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Development of colon targeted multiparticulate pulsatile drug delivery system for treating nocturnal asthma

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ABSTRACT

The present study was all about to deliver a drug after certain lag time. The study was to develop a multiparticulate pulsatile drug delivery system for montelukast sodium. This study was done to increase half life of drug by increasing lag time. The pulsatile drug delivery system has importance that it delivers the drug in gastrointestinal tract after certain lag time. The mixture of Eudragit RL100 and Eudragit S100 was used for enteric coating purpose. Continuous dissolution studies were carried out in simulated gastric, intestinal, and colonic fluid with pH 1.2 (0.1 N HCl), pH 7.4 and pH 6.8 (phosphate buffer), respectively. The lag time was completely depending on ratio of acrylate polymers i.e. ERL and ES and percentage coating level used. The formulation comprising 12% coating level and 1:4 ES: ERL ratio was found to be an optimized formulation. The in vitro study showed lag time 4 to 8 hours to release the total drug in different buffers used.

KEYWORDS

Montelukast sodium;
Lag time;
Multiparticulate;
Factorial design;
Circadian rhythm.

INTRODUCTION

Drug delivery technology is now a days regularly used to improve the quality of pharmacotherapy. Targeted pulsatile oral drug delivery may be a valuable approach when release of an active ingredient, because of its local action, is needed in a certain segment of the gastrointestinal tract or when release is desired after a certain lag-time (chronotherapy)[1]. There is a growing awareness of the importance of disease state and drug action in chronopharmaceutics and chronopharmacology. Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc. It has been reported that more shocks and heart attacks occur during morning hours[2]. Asthma attacks are also reported to be high in the morning. A pulsatile release profiles characterized by a lag time followed by rapid and complete drug release. Significant daily variations in pharmacokinetics or drug effects have been demonstrated in man. Depending upon the physiological and pathophysiological changes of circadian rhythmicity, nocturnal symptoms and overnight decrements in lung functions are a common part of the asthma clinical syndrome (Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. The dip is particularly pronounced in people with asthma, because bronchoconstriction and exacerbation of symp-

toms vary in a circadian fashion. Asthma is well controlled with oral corticosteroids, β2 agonists and leukotrine antagonists[4]. For such conditions a drug delivery system administered at bed time, but releasing drug during morning hours formulations with suitable lag time were developed in recent days for betterment of the patient[5]. The recent interest in multiple-unit dosage forms is the result of the advantages they offer over the single-unit systems. Multiple-unit dosage forms offer more predictable gastric emptying, less dependent on the state of nutrition, less variance in transit time through the gastrointestinal tract (GIT), a higher degree of dispersion in the digestive tract, less absorption variability, and a lesser risk of dose dumping than single-unit dosage forms. Various pharmaceutical approaches that have been used for targeting drug to the colon are mainly based on pH-dependant, time-dependant, and/or bacterially degradable systems[7,18]. Among these approaches, pH-dependant systems are simple, but the suitability of them for using alone as a colonic delivery in different physiological and pathological conditions in GIT has been doubtful. Therefore, the pH-dependant system was evaluated in combination with time-dependant system in order to alleviate the pH dependency of former system and to ensure drug release under different physiological conditions. The use of pH-dependant and time-dependant polymers as coating materials for colonic drug delivery has been reported previously. In those studies sustained release and pH-dependant polymers have been applied as separate coating layers on top of each other[8]. The combination of time- and pH-dependant polymer as a single coating has been used to provide the pulsatile drug release in the unit formulation[5]. There is no report on the use of mixtures of these two kinds of polymers as a single or in combination coating system for the development of a multiparticulate drug delivery system for montelukast sodium. The drug Montelukast sodium (MS) is very efficient against asthma and if it will be released during morning hours. So to release this drug during morning, it is coated with mixture time dependent and time dependent acrylate polymers. The objective of the present study was to optimize the formulation consisting of Eudragit® RL100 (ERL®), a time-dependant polymer, and Eudragit® S100 (ES®), a pH-dependant polymer for the coating of MS pellets to achieve the colon-targeted drug delivery system (CTDDS)[9]. Efûcient plasticization of Eudragit S100 was necessary to reduce the polymer's glass transition temperature and melt viscosity. So triethyl citrate used as a plasticizer. Unplasticized Eudragit S100 exhibit high glass transition temperatures (Tg) of 172 ^{0}C (determined by MDSC) and undergo thermal degradation above 180 ^{0}C. High TEC levels (30% based on the polymer weight, 20.8% absolute) were necessary to sufficiently lower the Tg and the processing temperature of polymethacrylic blends below the threshold temperature of thermal degradation[10]. Montelukast is an effective and well-tolerated preventative treatment for asthma and allergic rhinitis in adults and children[11]. The leukotriene receptor antagonist montelukast decreases bronchial responsiveness and exercise-induced symptoms in asthmatic childrenCys-LTs are key components in the early and late allergic airway response and also contribute to bronchial obstruction after exercise and hyperventilation of cold, dry air in asthmatics[12]. Montelukast modifies action of leukotrienes, which are the most potent bronchoconstrictors, by blocking cysteinyl leukotriene receptors. Systemic drug like mountelukast can reach lower airways and improves the peripheral functions which play a crucial role in the evolution of asthma[13].

