RESEARCH ARTICLE

Influence of operational variables in multi-particulate delayed release systems for colon-targeted drug delivery of celecoxib using extrusion spheronization

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The present research was aimed to formulate and evaluate pH and time-dependent multiparticulate systems for colon-targeted drug delivery of celecoxib (CXB) with maximum drug absorption, reduced peak plasma fluctuations, and minimum potential side effects. Multiple unit delayed release systems of the drug in MCC (Avicel® PH-102) grade were prepared using polymethacrylate polymers (Eudragit® L-100 and RSPO) as a granulating binder by the extrusion-spheronization technique and characterized for their shape, size, size distribution, friability, density, and moisture content. *In vitro* release studies were performed in 0.1N HCl, for first 2 h then further performed in phosphate buffer (pH 6.8) for 24 h. The resulting pellets were prepared by extrusion spheronization using different grades of polymethacrylate polymers as a granulating binder, showing a substantial decrease in drug release in initial 5 h (16.28-16.7%) and releasing most of the drug in 12-24 h. The geometric and arithmetic mean diameter ranged from (490 to 780 μm) and (636 to 734 μm), respectively. The minimum to maximum range for circularity, elongation and rectangle were found to be (0.847±0.009 to 0.965±0.078), (1.036±0.057 to 1.185±0.023), and (0.724±0.041 to 0.791±0.047) respectively showing the proper shape and size of the pellets. The content of CXB in the prepared pellets was observed between 98.70 and 99.47% justifying the uniform drug distribution. The *in vitro* dissolution studies showed that the retardant effect in initial 5 h and most of the drug release in 24 h depended on the ratio and concentration of different grades of methacrylate polymers used in the formulation. CXB-loaded MUPS prepared by the extrusion-spheronization technique using polymethacrylate polymers showed immense potential for colon-specific drug delivery of the drug.

Key words: *Celecoxib (CXB), colon targeting, extrusion-spheronization, multiparticulate system*

INTRODUCTION

Colon-targeted dosage forms are usually designed to delay the release for about 5 h that corresponds to drug release at the ileocaecal junction, where the dosage form dissolves upon exposure to the higher pH of the distal intestine or proximal colon. Tablets are the most commonly used dosage form for colon targeting. The biggest drawback from which such dosage forms might suffer is their possible retention at the ileocaecal junction. It has been postulated that a number of small pellets may overcome this barrier owing to their small size. Also, once in the colon, tablets move faster through the ascending colon than the pellets. Thus, multi-unit particulate systems (MUPS) can be considered as a potential drug delivery system with significant therapeutic and technological advantages over single unit dosage forms for colonic delivery exhibiting longer transit time.[1]

Colorectal cancer is an emerging cause of cancer deaths throughout the world and it is second leading cause of cancer-related mortality in the west.[2] More than 66,000 cases of colon cancer are reported to occur every year in the Indian subcontinent.[3] Colon-specific drug delivery is recognized to be advantageous and a rational strategy in the treatment of disorders of the large intestine, such as colon cancer, irritable bowel syndrome, ulcerative colitis, Crohn's disease, and infectious diseases.[4]

NSAID therapy has been widely implicated for its multifaceted use in the clinical management of colon tumorogenesis. Due to overexpression of COX-II

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DOI: 10.4103/0973-8398.68460

enzyme in the tumor cells, selective COX-II inhibitors (such as CXB) have been used for its therapeutic efficacy in colon cancer. Recently, clinical studies have revealed the significant role of celecoxib for inducing anticarcinogenic effects on various colon cancer cell lines[5,6] as well as showed efficacy in reducing the occurrence of colorectal adenomatous polyps.[7] Hence, celecoxib has revitalized the interest among the researchers for better management of NSAID therapies to widen the scope of therapeutic options for colon cancer.

Attempts have been made to achieve colon-targeted delivery from oral dosage forms via delayed, sustained, or controlled-release mechanisms. Drugs can be delivered locally and selectively to the colon if they are enclosed in a dosage form, such as a capsule or a tablet that cleaves in the colon because of a change in the pH or the action of bacterial enzymes. Local delivery of drug will reduce its dose, side effects, hepatic metabolism and in true enhance the therapeutic value.[8,9] Slower release rates or longer release periods can be obtained by extremely slow releasing matrices or by the application of thicker layers of conventional enteric coatings.

MUPS or pellets could be produced by a variety of techniques, out of which extrusion spheronization is the most upcoming technique. The extrusion operation can be considered to be a specialized wet granulation technique,[10] as well as an integral part of the overall spheronization process. The production of spheroids by extrusion-spheronization is widely used in the manufacture of controlled release as well as immediate release dosage forms. This is because spherical particles or spheroids offer a smooth surface and uniform size which allows uniform coating of each pellet. Pellets can attain high drug load which is necessary to achieve sustained blood levels of drugs for an extended period of time. It can be achieved from a polymeric matrix with the use of the extrusion-spheronization technique with drug loading ranging from 60 to 85%.

