Formulation and optimization of budesonide microspheres for site specific delivery by using 3^2 factorial design

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Abstract

A microparticulate system consisting of guar gum core coated with pH dependent polymer (HPMC AS MF) to deliver Budesonide specifically to terminal ileum and proximal colon has been reported. These microspheres are proposed to deliver the drug to ileo-cecal junction and proximal region of colon. Both guar gum microspheres and HPMC AS microspheres were prepared using Emulsion-solvent evaporation technique. Effect of formulation variables for double microencapsulation like coat: core ratio (4:1, 5:1, 6:1) and span 80 concentrations (2%, 3%, 4%) was studied using 3^2 factorial design. The obtained microspheres analyzed for particle size of microspheres, % encapsulation efficiency, % drug release after 2 h and % drug release after 5 h. In-vitro dissolution study of optimized formulations in presence of rat cecal content was carried out. The results of analysis of variance test for responses measured indicated that the test is significant.

Keywords: Budesonide, guar gum, HPMC AS MF, factorial design, microspheres, emulsion-solvent evaporation method

Introduction

Crohn's disease is a chronic inflammatory bowel disease of unknown origin primarily affecting the terminal ileum and proximal colon. Complications associated with Crohn's disease include deficiency of nutrients (like proteins and vitamins), arthritis, skin problems, and inflammation in the eyes or mouth (Baker 2001). In recent times, active Crohn's disease patients have failed to respond to treatment with aminosalicylate products (Castellanos et al. 2001). The National Cooperative Crohn's Disease Study (NCCDS) and the European Cooperative Crohn's Disease Study (ECCDS) trials have found that corticosteroids have demonstrated a statistically significant improvement and effectiveness for the treatment of the disease as compared to aminosalicylate (Feagan and Sandborn 2002).

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Budesonide is a second generation glucocorticoid used for symptomatic treatment of Crohn's disease and ulcerative colitis (Lewis 1999). Clinical trials of Budesonide have shown its effectiveness over other corticosteroid in the treatment of inflammatory bowel disease (Friend 2005). Budesonide exhibits high affinity to corticosteroid receptors with high ratio of topical to systemic anti-inflammatory activity (Lewis 1999, Friend 2005). As in Crohn's disease lesions are found in terminal ileum and proximal colon (Lewis 1999, Brunner et al. 2005, Krishnamchari et al. 2007), there is a need to fabricate a delivery system releasing the drug to ileum and throughout entire region of colon.

Several approaches have been used to target drug release to the colon (Van den Mooter and Kinget 1995, Lee and Mukharjee 2002). Out of these approaches, micro flora activated delivery systems are considered to be preferable and promising due to abrupt increase of bacteria population and associated enzymatic activities in ascending colon independent of GI transit time and pH (Lee and Mukharjee 2002, Krishnamchari et al. 2007). The present investigation is aimed to use inexpensive and naturally occurring guar gum to formulate Budesonide microspheres, further coated with pH dependent polymer (HPMC AS MF) to avoid the drug release in upper gastrointestinal tract and target maximum drug to lower gastrointestinal tract. Guar gum microspheres were coated with HPMC AS MF by using double microencapsulation. 3^2 full factorial design was used for optimization of double microencapsulation which is an efficient method indicating the relative significance of a number of variables and their interactions (Martin 1993, Lewis 1999, Rao et al. 2009).

Materials and Methods

Materials

Budesonide (BDS) was supplied as a gift sample by Arch Pharmalabs Ltd., India. Guar gum (GG) and HPMC AS MF were supplied by Lucid colloids Ltd. and Shin-Etsu Chemical, respectively. All other chemicals used in the study were of analytical grade obtained from the Research Lab.

Preparation and characterization of BDS loaded guar gum microspheres

BDS loaded guar gum microspheres were prepared by a classical emulsion solvent evaporation method (Sergio et al. 2005, Singh et al. 2008). Budesonide was dispersed in hydroalcoholic (water:methanol-10:3) solution of guar gum with continuous stirring. The gum dispersion was allowed to swell for 2 h and was emulsified in Light liquid paraffin previously mixed with 3 % v/v span 80 as emulsion stabilizer using mechanical stirrer at 2500 rpm. Temperature of the system was maintained at 30°C for initial 1 h and then was increased to 50°C. Stirring was continued until complete evaporation of solvent (3-4 h). Microspheres obtained were filtered and washed with 25 mL of n-hexane 3-4 times. The solid microspheres were vacuum dried for 24 h and then weighed.