MATERIALS AND METHOD

Materials

Drug MS was a kind gift of Glenmark Pharmaceuticals, Mumbai. Microcrystalline cellulose spheres (Celphere CP 203, 150-300 mesh) and hydroxy propyl cellulose (HPC-L) were supplied as free gift sample from Micro Labs, Bangalore. ERL® and ES® were obtained from Rohm Pharma (Gmbh, Germany). Triethylcitrate (TEC) and dichlorometh-ane (DCM) was supplied as a gift sample from Merck (Germany). Isopropyl alcohol (IPA) was obtained from Loba Chemicals (Mumbai, India). Other ingredients such as lubricants and glidants used to prepare the pellets were of standard Pharmacopoeial grade.

Experimental design

To optimize the formulation, the 32 design was implemented. The independent variables were ratio of ES to ERL (X1) and percentage coating level (X2).

The dependent variables (responses) were lag time (Y1) and drug release in 7 h in 6.8 pH buffer (Y2). The independent and dependent variables and the used levels are summarized in TABLE 1. The resulting formulations are listed in TABLE 2.

TABLE 1 : Independent and dependent variables and the levels used for factorial design

Factors (independent variables)	Levels used			Responses (dependent variables)
	1	0	-1	
X1= ratio of Eudragit S	0%	20%	40%	Y1= lag time (h)
100 to Eudragit RL 100	(1:0)	(1:2)	(1:4)	
X2= percentage coating level	6	12	18	Y2=drug release in 7 h(%)

TABLE 2 : Composition of experimental formulations

Sr. No.	Variable factors	
	X1(Eudragit S: Eudragit RL ratio)	X2 (Coating level) (%)
1	1:4	6
2	1:4	12
3	1:4	18
4	1:2	6
5	1:2	12
6	1:2	18
7	1:0	6
8	1:0	12
9	1:0	18

Preparation of drug-layered pellets

Drug-loaded pellets were prepared by a spray-drying technique. Montelukast sodium was homogeneously dispersed in an aqueous solution of HPC-L while stirring with a magnetic stirrer. The drug dispersion was passed through a 100 mesh sieve. The drug dispersion was then sprayed on celphere seeds using the fluidized bed coater, bottom spray (Miniglatt, Glatt GmbH, Binzen, Germany) with a 0.5 mm nozzle at a feed rate of 0.5–3 g/min using a peristaltic pump. The spraying process with the drug dispersion was continued to achieve the target drug loading level. The drug-loaded pellets were finally dried at 45°C for 15 min and were used for further coating with acrylic polymers. The composition of the drug-loaded pellets is given in TABLES 3.