Hence, an attempt was made to develop a multi-unit delayed release system for colon-specific delivery of CXB using microcrystalline cellulose. Eudragit®-RSPO, alone and Eudragit® L-100 and Eudragit®-RSPO in combination were used as the granulating binder for preparing pellets. These pellets were filled in hard gelatin capsules and enteric coated [using pan coater (Modern Mechanical Works, Delhi) at conditions: rpm 12-15 and 40-45°C] with 10% solution of Eudragit® S-100. The assessment of the formulations was done by performing the dissolution tests in 0.1N HCl, for first 2 h, and then it was further performed in pH 6.8 phosphate buffer for 24 h.

MATERIALS AND METHODS

Materials

The model drug CXB was a gift sample from Panacea Biotech, Lalru, India. Microcrystalline cellulose (Ranbaxy Laboratories Pvt. Ltd, Dewas, India), Eudragit® S-100, Eudragit® RSPO and Eudragit®-L 100 (Corel Pharma Chem., Ahemdabad, India) were kindly received as gift samples. All other ingredients and chemicals were of analytical grade.

Preparation of pellets using Eudragit®- RSPO or combination of Eudragit®-RSPO and Eudragit® L-100 aqueous dispersion as a granulating binder

CXB (4% w/w), mixed with specified amount of MCC(Avicel® PH-102 grade, batch size 50 g) was granulated using various concentrations of aqueous dispersions of Eudragit®-RSPO (4-12% w/v) or combination of Eudragit®-RSPO (2-8%w/v) and Eudragit® L-100 (4-10% w/v). The aqueous dispersions were prepared by gradual addition of 4 to 12 g of Eudragit® RSPO alone or 2-8 g of Eudragit® RSPO and 4 to 10 g of Eudragit® L-100 in combination using distilled water respectively and were mechanically stirred at 2000 rpm. The prepared wet powder mass was extruded through the extruder (Caleva extruder 25, England) at a fixed speed and subsequently spheronized (Caleva spheronizer 120, England) for 2 min at fixed rpm. The spheroids obtained were then dried in tray dryer (Narang Scientific Works Pvt. Ltd, New Delhi) at 50°C for 24 h. The prepared batches containing Eudragit® RSPO (RS_1-RS_7) or combination of Eudragit® RSPO and L-100 (PL_1-PL_7) were then evaluated for various physical parameters such as drug content, friability, moisture content, and *in vitro* drug release.

Formulation of enteric-coated capsules containing spheronized matrix pellets

The spheronized matrix pellets were filled in hard gelatin capsules and enteric coated with Eudragit® S-100(10% w/v solution, in 6:4 of acetone: propane-2-ol mixture). Different batches (RSC_1-RSC_4) were prepared by varying the percent weight gain by the capsules having Eudragit® S-100 in the coat.

The formulation compositions of all the batches prepared have been summarized in Table 1.

Evaluation and physical characterization

Shape analysis

Randomly selected pellets (~20) of each batch (from the modal class (16/25) fraction) were mounted on the light microscope fitted with camera lucida. The images of the pellets were drawn manually on a graph paper. The area of the images and the maximum as well as minimum radii were calculated from various shape factors using the following formulas.[11]

$$\text{Elongation} = \frac{\text{maximum radius}}{\text{minimum radius}} \quad (1)$$

$$\text{Rectang} = \frac{\text{area}}{4 \times \text{maximum radius} \times \text{minimum radius}} \quad (2)$$

$$\text{Roundness} = \frac{\text{area}}{\pi \times (\text{maximum radius})^2} \quad (3)$$

Table 1: Formulation compositions of batches prepared using extrusion spheronization (Batch size ~50 g)

Formulation code	CXB (grams)	MCC (Avicel PH-102) (grams)	% wt of Eudragit® RSPO used	% wt of Eudragit® L-100	% Weight gain using Eudragit® S-100
RS1	2.0	48	0	-	-
RS2	2.0	48	4	-	-
RS3	2.0	48	6	-	-
RS4	2.0	48	8	-	-
RS5	2.0	48	9	-	-
RS6	2.0	48	10	-	-
RS7	2.0	48	12	-	-
PL1	2.0	48	2	6	-
PL2	2.0	48	4	4	-
PL3	2.0	48	6	6	-
PL4	2.0	48	6	8	-
PL5	2.0	48	8	4	-
PL6	2.0	48	8	6	-
PL7	2.0	48	8	10	-
RSC1	2.0	48	0	-	5.56
RSC2	2.0	48	0	-	12.85
RSC3	2.0	48	0	-	17.93
RSC4	2.0	48	0	-	26.17

Photomicrography

The randomly selected pellets from the modal class fraction were mounted on the phase contrast microscope (Olympus BO-71, Japan) with the magnification adjusted to 3.3 × 4. The photomicrographs of the pellets were obtained in order to determine the shape of the pellets.

Size analysis

The microscopic evaluation of 270 particles from each batch (selected at random from the modal class fraction obtained through sieving) was done using projection microscope with the help of stage micrometer. The maximum and minimum radii of the pellets were calculated.