BDS loaded Guar gum microspheres were optimized for different formulation variables like drug: polymer ratio and concentration of guar gum in internal phase. Prepared BDS-GG microspheres were evaluated for percentage yield, microsphere size, percentage encapsulation efficiency and percent cumulative drug release.

Double microencapsulation of BDS loaded Guar gum microspheres by HPMC AS MF

Budesonide loaded Guar gum microspheres were further microencapsulated by HPMC AS MF using emulsion-solvent evaporation technique (Sergio et al. 2005, Singh et al. 2008). Weighed amount of

HPMC AS MF was dissolved in internal phase solvent mixture, ETH: DCM (1:1). BDS-GG microspheres were weighed and dispersed to above mixture. This dispersion was added in 100 mL light liquid paraffin containing span 80 as emulsion stabilizer. Stirring was continued for 2-3 h at 30°C and 1000 rpm using mechanical stirrer until volatile solvent evaporated completely. Microspheres obtained were filtered using Whatman filter paper no. 41 and washed 3-4 times by 25 mL n-hexane each time. Microspheres collected were air dried for 24 h.

Optimization of formulation variables for double microencapsulation process was done using a 3^2 full factorial design. For this design independent variables (X) were span 80 (stabilizer) concentration (X1) and Coat: core ratio (X2) whereas dependent variables (Y) were, microspheres size (Y1), % encapsulation efficiency (Y2), % drug release after 2 h (Y3) and % drug release after 5 h (Y4).

Evaluation of microspheres

Encapsulation efficiency of microspheres (Thies 1996)

Accurately weighed microspheres were transferred to 50 mL volumetric flask containing solvent mixture of 7.4 Phosphate buffer: methanol (7: 3). The samples were sonicated for 10 min and allowed to swell for 24 h in the orbital shaker. These solutions were filtered using the Whatman filter paper no. 41. The absorbance of the solution was measured at 247 nm using UV spectrophotometer. The study was repeated in triplicate.

In vitro drug release study

In vitro drug release studies were carried out using the rotating basket method (Apparatus I USP XXIII) with 100 rpm speed at 37 ± 0.5°C. The weighed amount of microspheres were wrapped in Cellophane membrane and kept in baskets. The drug release studies were carried in 900 mL of 0.1 N HCl as dissolution media for first 2 h (as the average gastric transit time is ∼ 2-3 h), then the dissolution medium was replaced with pH 6.8 phosphate buffer and tested for drug release for next 3h (as average small intestinal transit time was about 3-4 h) and finally dissolution was continued in pH 7.4 phosphate buffer. Samples (10 mL) were withdrawn at predetermined time interval (1 h) from each dissolution flask, filtered using Whatman filter paper, samples were analyzed for budesonide at 247.5 nm for 0.1N HCl, at 247 nm for 6.8 pH Phosphate and pH 7.4 Phosphate buffer using a UV visible double beam spectrophotometer (Model-UV1701, Shimadzu, Japan).

The ability of the most promising formulation of guar gum microspheres to release Budesonide in the physiological environment of the colon was assessed by carrying out release studies in dissolution medium containing rat cecal content (Haeberlin and Friend 1992). Wistar rats weighing 150-200 g and maintained on a normal diet were used. The rats were pretreated for 7 days with 1 mL of 2% w/v of aqueous dispersion of guar gum for enzymatic induction which provide best condition for assessing the susceptibility of guar gum to colonic bacterial degradation. Thirty minutes before the commencement of drug release studies rats were sacrificed, the abdomen was opened; the cecum was traced, ligated at the both ends, dissected & immediately transferred into buffer solution under anaerobic environment. The cecum bag was opened, its contents were individually weighed, pooled & suspended in the buffer solution continuously bubbled with CO_2 the suspension was filtered through glass wool and sonicated for 20 min at 4°C to disrupt the bacterial cells. This was finally added to the dissolution media to give a final cecal dilution of 4 % w/v. All the above procedure was carried out under CO_2 in order to maintain anaerobic conditions.

