Original Article

Development of Budesonide Oral Colon Specific Drug Delivery System using Interpolymer Complexation Method

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ABSTRACT

Background: Oral bioavailability of Budesonide is 10% due to its extensive first pass metabolism, its high volume of distribution and 85-90% of protein binding. Protection of drug release in stomach and targeting drug to colon which is an absorption site of drug is an attempt to improve therapeutic efficacy. The objective of this study was to develop interpolymer complex microspheres of Budesonide for oral colon specific drug delivery. **Methods:** Emulsion solvent evaporation method was used in the preparation of microspheres. Microspheres prepared at different polymer ratio and surfactant concentration were analysed for its mean particle size, surface morphology, flow property, drug release, % encapsulation efficiency. **Results:** Microspheres prepared with 3:5 polymer ratios F4 was optimized with respect to its % EE, *in vitro* drug release and percentage yield. Drug release from formulated tablets containing microspheres of 3:5 polymer ratios showed an extended release up to 12 h in pH buffer 7.4. Interpolymer complexation was confirmed by FT-IR studies, compatibility of drug with excipients by DSC indicated no significant changes with drug. SEM studies revealed formation of round microspheres with pervious and uneven surface. *In vitro* release data from microspheres was analysed by kinetic model fitting for mechanism of drug release. Microspheres showed 5-10% of drug release in pH 1.2 which was further prevented by formulating coated tablets of microspheres using cellulose acetate phthalate. **Conclusion:** Targeted colon specific drug delivery of Budenoside with extended release up to 12 h was successfully achieved by formulation of tablets containing microspheres prepared by interpolymer complexation technique.

Key words: Budesonide, Colon Specific Delivery, Interpolymer Complexation, Microspheres, Cellulose Acetate phthalate.

INTRODUCTION

Targeted drug delivery is an exclusive drug delivery system where drug is delivered specifically to the site of absorption or where action is desired and not surrounding tissues or cells. This method of targeting helps in delivery of medication at high concentration to target site which helps in improving efficacy and reducing side effects. Oral targeted delivery systems are best suitable for drugs having instability, low solubility and short half-life, a large volume of distribution, poor absorption, low specificity and narrow therapeutic index. Targeting drug to absorption site provides maximum therapeutic activity thereby reducing dose of drug which reduces toxicity to potent drugs and minimizes adverse effects.[1-5] Colon targeted drug delivery systems are used for the therapy of local colonic diseases like crohn's disease and ulcerative colitis. The different approaches include prodrug, pH and time dependent systems, microbial activated system, timed release system, osmotically controlled drug delivery system and pressure dependent release system.[6,7]

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Budesonide belongs to BCS class II, 2nd generation anti-inflammatory glucocorticoid used in the treatment of inflammatory bowel disease having biological half-life of 2.0-3.6 h excreted as its metabolites from the urine. Oral bioavailability of Budesonide is 10% due to its considerable first pass metabolism, high volume of distribution, 85-90% of protein binding. It is a suitable candidate of choice for colon drug delivery since it is well absorbed in the colon.[8]

Interpolymer complex microspheres is an approach for colon targeting which uses two polymers to form complex, the use of complex results in the change of physico-chemical properties of polymer which restrain the drug release in the stomach and carry drug to the colon were degradation of polymer by colonic enzymes will result in drug release at target site.[9-11]

This study is an attempt to develop oral colon targeted drug delivery system of Budesonide by interpolymer complexation using Emulsion solvent evaporation method.

MATERIALS AND METHODS

Materials

Budesonide was obtained as a gift sample from Cipla Pvt. Ltd. Goa. Chitosan (medium molecular weight) and Cellulose acetate phthalate was procured from Yarrow Chemical Products, Mumbai, India. Light liquid paraffin procured from Loba Chemie Pvt. Ltd. Mumbai, India. Span 80 was procured from Hi-Media Laboratories Pvt. Ltd., Mumbai, India. Acetone and n-Hexane was procured from Molychem, Mumbai, India.

Preparation of microspheres using emulsion solvent evaporation method

Weighed quantity of chitosan was dissolved in 25 ml of 5% acetic acid solution and kept on magnetic stirrer to form homogenous solution. The resulting mixture was then added to 100 ml of light liquid paraffin containing varying concentration of surfactant (Span80) with continuous stirring using propeller speed of 600 rpm for emulsification to form w/o emulsion.

In another beaker, required quantity of cellulose acetate phthalate was dissolved in 25ml of acetone: water (97:3) and placed on magnetic stirrer to form polymer solution. Weighed quantity of Budesonide was added to this polymer solution and mixed rigorously. This solution was transferred drop wise to the w/o emulsion formed in above step and stirred continuously with the help of propeller at 2000 rpm for 3 h till acetone evaporated to form microspheres. The emulsion was allowed to settle for 2-3 h to separate the oil phase which was then decanted, drug loaded microspheres were washed repeatedly with n-Hexane and dried at room temperature to get free flowing microspheres.[12,13] The Coded factors with their levels for composition of polymer ratio and surfactant concentration is shown in Table 1.

Experimental design

Experimental design using Design-Expert[12] was used to check the effect of independent variables i.e. Polymer ratio (CS: CAP) and surfactant concentration on dependent variables i.e. %CDR, %EE and mean particle size of microspheres. A 3^2 full factorial design was used to prepare 9 formulations of microspheres. In this model two variables were evaluated individually at three levels. The coded values for higher, intermediate and lower were taken as +1, 0 and -1 respectively. The coded and actual values of design are given in Table 2.

Evaluation of Microspheres

Size Distribution Analysis

Average size of microspheres was determined using compound microscope at 10X resolution power lens. A small quantity of microspheres were suspended in water and spread on glass slide and average particle size for 100 microspheres was measured for each batch in triplicate.[14]

Table 1: Coded factors with their levels.