Enteric coating of pellets

Six per cent (w/w) solutions of polymethacrylates (ERL® and ES®) were prepared in IPA:DCM (7:3) mixture. Based on the experimental design, the detailed composition of different batches was given in TABLE 4. The solution was plasticized with TEC (15%, w/w, with respect to dry polymer), and then talc was added as a glidant (5%, w/w, related to dry polymer). Forty-five grams of TP pellets were coated in a fluidized bed coating apparatus (Wurster insert, Werner Glatt). Coating conditions are, inlet temperature, product temperature, fluidization air, for drug layering and polymer coating are 55 and50, 48-52 and 38-40 respectively, suspension spray rate, atomization pressure are 0.5-3 and 0.40-0.60 respectively. Samples of coated pellets were removed from the apparatus when the coating load had reached 6, 12, and 18% (w/w). At each stage the pellets were gently fluidized or <™ 10 min.

TABLE 3 : Composition of drug-loaded celphere pellets

Composition	mg/capsule
Celphere CP 203	70
Solids in layering dispersion	
Montelukast sod.	10.4
HPC L	1.8
Methanol	3.9
Total	86.1

q.s.- 6 % W/W organic solution was prepared

Drug release study of enteric coated pellets

Accurately weighed enteric coated pellets equivalent to 10.4mg of Montelukast sodium were transferred to the dissolution medium. The test was carried out in a USP dissolution type I assembly (Electrolab, TDT-08L, India) at a rotation speed of 100 rpm 900 ml medium at 37°C in media with pH 1.2 (HCl 0.1 N), pH 7.4 and pH 6.8 (phosphate buffer) for 2 h, 3 h, and the remaining 3 h, respectively. The 5 ml aliquots of the dissolution fluid were removed at specified time intervals and assayed for the amount of MS by spectrophotometer (Shimadzu, UV 1700, Japan) at wavelength 287, 290,287.4 nm for 1.2,7.4,6.8 pH buffers respectively[5,9,14].

Differential scanning calorimetry (DSC)

The possibility of any interaction between MS, polymers, and other excipients was assessed by DSC (Mettler Toledo Stare DSC 822c, Germany). The thermogram of the samples were obtained at a scan-

ning rate of 10°C/min conducted over a range of 0–350°C under an inert atmosphere flushed with nitrogen at a rate of 20 ml/min.

FTIR Spectroscopy

FTIR spectrums were recorded for Montelukast sodium and for final formulation. (FTIR 8400S Shimadzu, Japan) FTIR spectrum was taken by KBr pellet method and was compared with the reference standard IR spectrums of the drugs. The interaction between excipients and drug was studied.

Scanning electron microscopy (SEM)

The beads of microcrystalline cellulose, drug coated and polymer coated formulation were coated with palladium for 5 min. Morphological examination of beads surfaces were performed at 10 kV at appropriate magnification using a scanning electron microscope (Jeol Model JSM-5800LV, Tokyo, Japan). The surface topography and cross sectional view was also analyzed with SEM[9].

Statistical analysis of data

The effects of independent variables upon the responses were modeled using a second order polynomial equation. The mathematical model of the effects of independent variables upon the dependent variables was performed using Stat-Ease Design Expert (Version 7.1.6) with a manual linear regression technique. A significant term ($p < 0.05$) was chosen for final equations. Finally, response surface plots resulting from equations were drawn.

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_1X_1^2+b_{22}X_2^2 \quad (1)$$

where Y is the dependent variable, b0 is the arithmetic mean response of the nine runs, and bi (b1, b2, b12, b11, and b22) is the estimated coefficient for the corresponding factor Xi (X1, X2, X1X2, X12, and X22), which represents the average result of changing one factor at a time from its low to high value. The interaction term (X1X2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X12 and X22) are included to investigate non-linearity. All nine batches of design have shown wide variation in lag time and percentage drug release in 7 h (4-8h and 85–99%, respectively). The fitted equations relating the response Y1 and Y2 to the transformed factor are shown in equations (2) and (4), respectively. A backward elimination procedure was adopted to fit the data into different predictor equations. The quadratic model generated by regression analysis were used to construct the three dimensional graphs in which the response parameter Y was represented by a curvature surface as a function of X. Numerical optimization using desirability approach was employed to locate the optimal setting of the formulation variables to obtain the desired response.