The drug release studies were carried out in USP XXIII dissolution test apparatus I at 100 rpm and 37°C with slight modification. A beaker (capacity 150 mL, internal diameter 55 mm) containing 100 mL of dissolution medium with rat cecal content (4% w/v) was immersed in the water contained in 900 mL

vessel, which was, in turn, immersed in the water bath of the apparatus. After completing the dissolution studies in 0.1 N HCl for 2 h and pH 6.8 phosphate buffers for 3 h, microspheres were placed in the baskets of the apparatus and immersed in the rat cecal content medium and dissolution was continued. Anaerobic conditions were maintained by bubbling CO_2 in dissolution media. 2 mL samples were taken at different time intervals and replaced with 2ml of fresh phosphate buffer bubbled with CO_2. The phosphate buffer solutions of pH 7.4 containing a similar concentration of rat cecal content and placebo microspheres served as a blank. The samples were filtered using Whatman filter paper and were analyzed for Budesonide at 247 nm.

Validation of optimization model

To validate the chosen experimental design and polynomial equations, three optimum formulations were selected by intensive search, performed over the entire experimental domain. The criterion for selection of optimum formulation was primarily based on the values of % drug entrapment efficiency, % drug release after 2 h and 5 h and particle size of microspheres. The resultant experimental data of response properties were subsequently compared with predicted values.

Particle size analysis

The size of microspheres was measured using an optical microscope and the mean size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer (Van den Mooter and Kinget 1995).

Morphology of microspheres

The samples for SEM were prepared by lightly sprinkling microspheres on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Afterwards, the stubs containing the coated samples were placed in the scanning electron microscope (JSM-6360A, JEOL, Japan) chamber. The samples were then randomly scanned and photomicrographs were taken.

Differential scanning calorimetry

Thermograms of samples were obtained by differential scanning calorimetry (Shimadzu, DSC 60). Samples (2 mg) were accurately weighed into aluminum pans and then sealed with aluminum lids. The thermograms of the samples were obtained at a scanning rate of 5°C/min over temperature range of 0 to 300°C.

X-Ray diffraction studies

X-ray diffraction study was performed in Philips PW3710 X- ray diffractometer using Cu K 2α rays with a voltage of 40 kV and a current of 25 mA. Samples were scanned for 2θ from 10 to 70°. Diffraction pattern for BDS, GG, HPMC AS MF, physical mixtures and microspheres were obtained.

Results and Discussion

BDS-GG microspheres were prepared using emulsion-solvent evaporation technique and effect of different formulation variables on formulation of BDSGG microspheres was studied. Formulation variables studied were guar gum (GG) concentration (2% to 4% w/v), and polymer: drug ratio (1:1 to 3:1). Table 1 gives % yield, mean microspheres size and encapsulation efficiency. It was observed that GG concentration and GG: BDS ratio significantly affects the sphericity, mean microsphere size, encapsulation efficiency as well as drug release from the microspheres. Encapsulation efficiency increased from 59.36 % to 74.02% with increase in GG:

BDS ratio from 1:1 to 2:1, since with higher GG: BDS ratio, enough quantity of polymer was available to encapsulate the drug. But with further increase in GG: BDS ratio to 3: 1, there was no significant change in encapsulation efficiency. Increase in GG: BDS ratio resulted in increased diameter of microspheres from 109.85 μm to 189.8 μm. As the concentration of GG in internal phase was increased from 2 to 3%, microsphere size was significantly increased from 106.81 μm to 141.81 μm with uniform size distribution whereas further increase in GG concentration to 4 %, increased the particle size but particle size distribution was uneven with excess of placebo microspheres. Encapsulation efficiency of microspheres was increased from 58.83 % to 74.02 % as the GG concentration was increased from 2 %w/v to 3 %w/v, due to increase in viscosity of internal phase. Further increase in GG concentration to 4 %w/v, did not affect the encapsulation efficiency.

Table 1. Compositions and characterization of various BDS-GG loaded HPMC AS MF microsphere formulations

Sr. No.	Batch Code	Code Value*		Microsphere Size (μm)	Encapsulation Efficiency (% w/w)	Cumulative % Drug Release	
		X_1 (Span 80)	X_2 (Coat: core)			After 2h	After 5h
1	FGH 1	-1	-1	191.35	75.07±2.43	11.64	36.33
2	FGH 2	-1	0	215.79	80.47±2.1	9.24	32.42
3	FGH 3	-1	1	240.84	84.95±1.87	6.89	28.58
4	FGH 4	0	-1	165.69	81.85±1.85	8.01	31.04
5	FGH 5	0	0	209.51	85.98±1.02	6.18	26.46
6	FGH 6	0	1	236.89	90.13±1.4	4.36	22.31
7	FGH 7	1	-1	174.69	84.92±1.64	7.90	28.62
8	FGH 8	1	0	191.58	88.86±1.7	5.98	23.98
9	FGH 9	1	1	221.81	91.15±1.2	4.08	18.75

Span 80:- (-1) level = 2% v/v, (0) level = 3% v/v, (1) level = 4% v/v. Coat: core ratio: - (-1) level = 4: 1. (0) level = 5:1, (1) level = 6:1.