Factors	Symbol	Low	Intermediate	High
Polymer Ratio (CS:CAP)	X_1	-1	0	1
Surfactant Concentration (span 80)	X_2	-1	0	1

*+1= High,0=Intermediate and -1= Low concentratio

Table 2: Formulation of microspheres by 3^2 factorial design using design expert®12 software.

Formulation code	Coded levels of variables		Actual levels of variables		Drug (mg)
	X_1	X_2	X_1	X_2	
F1	-1	-1	3:5	1	200
F2	0	-1	4:5	1	200
F3	1	-1	5:5	1	200
F4	-1	0	3:5	1.5	200
F5	0	0	4:5	1.5	200
F6	1	0	5:5	1.5	200
F7	-1	1	3:5	2	200
F8	0	1	4:5	2	200
F9	1	1	5:5	2	200

Where, X_1= Polymer ratio and X_2= Surfactant concentration.

Percentage Yield

To determine the efficiency of method for the preparation of microspheres the percentage yield was calculated by noting the weight of microspheres obtained from each batch with respect to total weight of material.[15] Percent yield was determined using the formula;

$$\% \text{ Yield} = \frac{\text{Weight of microsphere obtained}}{\text{Sum of weight of polymer and drug}} \text{ X } 100$$

Scanning electron microscopic (SEM) studies

Drug loaded microspheres were subjected for SEM studies using JEOL JSM-6360 to analyse the surface morphology of microspheres.

Entrapment Efficiency

Drug entrapment in the microspheres was determined in terms of percentage drug entrapment for each batch of formulation using the formula;[11]

$$\% \text{ EE} = \frac{\text{Practical drug content of microsphere}}{\text{Total amount of drug incorporated}} \text{ X } 100$$

100 mg of prepared microspheres were triturated in mortar and pestle then transferred to 100 ml of 7.4 pH phosphate buffer placed on magnetic stirrer for 1h to extract the drug, it was then filtered and drug content determined.

Differential scanning colorimetric (DSC) studies

DSC was performed for pure drug and optimized drug loaded microspheres to check the interaction between drug and polymers used (Shimadzu, Japan). Sample was placed in aluminium pans and the lids were crimped using a Shimadzu crimper. Thermal behaviour of the samples was explored under nitrogen purge at scanning rate of 10°C/min and in the temperature range of 30–320°C. Empty aluminium pans were used as reference.[16,17]

Fourier transform infrared spectrum

FT-IR (IR affinity-1Shimadzu) analysis was done to check the chemical interaction between drug and polymers. IR spectra was obtained for pure drug, chitosan, cellulose acetate phthalate, drug loaded microspheres and tableted microsphere. Sample was mixed thoroughly with 100 mg potassium bromide, IR was performed under vacuum at a pressure of about 12,000 psi for 3 m. base line correction was made using dried potassium bromide, the IR spectrum was obtained by scanning from 4000 cm^{-1} to 625 cm^{-1}.

Swelling Index (SI)

Weighed quantity of microspheres were placed in buffer solution of pH 7.4 for 24 h to allow swelling. The microspheres were filtered and weighed. Further, the microspheres were then dried in hot air oven at 40°C until there was no alteration in dried mass of sample.[18] The swelling index was calculated using following equation;

$$\% \text{ Swelling index} = \frac{\text{Mass of microshperes after sweeling-mass of dry microspheres}}{\text{Sum of dry microspheres}} \text{ x } 100$$

Flow property for microspheres

The flow property for microspheres was studied by determining Bulk density, Tapped density, Angle of repose, Carr's Index and Hausner's Ratio.[18] Bulk density and tapped density was determined using graduated cylinder; angle of repose using fixed funnel method.

In-vitro dissolution studies of microsphere

In vitro dissolution study was performed using USP type II (Paddle type) apparatus (LABINDIA® DS 8000) set at 50 rpm and 37±0.5°C. Weight of microspheres equivalent to 3 mg of Budesonide was taken for study. The drug release from microspheres was checked by performing dissolution study for 2 h in 0.1N HCl and10 h in pH 7.4 PBS. Sampling was done at predetermined time and sink condition was maintained. Aliquot was suitably diluted and absorbance for samples measured using Shimazdu UV 1900 Spectrophotometer at 247 nm.[19]

Model fitting analysis for *in vitro* release data

The results obtained from *in vitro* dissolution study data was analyzed for its release kinetic by fitting the release data into zero order, first order, matrix, Hixson-Crowell cube root equation and Ritger-Peppas equation to find out the r^2 value and the best fit model of release kinetic for drug from the prepared microspheres. Disso software was used for Model fitting.

Compression of formulated microspheres into tablets by direct compression method

250 mg tablet of optimized formulation of microspheres F4 (polymer ratio 3:5 and surfactant concentration 1.5%) were compressed using microcrystalline cellulose and magnesium stearate. Microspheres equivalent to 3 mg Budesonide was taken and compressed using RIMEK MINI PRESS-1 using 8 mm punches size. Formula for preparation of tablet is given in Table 3. The tablets were then coated with 5% cellulose acetate phthalate to prevent disintegration of tablet and drug degradation in stomach.[20]

Pre-compression tests for tablet granules

Powder flow properties

To study the flow properties of powder bulk density, tapped density, carr's index, hausner's ratio and angle of repose was determined.

Table 3: Composition for compressed tablet of microspheres.

Ingredients	Weight for 1 tablet (mg)
Microspheres	34.72
Micro-crystalline cellulose	210.28
Magnesium stearate	5

Post-compression tests for tablets

In vitro drug release studies for tablets

The *in-vitro* dissolution studies of tablets compressed for optimised microsphere and marketed product was performed using USP type II apparatus set at 50 rpm at 37±0.5°C. The dissolution studies were performed for 2 h in 0.1N HCl followed in 7.4 pH PBS for 10 h. The samples were withdrawn at predetermined time interval and replaced with equal quantity of buffer solution. The samples were suitably diluted and percent drug released was determined using Shimazdu UV 1900 UV-spectrophotometer at 247 nm.[19]

In vitro disintegration test

Disintegration time for compressed uncoated and coated tablets was determined using disintegration test apparatus. Compressed tablets were placed in baskets immersed in 900 ml of 0.1N HCl. The study was performed for 2 h at 37±2°C.