The sieving method (sieving sample size ~5g) was used for the size analysis of pellets of prepared batches. Pellets were separated into various size fractions, using a sieve shaker (sieves of no. 2, 10, 16, 25, 30, 40 and 50) vibrating at 1 mm amplitude for 20 min. The arithmetic mean diameter[12] of the pellets was calculated.

$$AMD = \sum (W_i X_i) / \sum W_i \quad (4)$$

where X_i: mean diameter of the pellets retained on each sieve; W_i: weight of the pellets retained on sieve *i*.

Span and the mass median diameter (geometric mean diameter) were employed to characterize the pellet size and size distribution. The mass median diameter of the pellets was taken to be the pellet diameter at the 50% mark on the respective cumulative percent oversize plot. The span of the pellet size distribution was calculated as the ratio of the difference between the pellets diameter at the 90% and at the 10% to the pellets diameter at the 50%. The product fraction that passed through the 300-μm-aperture size sieve was taken to be the fines fraction. The modal class fraction referred to the size fraction obtained from sieve with the highest weight of pellets.

Bulk density (ρ_b) and tapped density (ρ_t)

A 10 ml graduated measuring cylinder was taken into which pellets were poured gently through a glass funnel and then tapped from a height of 2 cm until there was no more decrease in the volume. Tapped density (ρ_t) was calculated as the quotient of the weight of the pellets and its final volume after tapping.

Carr's index and hausner ratio

Using the tapped and bulk densities, Carr's index (I_c) and Hausner's ratio (H_R) were calculated:

$$I_c = \frac{(\rho_t - \rho_b)}{\rho_t} \quad (5)$$

$$H_R = \frac{\rho_t}{\rho_b} \quad (6)$$

Friability

Five grams accurately weighed pellets (modal class fraction) were tumbled for 200 revolutions at 25 rpm in a Roche friabilator along with 12 steel balls (diameter 8.2 mm, weighing 2.487 g each) as attrition agents. After friability testing, the pellets were sieved (mesh #30). The weight loss (% F) after friability testing was calculated by the formula.[13]

$$\%F = \left(\frac{(Wi - Wr)}{Wr} \right) \times 100 \quad (7)$$

where 'w_i' was the initial weight of the pellets before friability testing, and 'w_r' was the weight of the pellets retained above the sieve (aperture size-0.355 mm) after friability testing. All the parameters were evaluated in triplicate (n=3).

Moisture content

The sample (5 g) was placed in the infra-red moisture analyzer (Popular Traders, Ambala Cantt., India), at 105°C and the LOD was recorded to see the moisture content in the samples.

Drug content

A known weight of the powdered pellets was dissolved in a known volume of methanol. This was further diluted with 0.1 N HCl having 0.5% SLS and filtered. The drug in the solution was analyzed using UV-visible spectrophotometer at λ_{max} of 248 nm. All the determinations were done in triplicate.

***In vitro* release studies**

For *in vitro* release studies, a constant sieve fraction i.e. the 16/25 mesh fraction was used for each batch to minimize the effect of change in total surface area of pellets upon dissolution rate. 250 mg of pellets (equivalent to 10 mg drug) were used. According to USP30 NF25,[14] USP dissolution test apparatus (Type II) was used for the release studies at a speed of 50 rpm having 0.1N HCl (pH 1.2) and pH 6.8 phosphate buffer (both with 0.5% Sodium lauryl sulfate) as dissolution media (37°C±0.5°C). Aliquots of samples were withdrawn after predetermined time intervals and were analyzed by UV spectrophotometry at a λ_{max} of 248 nm (0.1N HCl (pH 1.2) with 0.5% SLS) and 249 nm (pH 6.8 phosphate buffer with 0.5% SLS), respectively. All data represent mean ± SD (n=3).