RESULTS AND DISCUSSION

Basic structure of the coated pellets. The drug coated pellets and polymer coated pellets are formulated with the help of wurster coating process. This has been done with the help of glatt coater. In the coating step, the drug loading process had an efficiency of ~ 90% and ~ 80–85% in polymeric coating. The loss of final product occurred due to the formation of some agglomerates and fines in the product bed, and the loss

TABLE 4 : Composition of experimental formulations

	ES:ERL(1:4)			ES:ERL(1:2)			ES:ERL(1:0)		
	6%	12%	18%	6%	12%	18%	6%	12%	18%
	A	B	C	A	B	C	A	B	C
Drug Layered Pellets(mg)	70	70	70	70	70	70	70	70	70
ERL (mg)	3.36	6.72	10.08	2.8	5.6	8.4	---	---	---
ES (mg)	0.84	1.68	2.52	1.39	2.79	4.17	4.17	8.34	12.51
TEC (mg)	0.62	1.25	1.88	0.62	1.25	1.88	0.62	1.25	1.88
DCM (mg)	19.74	39.48	59.22	19.74	39.48	59.22	19.74	39.48	59.22
Total Weight of Enteric Coated pellets (mg)	75.2	79.4	83.6	75.2	79.4	83.6	75.2	79.4	83.6
Lubrication talc (mg)	1.87	1.985	2.08	1.87	1.985	2.08	1.87	1.985	2.08
Total Weight Of Lubricated Pellets (mg)	77.07	81.38	85.68	77.07	81.38	85.68	77.07	81.38	85.68

of coating solids to exhaust. The basic structure of the film-coated pellets has been schematically shown in Figure 1. In order to determine the levels of factors which yield optimum dissolution responses, mathematical relationships were generated between the dependent and independent variables.

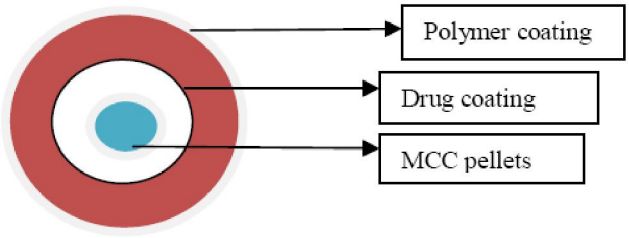

Figure 1 : The basic structure of the film-coated pellets

The equations of the responses are given below:

Final Equation in Terms of Coded Factors:

lag time (Y1) =+5.90+0.83 * X1-0.33 * X2+0.25* X1 * X2-0.64* $X1^2$-0.14 * $X2^2$ (2)

Final Equation in Terms of Actual Factors:

lag time =+5.04023+0.80460 * Eudragit S-5.26820E -003* % Coating level+0.020833 * EudragitS * % Coating level-0.15948- Eudragit S2-3.83142E-003 % Coating level2** (3)

Equation in Terms of Coded Factors:

Drug release after 7 hrs

(Y2) =+93.63-2.47 * X1-3.39 * X2-0.58 * X1 * X2-0.14* $X1^2$-1.62 * $X2^2$ (4)

Final Equation in Terms of Actual Factors drug release after 7 hrs

=+95.09915-0.51401 * Eudragit S+0.61258* % Coating level-0.048333 * Eudragit S* % Coating level -0.035664 * Eudragit S2-0.045060* % Coating level2 +2.08 8333% ratio of polymers^2 (5)

The equations represents the quantitative effect of independent variables (X1and X2) upon the responses (Y1 and Y2).