Weight variation

20 compressed tablets were selected randomly and all tablets were weighed individually. The percentage variation was determined by calculating difference between individual weights of tablet with average weight of 20 tablets. The percentage variation was determined using formula;

$$\% \text{ Weight variation} = \frac{\text{Individual tablet weight-Average weight}}{\text{Average weight}} \text{ X } 100$$

Friability test

Compressed uncoated tablets were subjected to friability test using Roche friabilator. Initial weight of 20 uncoated tablets was noted and loaded in friabilator, operated at 25 rpm for 4 m. Tablets are then de-dusted, weighed and difference in weight was noted. The formula used to determine friability.

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \text{ X100}$$

Where, W_1 = Initial weight of tablets

W_2 = Final weight of tablets

Drug content uniformity

Drug content of compressed uncoated tablets was determined by powdering 5 randomly selected tablets, weight of the powder equal to mean weight of 5 tablets was then transferred to 100 ml of pH 7.4 phosphate buffer in volumetric flask, dissolve completely on a mechanical shaker. The solution is then filtered, suitably diluted and absorbance measured using UV-spectrophotometer at 247 nm.

Hardness test

Monsanto hardness tester was used to determine hardness of the tablets and the values were determined in triplicate.

Thickness test

The vernier calipers was used to test the thickness of tablets. 3 tablets were randomly tested for their thickness and average value was considered.

Percentage weight gain of tablet

The optimized microspheres were compressed to tablets which was further coated by dip coating method using cellulose acetate phthalate as enteric coating material. The percentage weight gain of tablet after coating was determined using formula

$$\% \text{ Weight gain} = \frac{\text{Weight of coated tablet} - \text{weight of uncoated tablet}}{\text{Weight of coated tablet}} \text{ x } 100$$

Accelerated stability testing

The formulated tablets were checked for their stability by keeping the formulation at 40±2°C and 75±5% RH in stability chamber for 1 month. The tablets were then analyzed after every 10 days for its drug content and *in vitro* drug release study.

RESULTS AND DISCUSSION

The identity of drug was confirmed with its melting point found to be ±1.414 with no significant deviation from literature value of 226°C. Beer's concentration range for drug was in the range of 2-10 µg/ml. A linear calibration curve was obtained in pH 7.4 phosphate buffer solution with r^2 value of 0.9989.

Flow properties of microspheres

Results of flow property of microspheres studied for carr's index, hausner's ratio and angle of repose is tabulated in Table 4. Angle of repose for all formulations was ranging from 30.33° ±1.814 to 41.82°±0.012 which shows good to poor flow property of microspheres, the poor flow may be due to irregular shape and porous nature of microspheres formed by emulsion solvent

Table 4: Evaluation of formulated microspheres for flow properties.

Formulation code	Average Carr's index ± SD[a]	Average Hausner's ratio ± SD[a]	Average angle of repose ± SD[a]
F1	21.28±0.854	1.27±0.0116	35.03±1.475
F2	8.63±0.0849	1.09±0.00	30.33±1.814
F3	23.18±2.489	1.30±0.0348	35.55±2.713
F4	26.85±0.715	1.36±0.0173	41.82±0.012
F5	9.44±1.179	1.11±0.012	35.29±1.291
F6	40.22±0.358	1.673±0.010	33.93±1.592
F7	30.26±0.225	1.433±0.005	31.76±0.0058
F8	4.27±1.718	1.04±0.0205	34.20±1.447
F9	30.88±0.242	1.446±0.005	40.53±1.815

Where, SD[a]=standard deviation from the mean (n=3)

evaporation method. The Carr's index ranged between 4.27±1.718 to 40.22±0.358 indicating excellent to poor compressibility of microspheres. Poor compressibility may be due to cellulose acetate phthalate in the polymer matrix of microspheres. The optimized formula shows the compressibility of 26.85±0.715 which indicates poor compression, which was improved using micro-crystalline cellulose as a directly compressible diluent to form a tablet with acceptable hardness. Hausner's ratio varies from 1.04±0.0205 to 1.673±0.010 indicating good flow for 1.04 as per IP criteria and poor flow for 1.673. Hausner's value indicates flow cannot be improved by addition of glidants. The optimized formulation showed the Hausner's ratio of 1.36 which indicates that flow of the microspheres can be enhanced by the addition of glidant.

FT-IR results

Interpolymer complexation and drug excipient interactions were confirmed by FT-IR analysis as depicted in Figure 1. A characteristic peak of C=O stretching of phthalate group at 1743.65 cm^{-1} was observed for cellulose acetate phthalate (Figure 1a) and for chitosan the sharp peak at 3373 cm^{-1}which is due to –N-S- stretching of amine group (Figure 1b). The drug loaded microsphere (Figure 1a) showed the absence of characteristic peak of both chitosan and cellulose acetate phthalate which indicate formation of interpolymer complex between the two polymers. In FT-IR study (Figure 1c). Budesonide exhibits a peak at 3500.80 cm^{-1} which is corresponding to alcoholic –OH group. Presence of broad peak from 2956.87cm^{-1} to 2872.01 cm^{-1} due to C-H for CH_2 and $–CH_3$ groups. Peaks at 1724.36 cm^{-1} and 1666.50 cm^{-1} characteristic peaks of –C=O group due to ketone and strong

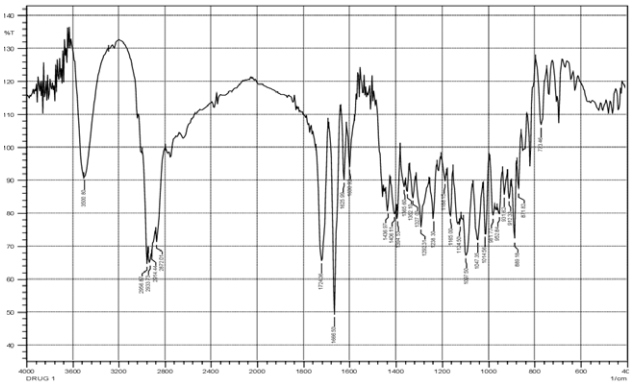

Figure 1(a): FTIR spectrum of Cellulose Acetate Phthalate.