RESULTS AND DISCUSSIONS

MUPS-containing Eudragit®-RSPO with maximum concentration (RS_7, 12%) exhibited highest diameter and span value of 780 μm and 1.55. The span value was also found to be the highest i.e. 1.55, at the highest concentration of Eudragit®-RSPO. Higher span values mean higher size distribution. It may be inferred that at increased concentrations, Eudragit®-RSPO lead to an increase in the diameter as well as size distribution. The plot between frequency and pellet size showed normal distribution [Figure 1a and b]. The values of length-number mean (d_{ln}), surface-number mean (d_{sn}), volume-number mean (d_{vn}), surface-length mean (d_{sl}), volume-surface mean (d_{vs}) diameters for batch RS_1 (0% Eudragit®-RSPO), were found to be lowest among all formulations (RS_1-RS_7 and PL_1-PL_7), having a value of 843, 848, 852, 853, 862 μm, respectively. However, RS_7 (12%,Eudragit®-RSPO) exhibited highest diameter among the batches (RS_1-RS_7), corresponding to 922 μm, 929 μm, 935 μm, 936 μm, 949 μm, respectively for the values of d_{ln}, d_{sn}, d_{vn}, d_{sl} and d_{vs} [Table 2]. The batches formulated by using combination of Eudragit®-RSPO and Eudragit® L-100 dispersion as the granulating binder (PL_1-PL_7), showed similar results. Highest diameter was observed in the case of PL_6 (d_{ln}, d_{sn}, d_{vn}, d_{sl} and d_{vs} values were found to be 924, 929, 933, 933, 941 μm, respectively) using a combination of Eudragit®-RSPO (8%) and Eudragit® L-100 (6%), respectively. For shape analysis, batch RS_4 showed highest circularity values of 0.955±0.054 at a concentration of 8% of Eudragit® RSPO [Table 3]. However, a negative effect on pellet roundness was observed in higher amounts.[15] Similar results were obtained, where increasing the concentration of Eudragit®-RSPO from 8% (RS_5-RS_7) leads to a decrease in circularity values. As the circularity values decreased, the elongation and rectang increases. The batches that were prepared with combination of polymer dispersion as a granulating binder (PL_1-PL_7) follow the same trend. Also, as the concentration of Eudragit®-RSPO increased from 4% (PL_2), circularity starts decreasing from 0.965±0.078 [Table 3]. The values of rectang and elongation increased which further correspond to a decrease in circularity. The densities of all batches (RS_1- RS_7) prepared using Eudragit®–RSPO aqueous dispersion as a granulating binder [Table 4] did not differ significantly. Similar results were found with Hausner's ratio

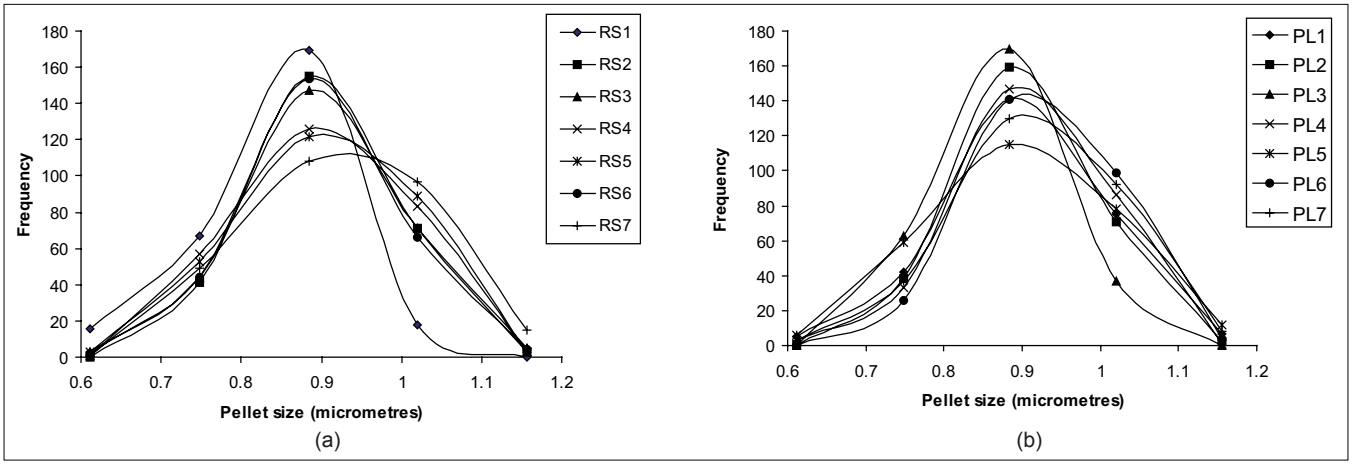

Figure 1: (a) Plot of frequency vs. size of pellets prepared with Eudragit®-RSPO aqueous dispersion as a granulating binder. (b) Plot of frequency vs. size of pellets prepared with combination of Eudragit®-RSPO and Eudragit® L-100 dispersion as a granulating binder

Table 2: Size analysis data obtained through optical microscopy for batches (RS_1 - RS_7) and (PL_1- PL_7)

Formulation code	Diameter (d) (μm)				
	d_{ln}	d_{sn}	d_{vn}	d_{sl}	d_{vs}
RS_1	843	848	852	853	862
RS_2	902	906	911	911	920
RS_3	899	904	910	910	920
RS_4	899	904	910	910	921
RS_5	902	908	914	914	925
RS_6	897	902	906	907	916
RS_7	922	929	935	936	949
PL_1	902	908	914	914	926
PL_2	902	906	910	911	919
PL_3	870	874	878	878	886
PL_4	908	913	917	918	927
PL_5	899	907	788	915	595
PL_6	924	929	933	933	941
PL_7	916	922	928	928	939

Table 3: Shape analysis of batches (RS_1-RS_7) and (PL_1- PL_7)