Drug release from BDS loaded GG microspheres

In vitro drug release from different BDSGG microspheres is shown in Fig. 1. All BDS-GG microspheres released 40-50 % of BDS within 2 h of dissolution. This might be because of release of drug present on surface of microspheres and lag time required for the hydration of guar gum. After hydration and swelling of guar gum, further release of drug slowed down and in 8 h only 65-75% of drug was released. With increase in guar gum concentration and GG: BDS ratio, there was decrease in drug release. This is because increase in concentration of guar gum and GG: BDS ratio increased viscosity of swollen matrix after hydration, resulting into sustained release of drug through microspheres. For optimized formulation (FG 2) guar gum concentration and GG: BDS ratio were 3% w/w and 2:1 respectively as shown in Table 1. From observed results, it was found that GG was unable to delay release of drug in the physiological acidic environment of the stomach and small intestine due to initial lag time required for hydration of guar gum. But once guar gum gets hydrated, it can efficiently retard the drug release from microspheres. So, there is need to coat the optimized batches of drug loaded guar gum microspheres by an enteric polymer which will prevent initial release of drug in upper gastrointestinal tract.
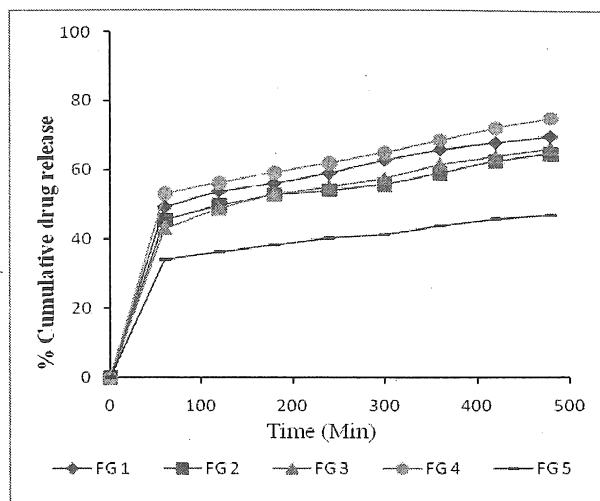
Figure 1. *In vitro* drug release from BDSGG microspheres

Optimization of formulation variables for double microencapsulation of BDS-GG microspheres by using 3^2 Full factorial designs

In the present study, for simplicity it was decided to perform a 2 variable study at their three experimental levels to achieve the set objectives efficiently. For optimization of double microencapsulation process a 32 full factorial design was applied. So, total nine batches were prepared by microencapsulating optimized budesonide loaded guar gum microsphere batch with HPMC AS MF and evaluated for the effects as shown in Table 1. Mathematical relationship generated using multiple linear regression analysis (MLRA) for the studied dependent responces is shown in Table 2. The polynomial equations can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative). The value of correlation coefficient for the dependent variables indicated good fit. Significance test for regression coefficient was carried out by applying student t- test.

**Table 2.** Regression analysis data for measured responses

Coefficients	Microsphere Size	% EE	Drug release after 2 h.		Drug release after 5 h.
	FM	FM	FM	RM	FM
b_0	207.57	85.90	6.18	6.18	27.06
b_1	-9.98	4.18	-1.64	-1.64	-3.50
b_2	24.63	2.62	-2.04	-2.04	-5.23
b_{12}	-	-0.75	0.23	-	-
b_{11}	-	-1.19	1.44	1.44	-
b_{22}	-	-1.87	0.012	-	-
R^2	0.9815	0.9955	0.9917		0.9620
Significance	0.0001	0.0010	0.0006		0.0001
F- value	159.05	132.8	199.45		76.01

The significance value of coefficient b12 and b22 for response 'drug release after 2 h' were found to be 0.1149 and 0.9432 respectively and hence they were removed from regression equation to generate the reduced model equation. All other coefficient b1, b2 and b11 showed significant values less than 0.1.