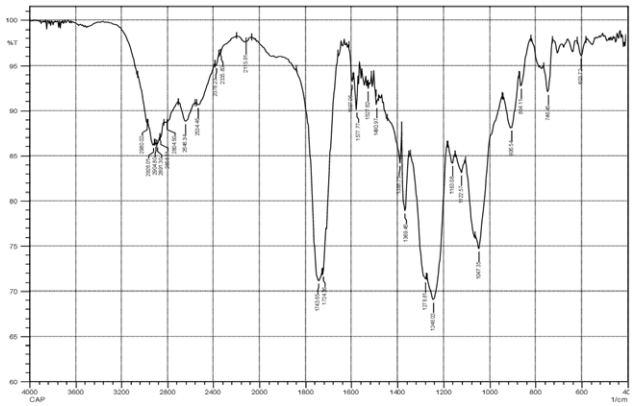

Figure 1(b): FTIR spectrum of Chitosan.

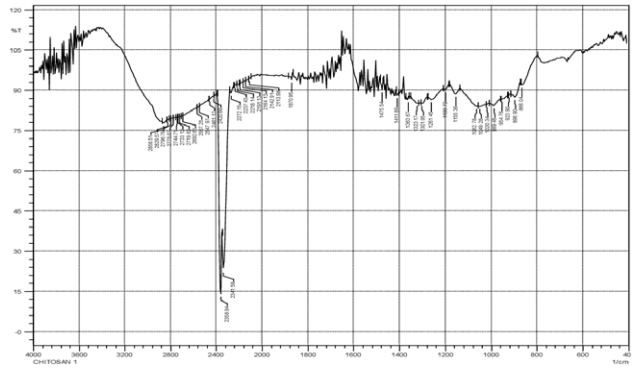

Figure 1(c): FTIR spectrum of pure Budesonide.

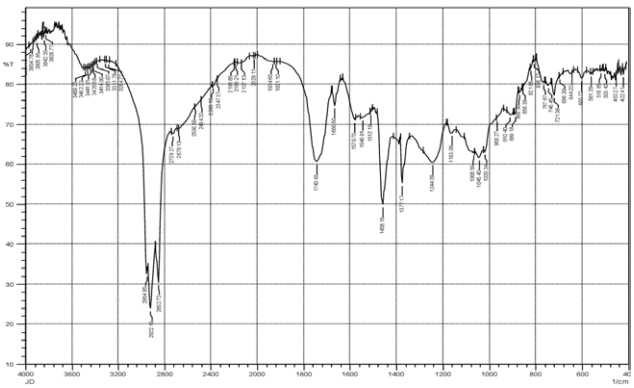

Figure 1(d): FTIR spectrum of budesonide loaded Microsphere.

peak at 1097.50 cm^{-1} due to C-O-C of ether. All the corresponding peaks relevant to drug were present in the final formulation of microsphere (Figure 1d) which indicate chemical stability between drug and polymers.

Differential scanning calorimetry

Nature of pure drug and interaction between drug and polymers was confirmed by DSC study, spectra obtained as depicted in Figure 2a and Figure 2b. The spectra for pure drug showed sharp endothermic peak at around 260°C which resembles melting point of pure drug whereas for the microspheres no sharp peak was observed due to dispersion of drug in the interpolymer complex matrix.

Scanning electron microscopy

SEM images as shown in Figure 3 for drug loaded microspheres reveals formation of round microspheres with pervious and uneven surfaces. The pervious surface is due to evaporation of acetone from the matrix during formation of the microspheres.

Percentage yield

The efficacy of method for preparation of microspheres is reflected by the percentage yield obtained. The yield was found to be in the range of 46.42±0.089 to 81±0.090% with the highest yield for F7 (polymer ratio 3:5 and surfactant concentration 2%). Results are shown in Table 5.

Percentage encapsulation efficiency

Dissolution rate of drug is dependent on the encapsulation efficiency of the microspheres. Results for drug content and percentage encapsulation efficiency are tabulated in Table 5. The drug content was found to be in the range of 2.37±0.0263 to 8.68±0.0374 with the highest drug content of 8.68 for formulation F4 (polymer ratio 3:5, surfactant concentration 1.5%), it showed highest percentage encapsulation efficiency of 53.64±0.228 and highest drug release from the microspheres. Increase in polymer ratio showed higher drug encapsulation.

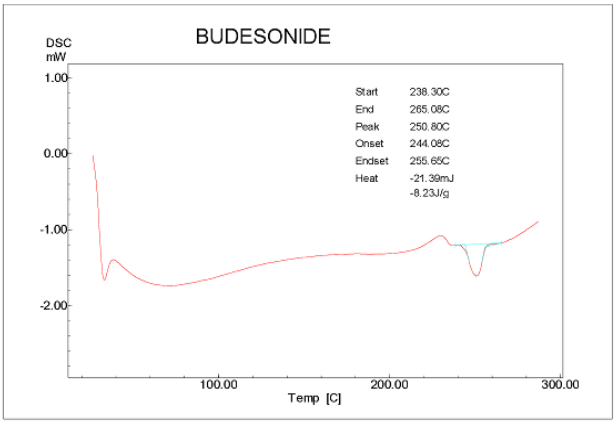

Figure 2(a): DSC Thermogram of pure Drug.