Analysis of variance (ANOVA) (TABLE 5) indicated the assumed regression models were significant and valid for each considered responses. The three-dimensional response surfaces were plotted to estimate the effect of independent variables on each response [Figures 3(A) and 3(B)]. Figure 3 (A) shows the effect of two formulation factors on lag time and indicates that increase in ratio of ES: ERLrises lag time significantly. ERL is a copolymer of ethyl acrylate,methyl methacrylate, and a low content of a methacrylic acid ester with quaternary ammonium groups (trimethy-lammonioethyl

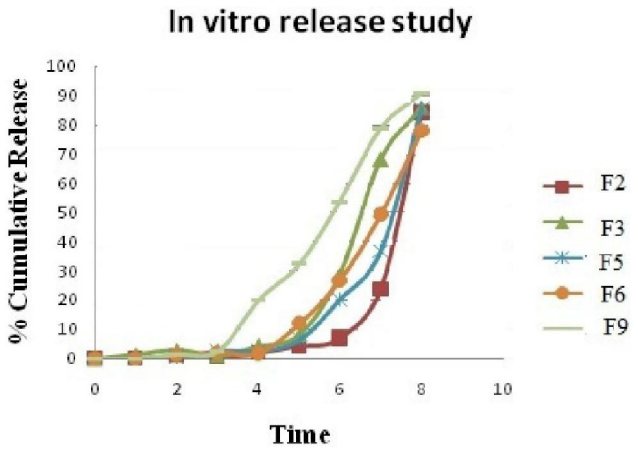

Figure 2 A : In vitro release study

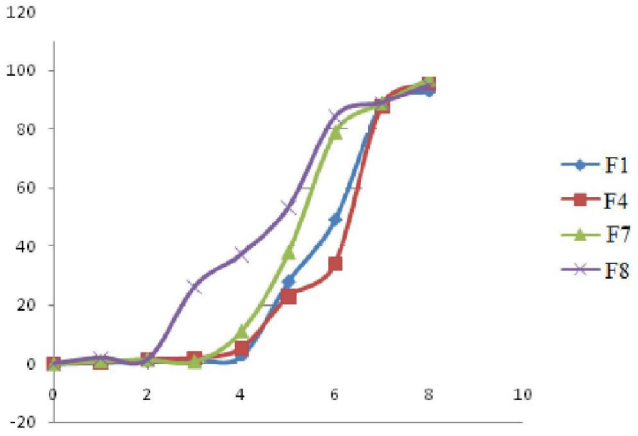

Figure 2 B : In vitro release study

methacrylate chloride). The ammonium groups are present as salts and make the polymers permeable. ES is a copolymer of methacrylic acid and methyl methacrylate, and the ratio of carboxyl to ester group is <• 1:2. Lower ratio of carboxyl group in ES causes less ionization in neutral to alkaline media than ERL, and hence shows slower solubilization[17]. The effect of coating thickness on lag time is lesser at low levels of ES and rises at a higher ratio (Figure 3 A). However, by using proper combinations of ES, ERL, and coating level, the release of drug from formulation after an optimum lag time will be ensured. Sometimes single polymer system does not releases drug at predetermined position so combination of polymers benefitial rather than single polymer[18]. A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. Constraints were applied to the factors (X1 and X2) and (Y1and Y2) for optimizing the desired formulation. The optimized formulation was evaluated for lag time

TABLE 5 : Analysis of variance (ANOVA) of dependent variables

Source	Sum of Squares	df	Mean Square	F Value	P Value	Prob > F
Analysis of Variationfor Y_1 (lag time in hr)						
Model	6.68	5	1.34	16.85	0.0009	significant
A-Eudragit S	4.17	1	4.17	52.59	0.0002	
B-% Coating level	0.67	1	0.67	8.41	0.0230	
AB	0.25	1	0.25	3.16	0.1189	
A^2	1.12	1	1.12	14.19	0.0070	
B^2	0.053	1	0.053	0.66	0.4422	
Residual	0.55	7	0.079			
Cor Total	7.23	12				
Analysis of Variancefor Y_2 (%drug realease in 6.8)						
Model	116.27	5	23.25	27.29	0.0002	significant
A-Eudragit	36.70	1	36.70	43.08	0.0003	
B-% Coating level	69.08	1	69.08	81.08	<0.0001	
AB	1	1.35	1.58	0.2492		
A^2	1	0.056	0.066	0.8047		
B^2	1	7.27	8.53	0.0223		
Residual	5.96	7	0.85			
Total	122.23	12				