Formulation code	Circularity ± S.D.	Elongation ± S.D.	Rectangle ± S.D.
RS_1	0.915±0.051	1.093±0.046	0.787±0.007
RS_2	0.847±0.009	1.185±0.023	0.724±0.041
RS_3	0.945±0.087	1.058±0.079	0.786±0.066
RS_4	0.955±0.054	1.044±0.746	0.785±0.058
RS_5	0.901±0.055	1.113±0.953	0.776±0.054
RS_6	0.940±0.096	1.063±0.057	0.786±0.069
RS_7	0.946±0.812	1.055±0.122	0.784±0.022
PL_1	0.959±0.017	1.039±0.076	0.784±0.047
PL_2	0.965±0.078	1.036±0.057	0.785±0.023
PL_3	0.904±0.981	1.108±0.036	0.787±0.055
PL_4	0.948±0.084	1.055±0.016	0.786±0.125
PL_5	0.960±0.691	1.041±0.005	0.785±0.063
PL_6	0.954±0.056	1.046±0.043	0.784±0.052
PL_7	0.937±0.062	1.074±0.067	0.791±0.047

Table 4: Evaluation of physical parameters for matrix pellets

Formulation	Friability (%)	Moisture content (%)	Assay (%)	Bulk* density(ρ_b) (g/ml)	Tapped* density (ρ_t) (g/ml)	Hausner's ratio	Carr's index
RS_1	0.30	2.0	99.26	0.75±0.001	0.82±0.012	1.08	0.08
RS_2	0.02	0.2	98.86	0.76±0.032	0.80±0.002	1.06	0.05
RS_3	0.05	1.8	99.03	0.75±0.008	0.81±0.005	1.08	0.07
RS_4	0.24	2.2	98.90	0.75±0.007	0.81±0.042	1.08	0.07
RS_5	0.06	2.0	99.08	0.76±0.005	0.82±0.017	1.08	0.07
RS_6	0.03	1.8	99.43	0.75±0.067	0.81±0.075	1.08	0.07
RS_7	0.03	2.0	98.95	0.74±0.003	0.79±0.006	1.06	0.06
PL_1	0.04	1.6	98.70	0.72±0.061	0.77±0.007	1.07	0.06
PL_2	0.05	1.8	99.13	0.74±0.007	0.79±0.010	1.06	0.05
PL_3	0.21	0.4	99.00	0.74±0.003	0.80±0.004	1.08	0.07
PL_4	0.20	1.2	99.30	0.76±0.005	0.82±0.056	1.08	0.07
PL_5	0.42	1.4	98.90	0.78±0.014	0.83±0.043	1.06	0.06
PL_6	0.21	1.2	99.10	0.78±0.043	0.85±0.003	1.08	0.08
PL_7	0.43	1.8	99.47	0.78±0.011	0.85±0.055	1.08	0.07

*Data represent (mean±SD); (n=3)

and Carr's index values. The Hausner's ratio was found to be nearly the same in all these batches. Batch (PL_7) prepared with combination of Eudragit®-RSPO and Eudragit® L-100 (PL_1-PL_7) as a granulating binder [Table 4] showed the highest value of bulk densities (0.78±0.011) and tapped densities (0.85±0.055), when the concentration of both Eudragit®-RSPO and Eudragit® L-100 was maximum i.e. 8% and 10%, respectively.

Photomicrographic analysis of pellets [Figures 2a, b, c, d] showed that on increasing the concentration of Eudragit®-RSPO, a negative effect on pellet roundness was observed as revealed from the photographic analysis. However, with a small increase in the concentration of Eudragit®-RSPO (up to 4%) in Batch RS_2 pellet roundness improved [Figure 2b] but the pellets having highest concentration (12%) of Eudragit®-RSPO (RS_7) showed less smooth outline [Figure 2c]. These results were supported by the findings of Krogars *et al*.[17] which suggested the Eudragit®-S-mediated improvement in the pellet roundness. The pellets having Eudragit® L-100 in the formulation along with Eudragit®-RSPO as a granulating binder (PL_7) were also spherical [Figure 2d].

Pellets prepared by using Eudragit®-RSPO dispersion as a granulating binder (RS_2-RS_7) showed minimal weight loss (below 0.5%) after the friability test [Table 3]. However, the batches prepared by using a combination of Eudragit® RSPO and Eudragit®L-100 as a granulating binder (PL_1–PL_7) showed that on increase in concentration of Eudragit® L-100 in the formulation in higher amount, the friability of pellets increases (Eudragit® L-100 i.e. 10% (PL_7) showed highest friability of 0.43%). All the batches (PL_1–PL_7) had friability