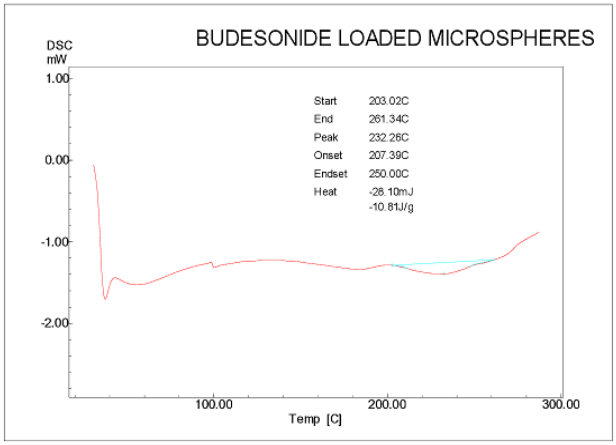

Figure 2(b): DSC Thermogram of Budesonide loaded Microsphere.

Table 5: Physico-chemical evaluation of formulated microspheres.

Formulation code	Average Drug content (mg) ± SD[a]	Average % EE ± SD[a]	Average Swelling index (%) ± SD[a]	Average Particle size (µm) ± SD[a]	Average % Yield ± SD[a]
F1	4.83±0.0340	26.34±0.187	56±4.163	49.56±0.882	60.46 ± 0.0974
F2	2.99±0.089	18.69±0.563	66.67±4.109	101.75±0.101	62.5±0.00
F3	8.1±0.0653	37.26±0.302	84±4.32	118.40±0.814	57.84±0.259
F4	8.68±0.0374	53.64±0.228	48.67±2.494	68.74±0.961	68.69±0.159
F5	4.28±0.028	30.60±0.202	60±1.63	102.30±0.987	71.5±0.00
F6	4.48±0.0094	45.70±0.0613	84.67±6.84	108.89±0.325	46.42±0.089
F7	5.34±0.0205	38.95±0.148	51.62±2.95	82.47±1.212	81±0.090
F8	3.82±0.057	25±0.376	56.67±2.109	102.38±0.587	65.5±0.00
F9	2.37±0.0263	27.54±0.193	87.33±3.40	111.85±0.651	52.76±0.0579

Where, SD[a]=standard deviation from the mean (n=3)

Mean particle size of microspheres

Mean particle size was found in the range of 49.56±0.882 µm for lower ratios of polymers i.e. 3:5 (CS: CAP) to 118.40±0.814 µm for higher ratio of polymers i.e. 5:5 (CS: CAP). Results shown in Table 5. The results indicated that particle size of microsphere increased with increase in polymer concentration. Surfactant concentration in the formulation does not show significant effect on the particle size. Hence it is only dependent on the ratio of polymers in the formation of microspheres.

Swelling index

The swelling index of microspheres showed its dependence on the concentration of chitosan present in the formulation due to its water holding and swelling capacity in the matrix. Swelling index was found to be independent with respect to concentration of cellulose acetate phthalate in the microsphere due to its water hating i.e. hydrophobic nature. The microspheres showed minimum swelling index of 48.67±2.494% for F4 which contains 3 parts of chitosan and maximum of 87.33±3.40% for microspheres containing 5 parts of chitosan in the formulation. Results for swelling index are shown in Table 5.

Post compression evaluation of tablets

Results of evaluation tests for uncoated and coated tablets are tabulated in Table 6. Compressed uncoated tablets were found to disintegrate within 20 min, as compared to compressed coated tablets with disintegration time more than 75 min. There was slight weight gain for coated tablets and friability was found to decrease due to coating of tablets.

In vitro drug release study

Dissolution studies of microspheres revealed that the release of drug in pH 1.2 (0.1N HCl) was prevented due to altered physico-chemical properties of polymer by formation of interpolymer complex and showed the maximum release of drug from microspheres in pH 7.4 buffer indicating that maximum concentration of drug will reach colon with minimum loss and degradation of drug in upper GIT i.e. stomach.

Release data obtained from varying polymer ratio and surfactant concentration has been depicted in Figure 4 (a,b and c) which showed that the highest drug release was observed with the microspheres containing low amount of chitosan i.e. 3:5 with all three levels of surfactant concentration (1%, 1.5% and 2%) i.e. F1, F4 and F7. The release of drug from the microspheres was dependent upon the chitosan concentration which acts as release retardant excipient in the microsphere formulation. The results showed that as the chitosan ratio in the microsphere increases release of drug from the microsphere decreases.

For the microsphere formulations with 5:5 polymer ratio (CS:CAP) at varied surfactant concentration i.e. F3, F6 and F9 showed slow release of drug from the formulation. Slow release is due to increased ratio of chitosan in the microspheres which results in the formation of rigid complex which retards instant drug release from the formulation. The cellulose acetate phthalate in the complex undergoes dissolution in intestinal pH and enzymatic degradation of chitosan in the colon causes drug to release at target site.

Surfactant concentration does not show much effect on drug release, but slight increase in the release was observed for the microspheres containing 2% in comparison to 1 and 1.5% surfactant concentration, indicating drug release is highly dependent on polymer ratio.

Prepared microspheres showed release of the drug for up to 12 h with small amount of drug release in pH 1.2 buffer which may be due to adsorbed drug on the surface of microspheres. Hence, the novel interpolymer complex microsphere can be promising for colon delivery without releasing drug in stomach.

In vitro release profile of compressed coated tablet containing optimised microspheres was compared with

Table 6: Evaluation for Compressed tablets of optimised microspheres.

Evaluation tests	For uncoated tablets	For CAP coated tablets
Weight variation (%) ± SD[a]	0.773	1.07
Disintegration time (min)± SD[a]	19.33±1.247	75.66±2.054
Friability (%)± SD[a]	0.508±0.0557	0.215±0.076
Thickness (mm)± SD[a]	4.43±0.0291	4.46±0.0489
Hardness (kg/cm2)± SD[a]	4.0±0.0	4.45±0.0
Drug content (mg)± SD[a]	2.77±0.0339	2.77±0.0339
Weight gain after coating (%)± SD[a]	-	5.17

Where, SD[a]=standard deviation from the mean (n=3).

