146.40±7.65
12.	RLRS2	96.64	72.57±.92	149.24±6.40
13.	RLRS3	98.45	78.85±2.64	153.50±4.62
14.	RLRS4	97.95	80.83±.82	161.02±7.35
15.	RLRS5	96.24	84.08±1.62	168.13±6.46

Results shown are average of three readings ±SD

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 time dependent polymers varied from 118.20±23.52µm to 168.13±6.46µm for all the formulations (RL1 to RLRS5). The mean particle size of Eudragit RL100 microspheres was found smaller (136±18 µm) than that of Eudragit RS100 microspheres (143±18 µm). But the microspheres prepared with the RL/RS100 were of larger size (157±11 µm) as compared to the microspheres of the two separate polymers. 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.

It can be clearly observed from the photographs 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 photographs. The microspheres were almost spherical and have somewhat folded and invaginated surface.

Table: 3. Flow Properties of Time dependent 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.	RL1	22.14°±1.2	0.417±0.016	0.496±0.005	15.93	1.19
2.	RL2	21.09°±.87	0.429±0.010	0.502±0.006	14.54	1.17
3.	RL3	23.53°±.75	0.448±0.007	0.513±0.009	12.67	1.15
4.	RL4	23.27°±1.1	0.389±0.011	0.438±0.008	11.19	1.13
5.	RL5	24.67°±.1.24	0.405±0.013	0.466±0.011	13.09	1.15
6.	RS1	23.45°±0.87	0.486±0.009	0.552±0.015	11.96	1.14
7.	RS2	22.40°±0.42	0.461±0.021	0.529±0.006	12.85	1.15
8.	RS3	25.26°±1.36	0.439±0.008	0.497±0.004	11.67	1.13
9.	RS4	24.23°±0.96	0.427±0.011	0.479±0.008	10.86	1.12
10.	RS5	25.46°±0.65	0.364±0.018	0.421±0.015	13.54	1.16
11.	RLRS1	24.54°±1.4	0.458±0.010	0.512±0.012	10.55	1.12
12.	RLRS2	26.26°±.45	0.453±0.004	0.518±0.009	12.55	1.14
13.	RLRS3	26.44°±.95	0.442±0.009	0.502±0.007	11.95	1.14
14.	RLRS4	25.68°±.74	0.411±0.015	0.455±0.008	9.67	1.11
15.	RLRS5	24.45°±1.2	0.406±0.013	0.453±0.010	10.38	1.12

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

The values of angles of repose were in the range of 21.09°±0.87to 26.44°±0.95, the values of Carr's index were in the range of 9.67% to 15.93% and the values of Hausner ratio were ranged from 1.11to 1.19for all the formulations. 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 55.43±1.54% to 84.08±1.62 in all the formulations given in Table: 2. All the formulations show good entrapment efficiency. The entrapment efficiency of Eudragit RS100 microspheres (66±8%) was found better than that of Eudragit RL100 microspheres (64±9%). But it was found excellent for the formulations when the combinations of these two polymers (77±7%) were used. This can be explained on the basis of permeation characteristics that Eudragit RL100 containing higher amount of quaternary ammonium groups facilitates the diffusion of a part of entrapped drug to the surrounding medium during preparation of microsphere. In opposite, Eudragit RS100 has thick polymeric surfaces due to the presence of lower amount of quaternary ammonium groups, which restrict the migration of drug particles to the surrounding medium. The microspheres prepared using both the polymers exhibited the highest encapsulation efficiency, indicating the formation of the most stable emulsion and the most suitable microsphere structures in the RL/RS (1:1) mixture.[6, 23]

It was also found that the entrapment of CPB increased by increasing the polymer ratio. The entrapment of CPB depends upon its solubility in the solvent and continuous phase. Hence CPB being soluble in the solvent it required high concentration of polymer in dosage form for better formulation development. An increase in the concentration of polymer in a fixed volume of organic solvent resulted in an increase in entrapment efficiency.

In vitro drug release study of time 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) in Fig: 4 to Fig: 6. The drug release was found to be 6.79±1.85% to 3.59±1.23% for RL1 to RL5, 7.07±1.23% to 3.22±1.56 % for RS1 to RS5 and 3.86±.74% to 2.99±.82% for RLRS1 to RLRS5 at the end of 4 hrs. At the end of the study (12 hrs.) the cumulative drug release was found to be 96.80 to 89.17% for RL1 to RL5, 94.49 to 71.82% for RS1 to RS5 and 97.07 to 83.66% for RLRS1 to RLRS5.