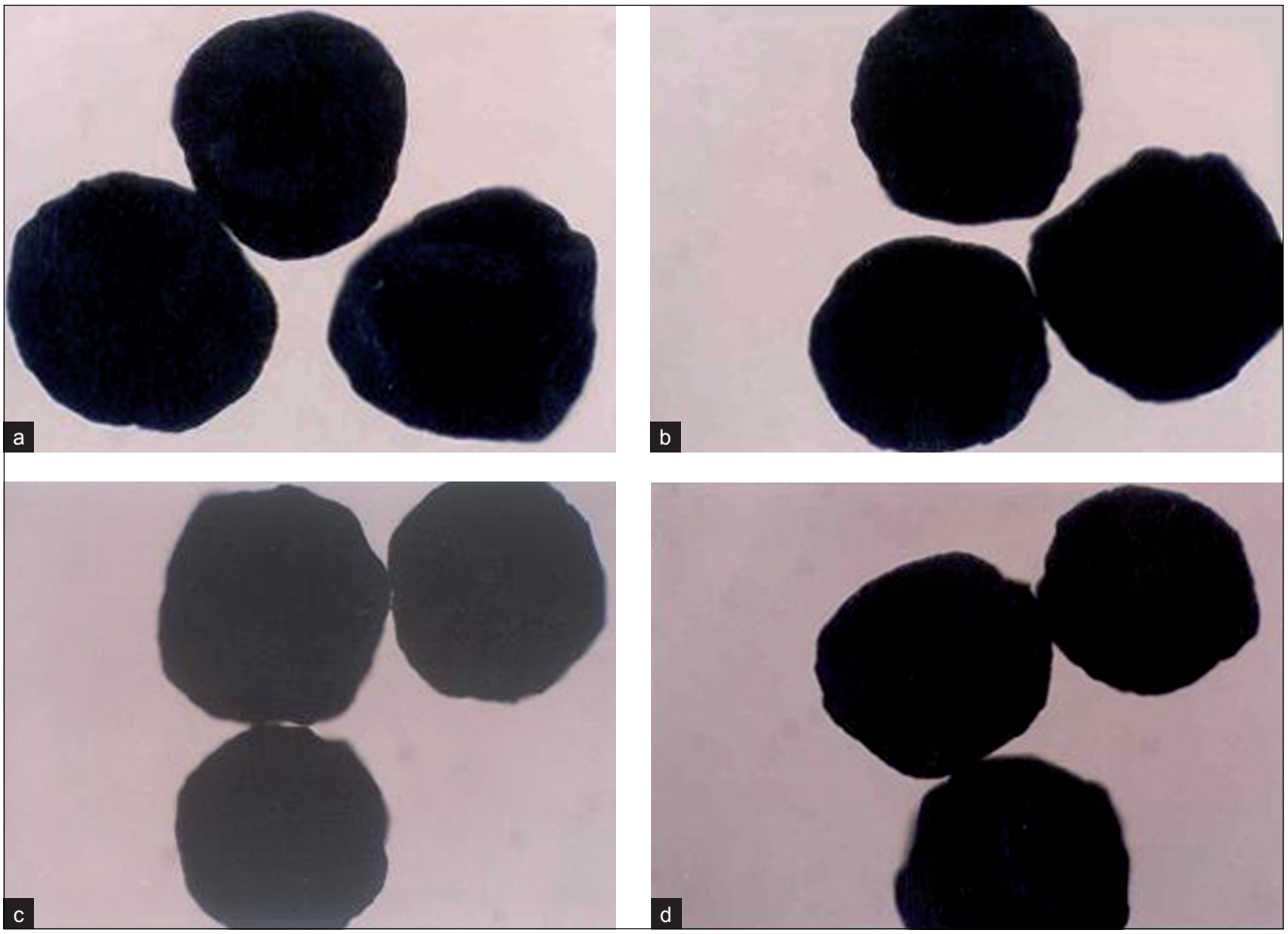

Figure 2: Photomicrographs of drug-loaded matrix pellets containing (a) MCC (RS_1), (b) MCC and 4% Eudragit®-RSPO (RS_2), (c) MCC and 12% Eudragit®-RSPO (RS_7) and (d) MCC, 8% Eudragit®-RSPO and 10% Eudragit® L-100 (PL_7)

values less than 0.5%. The content of CXB varied between 98.70 and 99.47% and moisture content varied between 0.2 and 2.2.

Considerations for targeting at a specific site

The batches (RS_1- RS_7) containing different concentrations of Eudragit®-RSPO were prepared and evaluated for their potential to retard drug release rate *in vitro* [Figure 3a]. Batch RS_1 showed 9.45±0.02% of drug release in acidic media and 41.6±0.008% of drug release in the first 5 h (upper GIT transit time) of the dissolution study. The total amount of drug released in 24 h was 100.8±0.001% [Figure 3a]. In the case of Batch RS_2 (4% of Eudragit®-RSPO), the amount of drug released in 5 h was reduced to 30.7±0.004% and the amount of drug released in acidic media was also reduced to 7.46±0.005%.