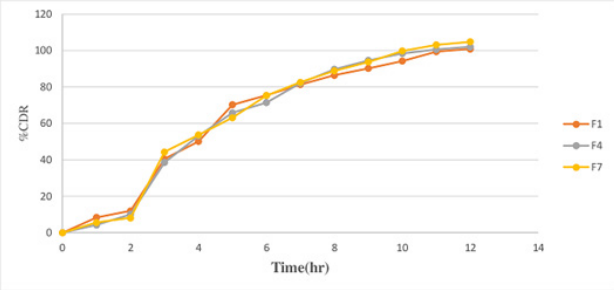

Figure 4(a): Drug release profile for formulated microsphere F1, F4 and F7.

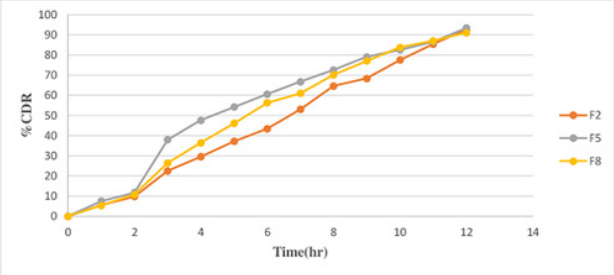

Figure 4(b): Drug release profile for formulated microsphere F2, F5 and F8.

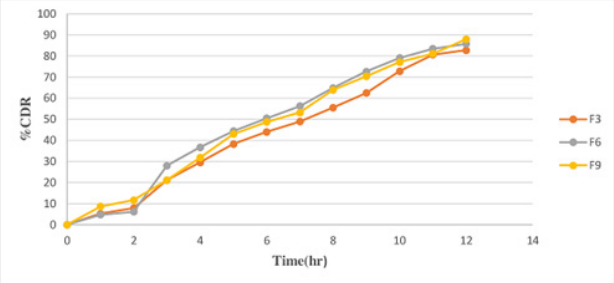

Figure 4(c): Drug release profile for formulated microsphere F3, F6 and F9.

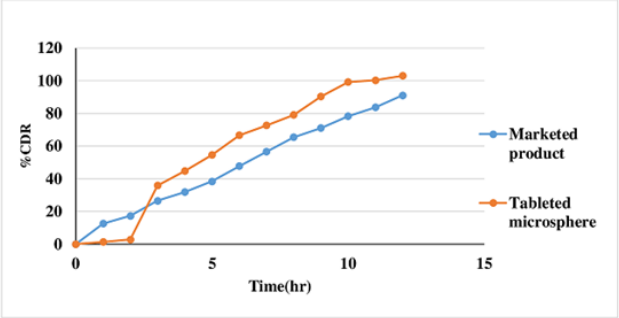

Figure 5: Comparative drug release profile of compressed coated tablets of Budesonide with its marketed product.

marketed product of Budenoside and results depicted in Figure 5. The release of the drug from the tablet coated with cellulose acetate phthalate as enteric coating material does not disintegrate in pH 1.2. It completely prevents drug release and its degradation in pH 1.2. As the tablet moves into intestinal pH, the solubility of cellulose acetate phthalate in intestine pH results in release of drug which is available for absorption in the colon. Whereas marketed product was found to disintegrate when in contact with gastric contents and showed release of the drug in pH 1.2 buffer indicating drug degradation in the stomach and hence ineffective concentration reaching colon for absorption.

Factorial design

The effect of polymer ratio and surfactant concentration on % CDR, % EE and mean particle size was analysed with the help of 3D surface response method, 2D contour plot, perturbation plot and effect of individual factor on the response.

The result for % CDR indicates that drug release from microsphere is inversely proportional to polymer

Table 7: Model fitting analysis for drug release mechanism.

Formulations	Zero order	First	Matrix	Peppas	Hixson-crowell	N	K
F1	0.9476	0.8703	0.9499	0.9566	0.9285	1.0658	9.2137
F2	0.9970	0.9135	0.9118	0.9939	0.9596	1.1665	5.4495
F3	0.9957	0.9552	0.9192	0.9868	0.9781	1.1706	5.0574
F4	0.9571	0.9306	0.9450	0.9551	0.9303	1.1435	7.8932
F5	0.9655	0.9691	0.9568	0.9638	0.9919	1.0294	8.5788
F6	0.9848	0.9722	0.9297	0.8641	0.9876	1.4002	4.1161
F7	0.9576	0.8221	0.9429	0.9426	0.9118	1.2481	6.5436
F8	0.9254	0.9179	0.8778	0.8043	0.9351	1.0497	6.6016
F9	0.9958	0.9591	0.9326	0.9897	0.9840	1.0116	7.4915
Compressed coated tablet of microspheres	0.9755	0.8399	0.9221	0.9194	0.9039	2.0003	1.7320
Marketed product (Tablet)	0.9966	0.9437	0.9414	0.9926	0.9785	0.8489	10.7206

Where N= diffusional exponent value and K= release kinetic constant.