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For the particle size of microsphere, encapsulation efficiency, drug release after 2 and 5 h calculated F-values were 159.05, 132.8, 199.45 and 76.01 respectively as shown in Table 2.

Hence it can be concluded that the variables selected contribute significantly in the regression of measured responses Y1, Y2, Y3 and Y4.

Response surface plot and contour plot generated using equations are presented in Fig. 2 and 3 to observe the effects on the responses studied such as particle size of microsphere, encapsulation efficiency, drug release after 2 h and drug release after 5 h for BDSGG loaded HPMC AS MF microspheres by changing independent variables.

(a)   (b)
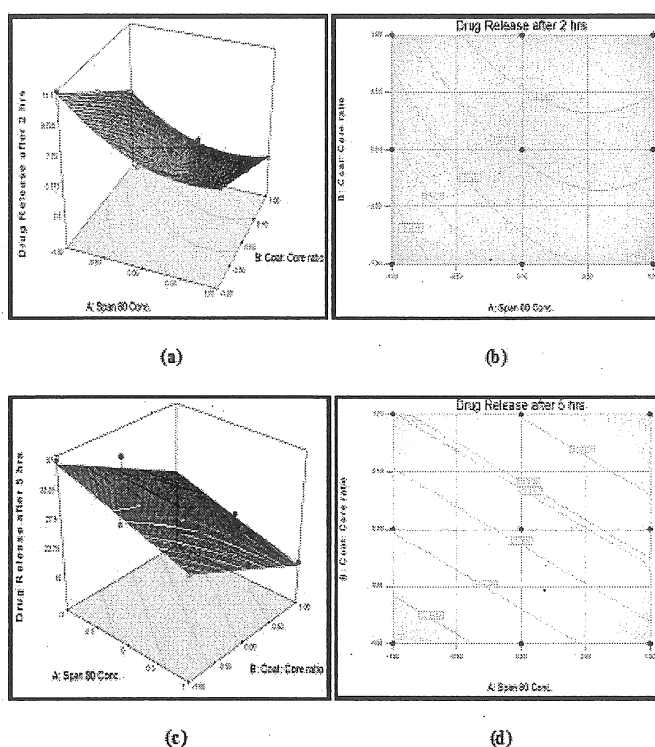
(c)   (d)
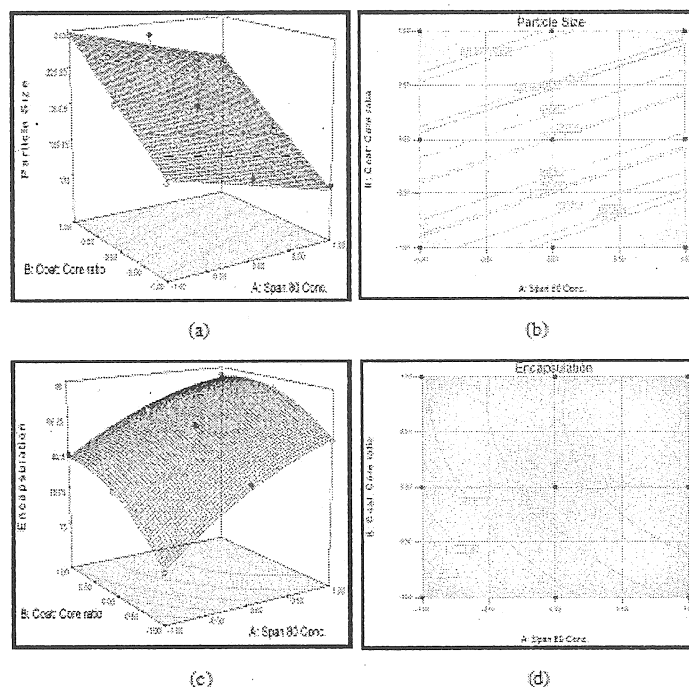
Figure 2. Effect of coat:core ratio and span 80 concentrations on the particle Size of BDSGG loaded HPMC AS MF microspheres a) response surface plot and b) contour plot. Effect of coat: core ratio and span 80 concentrations on the encapsulation efficiency c) response surface plot and d) contour plot.

From response surface and contour plot as shown in Fig 2a and 2b, it can be seen that negative coefficient of (X1) indicated decrease in microspheres size (Y1) and positive coefficient of X2 (coat: core ratio) indicated increase in response of microspheres size (Y1) with increase in coat: core ratio.