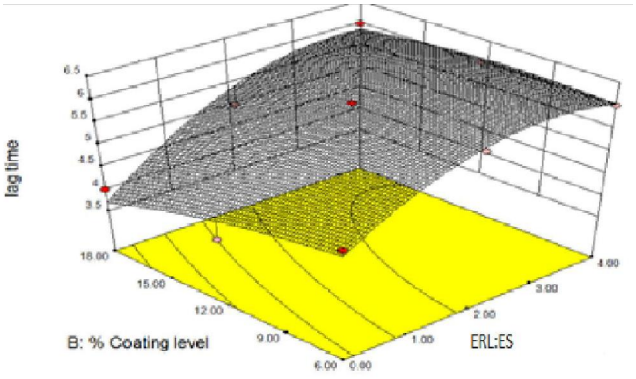

Figure 3 A : Response surface plot for Y1 response (lag time)

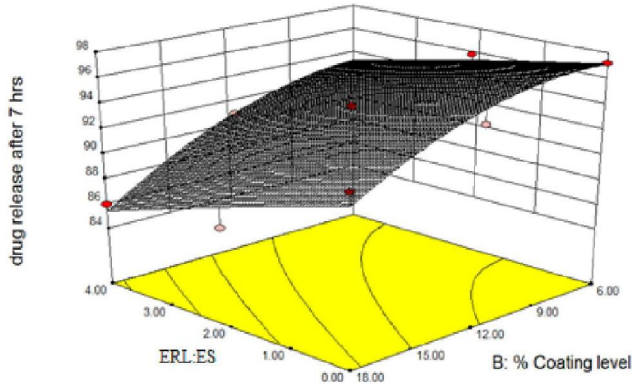

Figure 3 B : Response surface plot for Y response (% release in 7 h)

and percentage drug release after 7 h. The values of predicted and observed responses are shown in TABLE 6. The drug release profiles of different enteric coated formulations were given in Figure 2. According to the design best formulation obtained who produced desired responses. The best parameters for optimised batch are 12% coating level and 1:4 ES:ERL. By substituting X1 and X2 by the amounts of optimized formulation in equations (3) and (5), predicted responses were obtained. In order to check the validity of the optimization procedure, a new batch of pellets with the predicted levels was prepared. The result showed that the observed responses were inside the constraints and close to predicted responses, and, therefore, factorial design is valid for predicting the optimum formulation (TABLE 6).

The pellets were prepared according to optimum formulation and released no drug at pH 1.2 (0.1 N HCl), pH 7.4, and showed burst release at pH 6.8.

Drug release study

Drug release study was done with the help of USP dissolution apparatus type II. I found very little quantity of drug in 1.2 and 7.4 pH buffer in first 6 hrs but significantly drug release rise in 6.8 pH buffer after 6 hrs. This 6.8 pH is found in intestine so it will release the near about 90% quantity of montelukast sodium in

intestine. For intestinal release and after 6 hrs release, used site specific polymer (Eudragit S100) and time dependent polymer (Eudragit RL100). The release profile of drug-layered pellets at pH 1.2, 7.4, and 6.8 is shown in Figure 2(A) and (B). The drug-loaded pellets were coated with polymeric layer successively using a solvent coating technique. The polymeric layer was the water insoluble ERL and ES. The importance of this polymer layer is to protect the drug from metabolized in stomach and to deliver the drug after some lag time. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4, and 6.8 were sequentially used, referred to as sequential pH change method[15,16]. At pH 1.2 (gastric fluid) none of the formulations released their drug content up to 2 h.