To further exercise more control over the amount of drug release in the upper part of GIT, batch RS_3 was formulated (Eudragit®-RSPO 6%). The amount of drug released during first 5 h was slightly reduced to 29.0% and correspondingly, the amount of drug released in 24 h was also decreased to 88.1±0.012%. However, in Batch RS_4 (Eudragit®-RSPO 8%), the amount of drug released during the first 5 h was found to be 24.4±0.0%. Also the total drug released during 24 h of dissolution studies was also reduced to 84.3±0.005%. By increasing the concentration of Eudragit®-RSPO to 9%, 10%, and 12% (RS_5, RS_6, and RS_7, respectively) retarded the drug release in initial hours. In the case of formulation RS_7 containing highest amount of Eudragit®-RSPO, it was observed that the drug release during the initial hours (5 h) of the dissolution study was suppressed to 16.28±0.006% (RS_7), and the amount of drug released in acidic media was also reduced to 4.16±0.012%. The total amount of drug could not be released in the colon during its transit time suggesting their unsuitability for colonic delivery of the drug. The slow release rate may be due to higher coating levels of the enteric coating polymer, because of the increased diffusion path length and tortuosity at higher coating levels.[16] Thus, the total amount of drug could not be released from the pellets. Among the formulations studied batch RS_4 showed lesser drug release in the conditions of upper GIT and at the same time 84.3±0.005% was released after 24 h of dissolution study suggesting its use for delivery of drug to the terminal parts of the GIT. Further modification was done to minimize the initial drug release.

It is desired that for successful colonic delivery, the formulation in the colon should be triggered by some stimuli to release the drug within the colon. In the current research, pH was used as a trigger to achieve colon-specific drug delivery. Batches using combination of Eudragit®-RSPO and Eudragit® L-100 dispersion (PL_1-PL_7) as a granulating binder were formulated and inclusion of Eudragit® L-100 was done in order to prevent initial drug release. From the results [Figure 3b], it is evident that more control on drug release was achieved during the first 5 h of the dissolution study.

In the batch PL_1, (2% Eudragit®-RSPO and 6% Eudragit® L-100), the amount of drug released in acidic media was found to be 6.7±0.004% and the amount of drug released during first 5 h was found to be 33.6±0.001% [Figure 3b]. It was seen that whole of the drug (99.9±0.132%) was released from the pellet formulation. In an attempt to decrease the drug release during the first 5 h of dissolution, the amount of drug released during upper GIT transit was reduced to 32.0±0.006%. In this formulation, the whole of the drug was released in 24 h. The concentration of Eudragit®-RSPO was increased to 6% (PL_3) in order to minimize the amount of drug released during first 5 h of the dissolution study. Desired results were not obtained after 24 h of dissolution, as the amount of drug released came out to be 84.9±0.030%. This could have been possible due to the increase in the concentration of Eudragit®-RSPO, a sustained release polymer which may have caused recession in total amount of drug released in 24 h. So, now the concentration of Eudragit®-RSPO was kept fixed to 6% (PL_4) and the amount of Eudragit® L-100 was increased to 8% to achieve successful colonic delivery. The amount of drug released in acidic media was reduced to 5.63±0.004% and the total amount of drug released during the first 5 h was 20.2±0.007%. About 78% of the drug was released during 24 h.

Further modification in the formulation was done by increasing the concentration of Eudragit®-RSPO to 8% and decreasing the concentration of Eudragit® L-100 to 4% (PL_5). The results were not very promising, as the amount of drug delivered during 24 h of the dissolution study was not complete. In further modifications, the amount of Eudragit®-RSPO was kept constant to 8% and the concentration of Eudragit® L-100 was increased to 6% (PL_6) and 10% (PL_7), respectively. The results were encouraging, as the amount of drug released in first 5 h of dissolution was decreased to 17.86±0.005 and 16.7±0.014% respectively for formulation PL_6 and PL_7 respectively, also the desired amount of drug could be released. The results showed that formulations PL_4 (6% Eudragit®-RSPO; 8% Eudragit® L-100), PL_6 (8% Eudragit®-RSPO; 6% Eudragit® L-100), and PL_7 (8% Eudragit®-RSPO; 10% Eudragit® L-100) were able to release maximum amount of the drug from the dosage form. Hence, it is inferred that these batches are suitable for delivering the CXB specifically to the colon. In another approach, the plain pellet-filled capsules were enteric coated to prevent drug release in upper