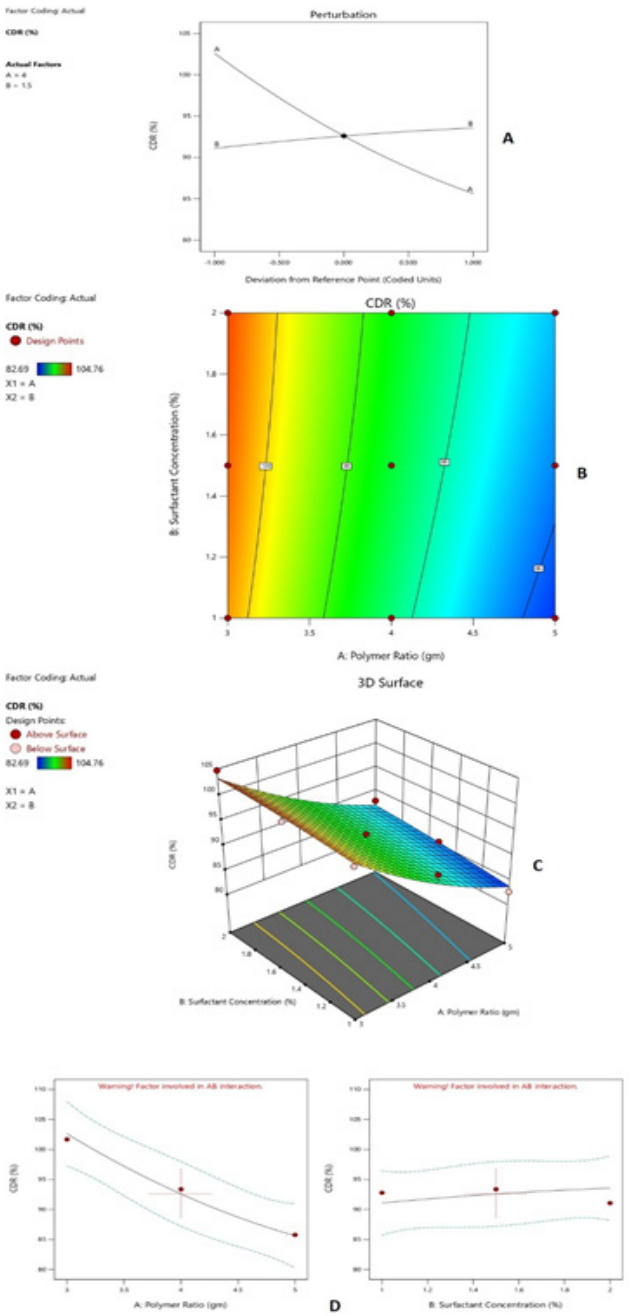

Figure 6: Effect of polymer ratio and surfactant concentration on %CDR (a) perturbation plot (b) contour plot (c) 3D response surface plot (d) effect of individual factor on %CDR.

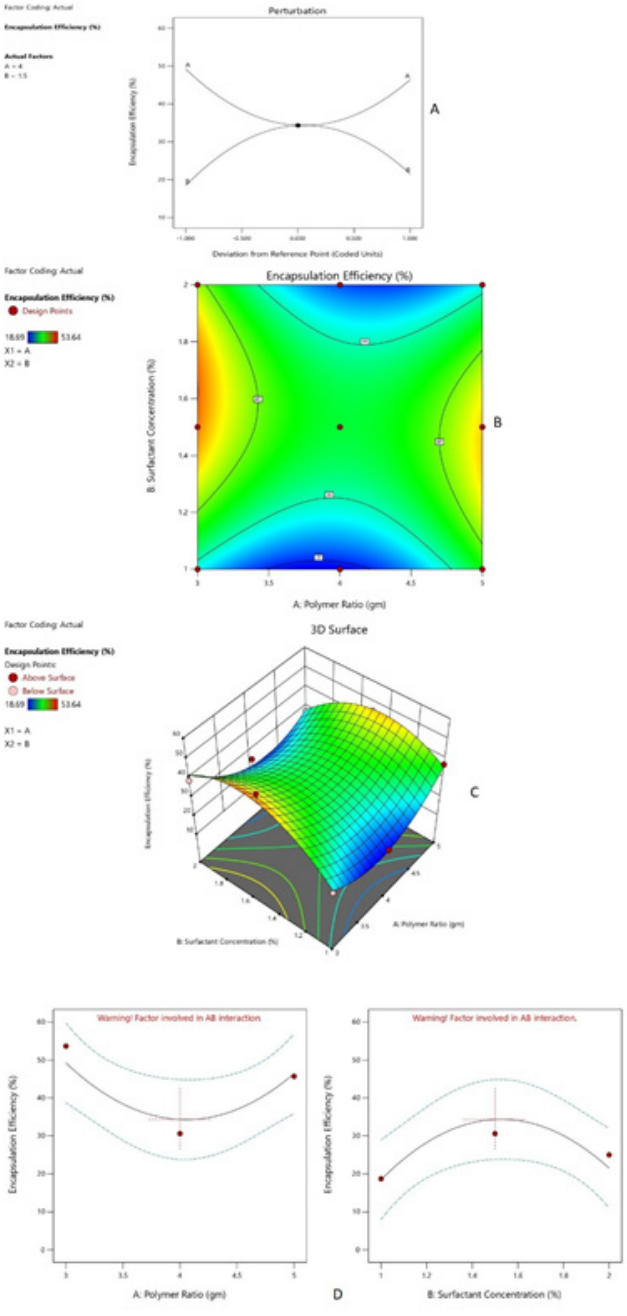

Figure 7: Effect of polymer ratio and surfactant concentration on %EE (a) perturbation plot (b) contour plot (c) 3D response surface plot (d) effect of individual factor on %EE

concentration. This is due to the formation of more rigid complex as the polymer composition in the microspheres increases. Increase in surfactant concentration showed no significant variation in drug release indicating polymer ratio as the main contributing factor in the drug release. Perturbation plot and individual response plot depicted in Figure 6 shows little increase in the % CDR as surfactant concentration increases.

The effect of polymer ratio on % EE as shown in Figure 7 where maximum % EE was observed for 3:5 polymer ratio. %EE was found to increase with surfactant concentration up to 1.5% and decreases for further increase in concentration indicating both polymer ratio and surfactant concentration are contributing factors for % EE.

The particle size for different formulations of microsphere was studied and their results shown in Figure 8 reveals increase in the particle size as the polymer ratio in the microspheres increases due to formation of larger complexes of microspheres.