At 3%, middle level (0) of span 80 concentration, when coat: core ratio was increased from 4:1 to 6:1 microsphere size increased from 165.69 to 236.89 μm, this is because at any concentration of span 80 with increase in coat: core ratio excess of polymer was available to coat microspheres increasing coat thickness resulting in increased size of microspheres. The response surface and contour plots showed positive effect on encapsulation efficiency with increasing coat: core ratio and span 80 conc as shown as Fig 2c and 2d, respectively. At lower level (-1) i.e. 2% of span 80, encapsulation efficiency increased from 75.07% to 84.95%, with increase in coat: core ratio (4: 1 to 6: 1). This is because at lower and middle level of stabilizer, increase in coat: core ratio

provided sufficient amount of polymer to entrap maximum guar gum microspheres. At higher level (1) of span 80 there was not much significant effect on encapsulation efficiency by increase in coat: core ratio since there was formation of placebo microspheres resulting in negligible change in encapsulation efficiency. The response surface and contour plots as shown in Fig. 3a and 3b respectively showed decreasing effect on drug release after 2 h with increasing coat: core ratio and span 80 conc. This is because of availability of sufficient polymer to coat microspheres evenly and at level (0) of stabilizer, emulsion formed was stable which leads to even polymer coat, thus decreasing drug release. When both variables were at high level, their interactive effect were not significant hence eliminated in the reduced equation. Response surface plot and contour plot, Fig. 3c and 3d respectively, showed a negative effect on drug release after 5 h (Y4) with increasing P: D ratio and span 80 conc. At all three levels of span 80 concentration (X1), when coat:core ratio was increased from lower level (-1) to higher level (1), there was linear decrease in drug release after 5 h. The interactive effect of both variables was not found to be significant.

(a)   (b)

(c)   (d)

Figure 3: Effect of coat: core ratio and span 80 concentrations on the drug release after 2 h of BDSGG loaded HPMC AS MF microspheres a) response surface plot and b) contour plot. Effect of coat: core ratio and span 80 concentrations on the drug release after 5 h of c) response surface plot and d) contour plot.

Validation of Optimum BDSGG loaded HPMC AS MF microspheres

From the polynomial equations generated for each responses using Design Expert Software (7.1.4), intensive grid and integrated search was performed over the experimental domain and three optimum formulations were selected (FGH 10-12) as shown in Table 3. The composition of the checkpoints, the predicted and experimental values of all the response variables

(microspheres size, encapsulation efficiency and percentage cumulative drug release after 2h and 5 h) and the percentage error in prognosis.

**Table 3.** Comparison of experimental results with predicted responses of Microsphere formulations

Batch Code	Composition		Response	Predicted Value	Experimental Value	Percentage Error
	X_1 (Span 80)	X_2 (coat: core)				
FGH 10	4.1 % v/v	5.06: 1	Microsphere size (µm)	210.21	215.89	1.091
			Rel $_{2h}$ (%)	5.82	5.91	0.3122
			Rel $_{5h}$ (%)	26.18	26.57	0.3122
			EE (%)	86.54	87.02	0.1414
FGH 11	4.14 % v/v	5.12: 1	Microsphere size (µm)	210.23	217.98	1.3919
			Rel $_{2h}$ (%)	5.733	5.82	0.4663
			Rel $_{5h}$ (%)	25.93	26.13	0.2236
			EE (%)	86.73	87.23	0.3535
FGH 12	4.12 % v/v	5.14: 1	Microsphere size (µm)	220.29	214.78	-1.1736
			Rel $_{2h}$ (%)	6.94	7.01	0.1322
			Rel $_{5h}$ (%)	27.15	28.84	0.6519
			EE (%)	89.75	87.31	-0.7810
Mean (± S.E.M.) of Percentage Error						

The linear correlation plots drawn between the predicted and observed responses demonstrated higher values of R2 (ranging between 0.997 and 1) and indicating excellent fitting of model (P<0.001). Upon comparison of the observed responses with that of the anticipated responses, the percentage error varied between – 1.1736 and 1.3919. Thus, the low magnitudes of error as well as the significant values of R2 in the current study indicated a high prognostic ability of microspheres formulations of BDS using RSM optimization.