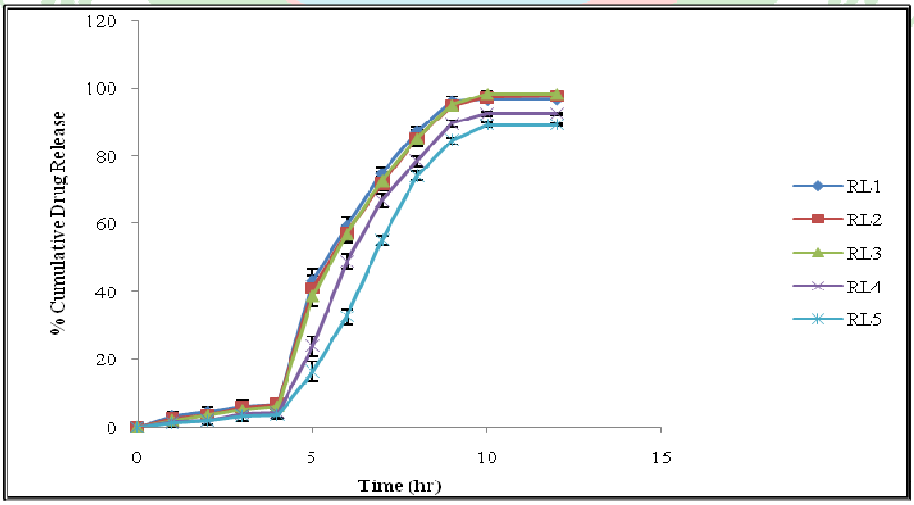

Figure: 4. Cumulative Release Profile of Eudragit RL 100 microspheres (Zero order plots)

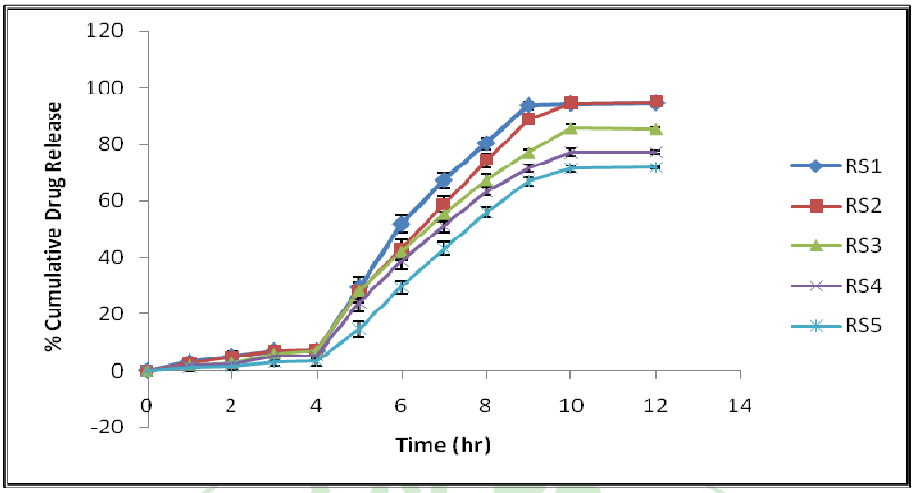

Figure: 5. Cumulative Release Profile of Eudragit RS 100 microspheres (Zero Order plots)