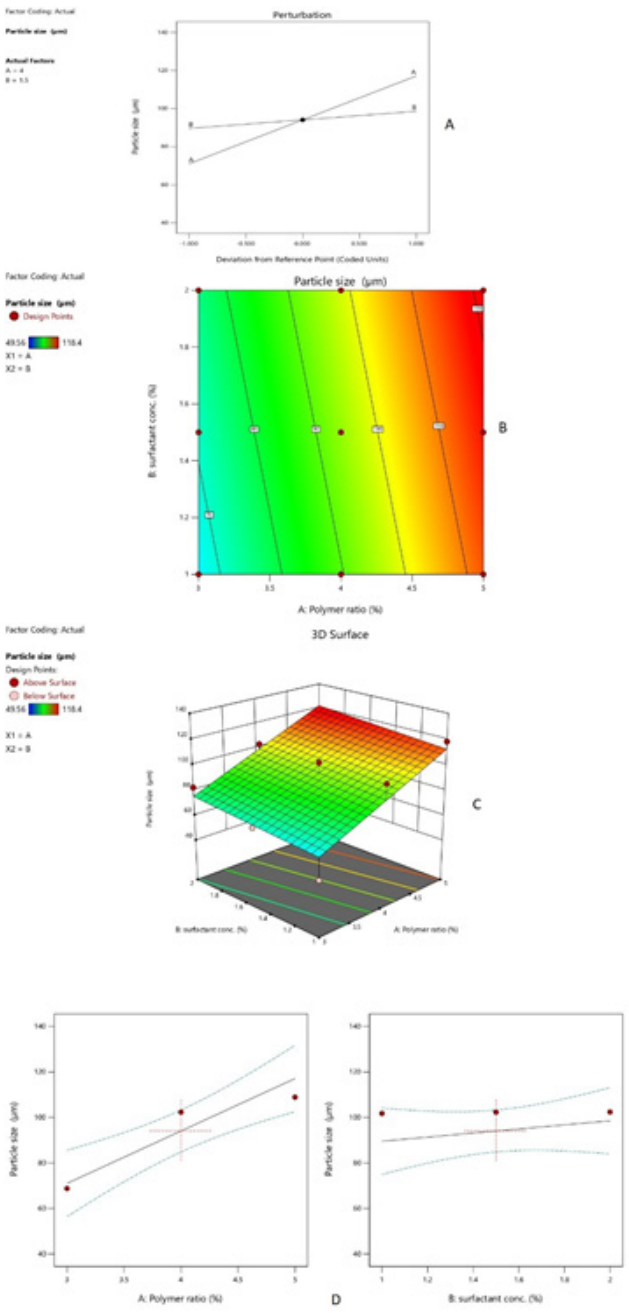

Figure 8: Effect of polymer ratio and surfactant concentration on mean particle size (a) perturbation plot (b) contour plot (c) 3D response surface plot (d) effect of individual factor on mean particle size.

Surfactant concentration does not show marked contribution to mean particle size of the microspheres. Hence both polymer ratio and surfactant concentration show individual effect on the responses.

In vitro Release Kinetics

Model fitting analysis for prepared microspheres as tabulated in Table 7 indicates varied release mechanisms. Drug release for formulated tablet was found to follow zero order release and Hixson-crowell cube root model for drug release kinetic.

CONCLUSION

Drug loaded microspheres for oral colon drug delivery was prepared by interpolymer complexation using emulsion solvent method. The microspheres help in the prevention of drug release in 1.2 pH buffer by change in properties of the polymers involved in complex formation. Microspheres showed extended and complete release of drug in colon. Compressed coated tablets containing microspheres prevented drug release from the surface of microspheres in stomach. Hence, targeted drug delivery of Budenoside can be promising in enhancing efficacy of therapeutic effect.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

CS: Chitosan; **CAP:** Cellulose acetate phthalate; **IPC:** Interpolymer complex; **GIT:** Gastrointestinal tract; **Conc:** Concentration; **CDR:** Cumulative drug release; **%:** Percentage; µg: Microgram; **mg:** Milligram; **rpm:** Rotation per minute; **DSC:** Differential scanning calorimetry; **FTIR:** Fourier transform infrared; **h:** Hour; **m:** Minute; λmax: Maximum absorbance; **nm:** Nanometer; **PBS:** Phosphate buffer solution; **EE:** Encapsulation efficiency; **SI:** Swelling index.

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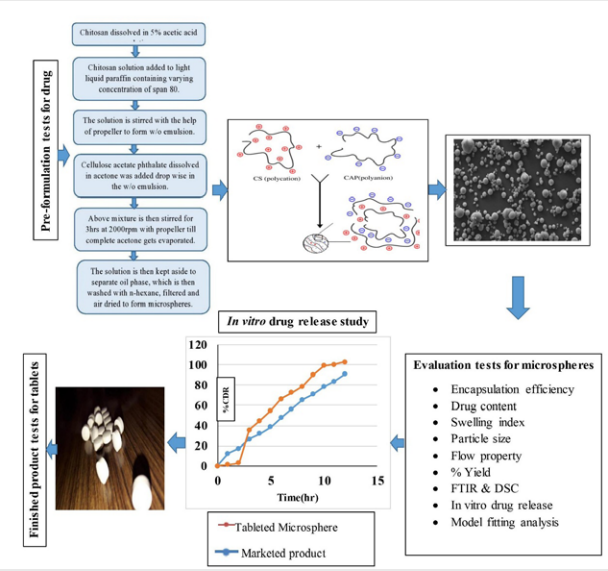
PICTORIAL ABSTRACT



SUMMARY

- Emulsion solvent evaporation method was used to prepare interpolymer complex microspheres of Budesonide to prevent drug release in stomach.
- Microspheres prepared with 3:5 polymer ratios were found to be optimized with respect to drug content, % encapsulation efficiency, Percentage yield and drug release.
- Drug and excipients compatibility and formation of complex between chitosan and cellulose acetate phthalate was assessed by FTIR spectral analysis.
- Compressed coated tablets of microspheres prevents drug release and its degradation in pH 1.2. Whereas released drug in 7.4 phosphate buffer in a sustaining manner.
- Compressed coated tablets were found to be stable at 40°C and 75% relative humidity and showed extended drug release up to 12 h. Hence, Interpolymer complexation technique by emulsion solvent method can be promising for targeting drug release to colon.

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