In vitro release studies with and without rat cecal content

Fig. 4 shows percent cumulative drug release of optimized formulations of BDS-GG loaded HPMC AS MF microspheres (FGH 10-12). The criteria for selection of optimum formulation was primarily based upon the dependent responses (encapsulation efficiency, drug rel. 2h, drug rel. 5h and microspheres size) of BDSGG loaded HPMC AS MF microspheres. It was observed that only 6-8% of drug released from optimized batches (FGH 10-12) of BDSGG loaded HPMC AS MF microspheres after 2 h of dissolution. After dissolution of 5 h (intestinal environment i.e. pH 6.8 PBS) 22-30% drug release was observed, whereas after 8 h of dissolution drug release found to be 55-60 % because HPMC AS MF coat gets dissolved and hydration and swelling of guar gum resulted into retardation of drug release from microspheres.

The ability of drug release from microspheres containing natural polymer by enzymatic action of colonic bacteria was assessed for optimized batch of BDSGG loaded HPMC AS MF microsphere (FGH 10-12) by performing drug release studies in medium containing rat caceal content. From obtained release, it was observed that After 5 h, when rat cecal content was added to dissolution medium the release was increased suddenly due to degradation of guar gum by caceal bacteria. Almost 100% drug was released from the optimized BDSGG-HPMC AS MF microspheres within 6 to 7 h, as the guar gum was degraded by the enzymes secreted by colonic bacteria as shown in Fig. 4.
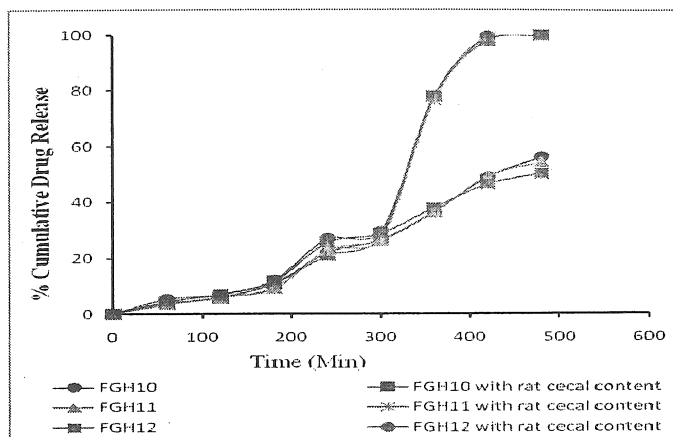
Figure 4. *In vitro* dissolution study of optimized formulation of BDSGG loaded HPMC AS MF microspheres without and with rat cecal content of optimized formulation.

Morphology of microspheres

Scanning electron microscopy of the BDSGG microspheres revealed a spherical structure with a slight rough surface morphology shown in Fig. 5a and 5b and exhibited a range of sizes within batch. Fig 5c shows encapsulation of two or more BDSGG microspheres in single HPMC AS MF microsphere, smooth surface of the microspheres.
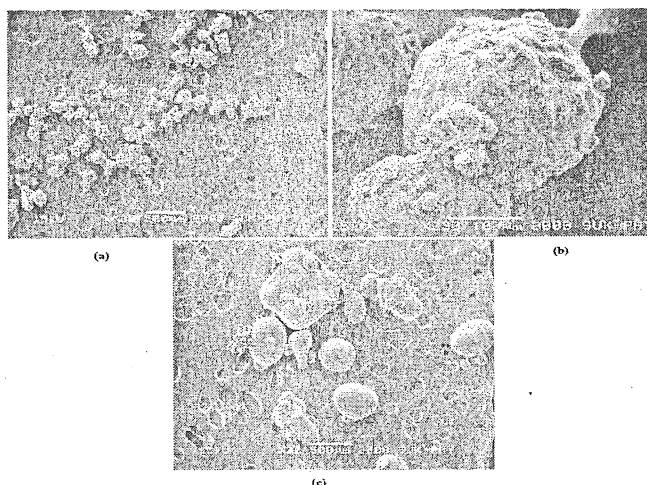

Figure 5. Scanning electron microscopy (a) and (b) of BDS loaded GG microspheres and (c) BDSGG loaded HPMC AS MF microspheres