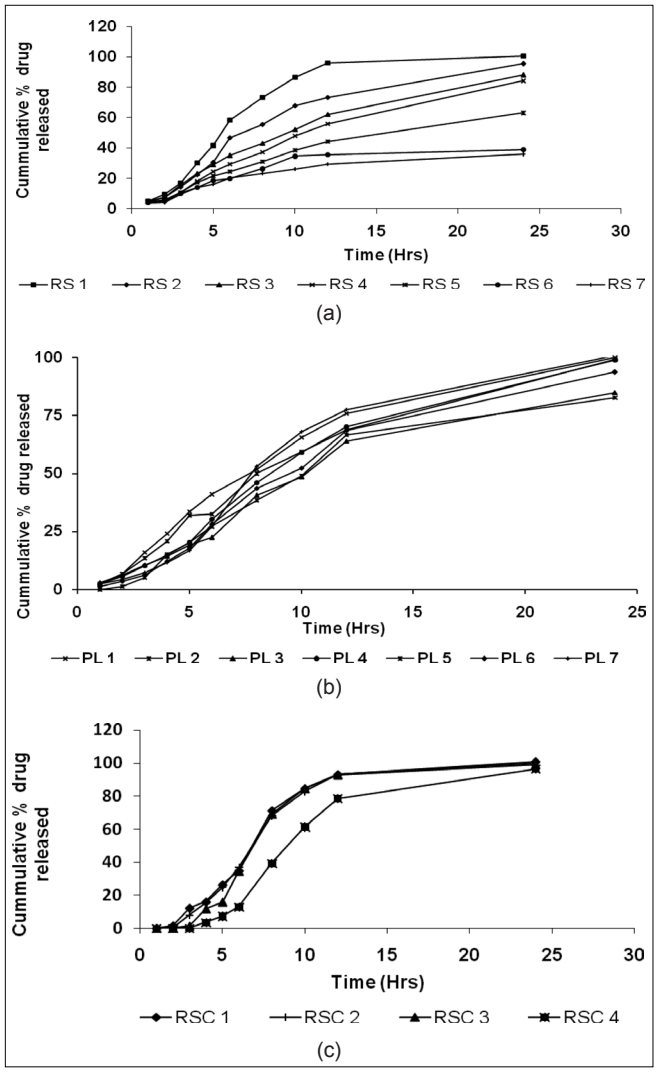

Figure 3: *In vitro*-release profile of pellets (a) Granulated with Eudragit®-RSPO, (b) Granulated with combination of Eudragit®- RSPO and Eudragit® L-100, (c) Encased in enteric coated capsules using Eudragit® S-100

G.I. segments. The spheronized matrix pellets were filled in hard gelatin capsules and enteric coated with Eudragit® S-100. In order to release an appropriate amount of drug at different intervals, batches were formulated by varying the thickness of enteric coating of capsules (RSC_1-RSC_4). The drug release from RSC_1 (coat wt. 5.56% w/w) was observed to be 26.3±0.041% during 5 h of dissolution. The requisite amount of drug was released at 24 h. On increasing the coat wt. to 12.5% (RSC_2), no drug released at pH 1.2 but at 5 h release was reduced to be 24.7±0.023% and 99.7±.005% at 24 h. To further decrease the drug release, the coat wt. was increased to 17.93% (RSC_3). No drug was released in 0.1N HCl and only 15.9±.004% was observed at 5 h and 99.1±.007% during 24 h. Furthermore, increasing the enteric coat to 26.17%, batch RSC_4 was formulated and no release was found in 0.1 N HCl. Only 7.26±.004% was observed at 5 h and more than 96% in 24 h [Figure 3c]. Hence, batch RSC_4 was found to be suitable for the colon delivery of drug at specific site.

MUPS-containing Eudragit®-RSPO at concentration (12%, RS_7,) exhibited highest diameter and span value of 780 μm and 1.55 and the projected area of pellets also increased. Higher span values indicate higher size distribution.[17] Polymethacrylates improved pellet roundness and have a negative effect on pellet roundness in higher amounts. Hence, with increasing the concentration of Eudragit®-RSPO or combination of Eudragit®-RSPO and Eudragit®-L leads to a decrease in circularity of the matrix pellets in all batches and an increase in rectang and elongation. The density (bulk and tapped) measurements of all batches did not differ significantly and lead to similar Carr's index and Hausner's ratio. Pellets produced by extrusion spheronization often exhibit very low friability. However, the inclusion of Eudragit®-RSPO led to minimal weight loss after the friability test in comparison to those pellets having no Eudragit®-RSPO. Eudragit®-RSPO, a pH–independent nature of the polymer showed a retardant effect on drug release, but could not achieved appreciable lowering of drug release during the first 5 h. At an optimal concentration, the combination of Eudragit®–RSPO Eudragit® L-100 in enteric coating showed all the attributes for successful colonic delivery. Further, the spheronized pellets which exhibited the desired amount of drug release in 24 h but could not retard the initial drug release which were filled in capsules and enteric coated with Eudragit® S-100 provided the desired release.

CONCLUSION

Eudragit®-RSPO showed a retardant effect on drug release. However, appreciable lowering of drug release during the first 5 h of dissolution could not be achieved due to the pH–independent nature of the polymer. Using a pH-dependent polymer, the combination of Eudragit®-RSPO and Eudragit® L-100 in various ratios, greater retardation in drug release on arrival in the simulated intestinal binder could be achieved. Spheronized matrix pellets which showed the desired amount of drug release in 24 h but could not retard the initial drug release were filled in capsules and enteric coated with Eudragit® S-100 for colon-targeting systems. Thus, MUPS prepared by the extrusion-spheronization technique using methacrylate polymers showed immense potential for colon-specific drug delivery of the drug as they release minimal drug till 5 h and releasing most of the drug at 24 h. Hence, MUPS-based system for delivery of CXB can be the potential targeted system for the chemoprevention of adenomatous polyps in patients with colorectal cancer.

ACKNOWLEDGEMENT

We greatly acknowledge the Panacea Biotech, Lalru, India, for providing the gift sample of drug CXB.

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Source of Support: Nil, **Conflict of Interest:** None declared.