Differential scanning calorimetry (DSC)

The DSC thermogram shows a sharp endothermic peak at 138.68 ^{0}C for MS (Figure 4A). While in final optimum formulation, the endothermic peak was observed at 140.45 ^{0}C (Figure 4B). Evaluation of the thermogram revealed no interaction between the polymer and drug in the formulation.

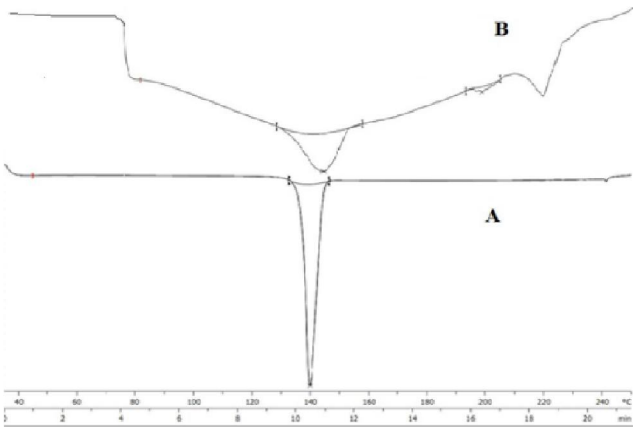

Figure 4 : DSC thermograph of montelukast sodium (A) and optimal formulation (B)

FTIR sectroscopy

IR spectrums showed no interaction between excepients and drug as drug shows all main peaks for principal functional groups (Figure 5A and 5B). Spectrum of formulation gives range at 1760 which means drug showed it contains –COOH group. Also it showed 3056 for aromatic stretching, 1651 for CN stretching etc.

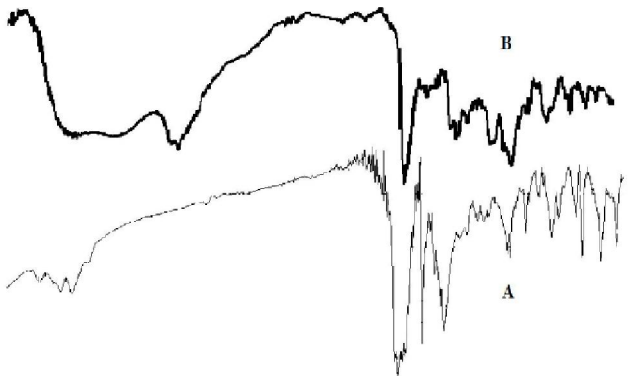

Figure 5 : FTIR graph of montelukast sodium (A) and optimized formulation (B)

Scanning electron microscopy (SEM)

Figure 6 shows SEM of optimum formulation (a) MCC pellets (30x) (b) drug layered (30×), (c) cross sectional view of drug layered pellets (120x) (d) polymer coated (30×) and (e) cross sectional view of polymer coated pellet. The surface of pellets shows smooth and uniformly coated spherical structure. Cross sectional view of drug layered pellets shows clearly distinct layers of drug coating and inner pellet material. Cross sectional view of polymer coated pellets shows dense structure as goes centre to periphery.

Stability study

Stability studies were performed as per ICH guidelines. Physicochemical parameter determine at the interval of 15, 30, 60 days are shown in TABLE 7. It was found that the pellets of optimized batch (F2) were stable even at exaggerated condition of temperature and humidity.

CONCLUSION

This study could be used to formulate multiparticulate pulsatile drug delivery system. The pulsatile delivery of drug is obtained by using polymethacrylates over a period of 4 to 8 hours. This is very beneficial for chronological conditions. The optimized formulation obtained with the help of design study programme. The structured incorporation of time and site specific polymers improves controlled and delayed drug delivery in colon. This formulation will be beneficial for allergic rhinitis and exercise induced asthma.

The ratio of Eudragit RL 100:S100 and percentage coating level affects the drug release lag time in GIT. Thus this type of formulation gives relief in asthma especially which occurs at early in morning.

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