Differential scanning calorimetry

The DSC study of the microspheres indicated endothermic peak at 251-252°C for Budesonide as shown in Fig. 6a. There was no significant change in the peak position of Budesonide in physical mixture of drug with polymer but slight change in peak intensity of observed as shown in Fig. 6d. The change in peak intensity of Budesonide in BDSGG loaded HPMC AS MF microspheres indicated change in its crystalline nature Fig. 6e. During the process of microencapsulation internal solvent was ETH: DCM in which drug might have solubilized and

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might have reprecipitated changing its crystallinity due to fast evaporation of solvent during the process.
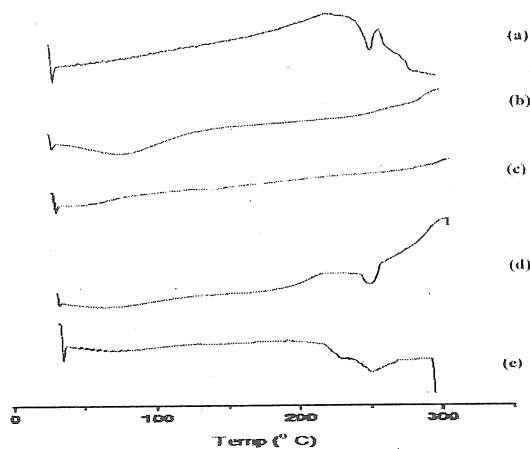
Figure 6. DSC thermographs of (a) Budesonide, (b) guar gum, (c) HPMC AS MF, (d) Physical mixture of Budesonide, guar gum and HPMC AS MF and (e) BDSGG loaded HPMC AS MF microspheres

X-Ray diffraction study

X-ray diffraction pattern of Budesonide, physical mixture of Budesonide, guar gum and HPMC AS MF and BDSGG-HPMC AS MF microspheres is shown in Fig 7. Microspheres did not contain any peaks associated with crystalline nature of BDS Fig. 7e, suggesting that drug might have changed into amorphous state during microencapsulation process due to solubilisation in internal solvent and early reprecipitation because of highly volatile solvent.
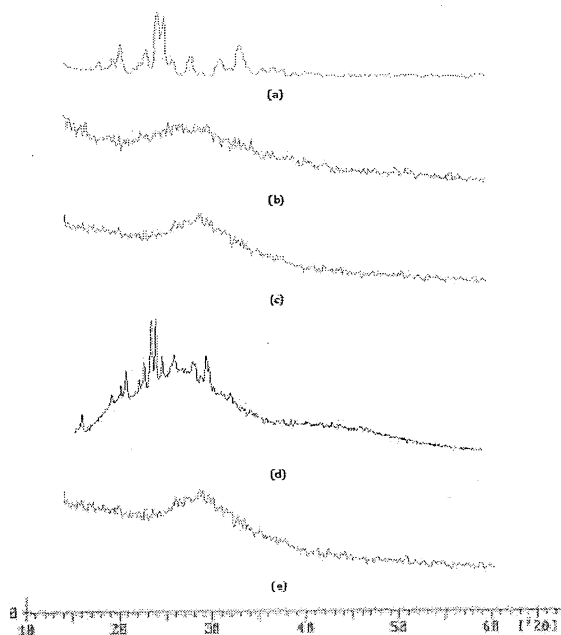
Figure 7. X-ray diffraction pattern of (a) budesonide, (b) guar gum, (c) HPMC AS MF, (d) physical mixture of budesonide, guar gum and HPMC AS MF and (e) BDSGG loaded HPMC AS MF microspheres.

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Conclusion

In this work, a dosage form intended for specific drug delivery along the ileo-cecal junction and proximal colonic region is described, the system consist of microflora activated system (GG microspheres) which was further encapsulated by pH sensitive polymer (HPMC AS MF microspheres). The results of 3^2 factorial design for optimization of double microencapsulation of BDSGG loaded HPMC AS MF microspheres revealed that span 80 concentration (X1) and coat: core ratio (X2) significantly affected responses such as particle size of microspheres, encapsulation efficiency and drug release after 2 and 5 h. Based on polynomial equations, grid and integrated search were performed and model was validated. Optimized formulation exhibited particle size in the range of 210-220 μm, 86-89% encapsulation efficiency 6-8% drug release after 2 h and 25-28% drug release after 5 h. In vitro dissolution with rat cecal content of optimized formulation showed 100% drug release after 6-7 h of dissolution. So, it can be concluded that optimum formulations can release maximum drug at ileo-cecal junction and in proximal part of colon to treat Crohn's disease and UC.

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