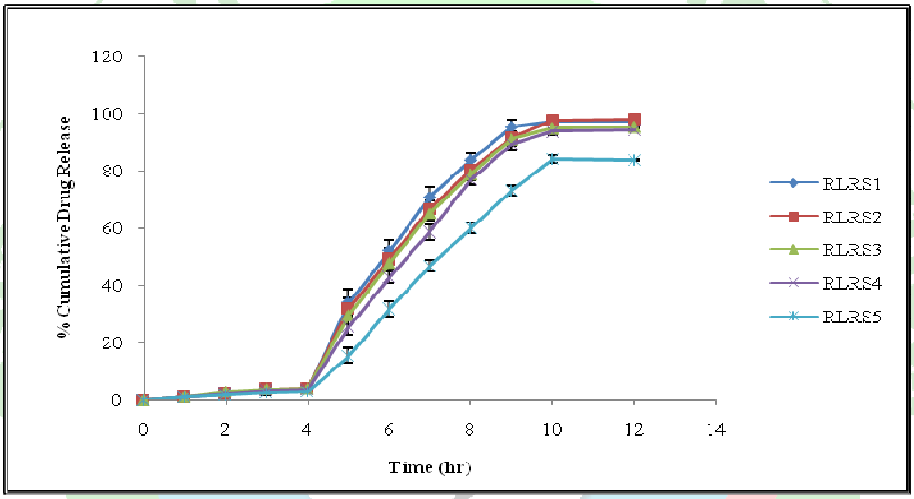

Figure: 6. Cumulative Release Profile of Eudragit RL/RS 100 microspheres (Zero Order plots)

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.

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 consequently the amount of drug present close to the surface decreases and the diffusion path length that the drug has to traverse increases.

All formulations showed a lag time of 4 hours and released very less drug (5 ± 2.5%) at the end of the 4 hr. This lag time may be explained on the basis that all the formulations were prepared using time based polymers Eudragit RL100 and RS100 which are water-insoluble but water swellable polymers over the entire pH range; the active ingredients are gradually dissolved by penetrating dissolution media. 2 time This initial release is due to surface drug and drug present close to the surface.

After lag time, all the formulations gave burst release in 5 hr. Formulations of Eudragit RL100 showed higher burst release (30±14%) and release almost its drug load within 8 to 9 hr (90±6%). The high release rate of RL100 formulations as compared to the formulations of RS100 and RL/RS100 attributed to higher amount of quaternary ammonium groups present in RL100, which renders it more permeable and accelerates the drug release. [6]

Formulations of Eudragit RS100 showed slow release with less burst effect (22±8%) and unable to release its complete load up to 12 hr (83±12%).These observations could be attributed to the fact that RS100 microspheres have thicker polymeric surface (less amount of quaternary ammonium groups) which slows the entry of surrounding dissolution medium in to the microspheres and hence less quantity of drug leaches out from the polymer matrices of the microspheres.

Formulations of Eudragit RL/RS100 (1:1) exhibited more pronounced release up to 12 hr (90 ± 7%) with less bursting effect (25 ± 10%). This can be explained on the basis that addition of Eudragit RL100 increases the porosity and permeability of the RS100 matrix to the surrounding dissolution medium, hence more controlled rate of drug release is observed.

Amongst all the formulations RLRS4 showed more promising results. It showed less burst effect (25.77%) and gave controlled drug release up to12 hr (94.10%).

Drug release mechanisms were determined by fitting *in vitro* drug release data to various kinetic models Table: 4. 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.[18]

Table: 4. Kinetic parameters of Time dependent 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
RL1	10.566	0.9022	-0.1537	0.8729	RL1	10.566	0.9022	-0.1537
RL2	10566	0.912	-0.1562	0.8755	RL2	10566	0.912	-0.1562
RL3	10.682	0.9109	-0.1692	0.8576	RL3	10.682	0.9109	-0.1692
RL4	10.114	0.9032	-0.1143	0.8776	RL4	10.114	0.9032	-0.1143
RL5	9.6142	0.8962	-0.0971	0.8551	RL5	9.6142	0.8962	-0.0971
RS1	10.157	0.9133	-0.1278	0.8622	RS1	10.157	0.9133	-0.1278
RS2	9.9067	0.9287	-0.1213	0.8522	RS2	9.9067	0.9287	-0.1213
RS3	8.951	0.9335	-0.0824	0.8989	RS3	8.951	0.9335	-0.0824
RS4	8.1996	0.9238	-0.0656	0.9094	RS4	8.1996	0.9238	-0.0656
RS5	7.6361	0.9103	-0.0562	0.8884	RS5	7.6361	0.9103	-0.0562
RLRS1	10.67	0.9061	-0.153	0.8567	RLRS1	10.67	0.9061	-0.153
RLRS2	10.53	0.917	-0.1547	0.8395	RLRS2	10.53	0.917	-0.1547
RLRS3	10.286	0.9135	-0.1285	0.8678	RLRS3	10.286	0.9135	-0.1285
RLRS4	10.1	0.9136	-0.1193	0.858	RLRS4	10.1	0.9136	-0.1193
RLRS5	8.7172	0.9117	-0.0761	0.8601	RLRS5	8.7172	0.9117	-0.0761

CONCLUSION

In this study, colon targeted microspheres of anticancer drug Capecitabine were formulated successfully using time dependent polymers Eudragit RL100, RS100 separately and in combination (1:1) for colonic delivery of drug. Almost 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 up to 4 hrs. This shows that time based 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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References

1. *Agnihotri Sunil A., M Tejraj Aminabhavi, "Novel interpenetrating network chitosan-poly(ethylene oxide-g-acrylamide) hydrogel microspheres for the controlled release of capecitabine" International Journal of Pharmaceutics,2006, 324:103–115*
2. *S Jose, K Dhanya, TA Cinu, "Colon targeted drug delivery: Different approaches" J Young Pharmacists, 2009, 1(1):13-19*
3. *Basit Abdul ,Bloor John , "Perspectives on Colonic Drug Delivery", Business Briefing: Pharmatech, 2003,185-190*
4. *N.Bipul, Nath L.K., K. Pradeep , "Preparation And In Vitrodissolution Profile of Zidovudine Loaded Microspheres Made of Eudragit Rs 100, Rl 100 And Their Combinations" Acta Poloniae Pharmaceutica Drug Research, 2011, 68 (3) 409-415.*
5. *Vyas, S.P. Khar, R.K., "Targeted and Controlled Drug Delivery Novel Carrier System", Ist Edition, CBS Publishers and Distributors, New Delhi, 2002: 417-54.*
6. *Martin A, Swarbrick J, Cammarata A, editors. Physical Pharmacy, Physical chemical principles in the pharmaceutical sciences. 3rd ed. Indian edition. Mumbai: Varghese Publishing house; 1991: 492-521.*
7. *Xiu-Li Zhao, Ke-Xin Li, Xiu-Feng Zhao, Da-Hai Pang, And Da-Wei Chen "Study on Colon-Specific 5-Fu pH-Enzyme Di-Dependent Chitosan Microspheres" Chem. Pharm. Bull, 2008,56(7) 963—968*
8. *Chaurasia Mohini, Chourasia K. Manish , Nitin K. Jain, Aviral Jain, Vandana Soni, Yashwant Gupta, "Cross-Linked Guar Gum Microspheres: A Viable Approach for Improved Delivery of Anticancer Drugs for the Treatment of Colorectal Cancer " AAPS PharmSciTech2006; 7 (3):1-9*
9. *Paulo Costa, Jose Mannel Sousa lobo, "Modeling and Comparison of Dissolution Profiles" European Journal of Pharmaceutical Sciences,2001,13:123-133*
10. *J.E. Devereux, J.M. Newton, M.B. Short, The influence of density on the gastrointestinal transit of pellets. Journal of Pharmacy and Pharmacology1990, 42(7):500-501.*
11. *S.S. Davis, J.G. Hardy, M.J. Taylor, The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). International Journal of Pharmaceutics,1984, 21(3) :331-340.*
12. *L.C. Kaus, J.T. Fell, H. Sharma, D.C. Taylor, On the intestinal transit of a single nondisintegrating object. Int. J. Pharm, 1984,14, 143-148.*
13. *S.S. Davis, J.G. Hardy, J.W. Fara, Transit of pharmaceutical dosage forms through the small intestine. Gut,1986, 27(8): 886-892.*
14. *J.H. Cummings, S.A. Bingham, K.W. Heaton, M.A. Eastwood, Fecal weight, colon cancer risk, and dietary intake of nonstarch polysaccharides (dietary fiber). Gastroenterology,1992, 103(6):1783-1789.*
15. *A.M. Metcalf, S.F. Phillips, A.R. Zinsmeister, R.L. MacCarty, R.W. Beart, B.G. Wolff, Simplified assessment of segmental colonic transit. Gastroenterology,1987, 92(1): 40-47.*
16. *A.H. El-Kamel, M.S. Sokar, S.S. Al Gamal, V.F. Naggar, "Preparation And Evaluation Of Ketoprofen Floating Oral Delivery System" International Journal of Pharmaceutics , 2001,220,13 – 21*
17. *M. Zahirul I. Khan , Zeljko Prebeg, Nevenka Kurjakovic, "A pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers" Journal of Controlled Release, 1999, 58, 215–222*
18. *R.Manju , Shailendra Saraf, and Swarnlata Saraf, "Influence of Selected Formulation Variables on the Preparation of Enzyme-entrapped Eudragit S100 Microspheres" AAPS PharmSciTech , 2007, 8 (4)*