ORIGINAL ARTICLE

Bilayer Tablet: Montelukast Sodium Nanoparticles with Sustained Release Mesalamine for Ulcerative Colitis

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Abstract

Introduction: Oral drug administration is highly preferred for its ease and patient compliance, with tablets and capsules leading the market. Bilayer tablets, composed of two layers, support targeted delivery by different layer releases at different sites and allow for easy identification. Targeted colonic drug delivery is particularly effective for conditions like ulcerative colitis, enhancing drug concentration at the site while minimizing side effects. Techniques such as ionic gelation and the use of pH-sensitive polymers like Eudragit are key to achieving controlled release, specifically in the colon. **Materials and Methods:** The montelukast sodium nanoparticles were done by implementing ionic gelation method using chitosan a biocompatible polymer, sodium tripolyphosphate as a negative inorganic compound to cross-link the chitosan and to produce nanoparticles. The prepared solution undergoes homogenization at 35,000 rpm for 5 min and sonication for 10 min and then subjected to lyophilization. The nanoparticles were evaluated for particle size, zeta potential, entrapment efficiency, and scanning electron microscopy. Dry granulation method was used to prepare another portion of bilayer tablet, mesalamine sustained release (SR) portion with the addition of polymer Eudragit L100 and S100 on the ratios of F1 (2.5:2.5), F2 (2:3), F3 (3:2), F4 (4:1) and F5 (1:4), excipients such as magnesium stearate as lubricant, talc as glidant and sodium starch glycolate as a disintegrant. After the compression of each layer sequentially (mesalamine SR and montelukast nanoparticles), bilayer tablet was formed which then evaluated for weight variation, friability, hardness, thickness, disintegration time, *in vitro* dissolution profile, and release kinetics model. **Results and Discussion:** Among five formulations of bilayer tablets, F5 (1:4) (Eudragit L100: Eudragit S100) formulation is considered as better due to its increased drug content of mesalamine was 98.12% and montelukast sodium was 96.3%, *in vitro* dissolution study of montelukast sodium followed first order kinetics with 98.7% drug release and mesalamine was 82.16% release with zero order kinetics. **Conclusion:** The single bilayer tablet proves the suitability of sustained-release mesalamine and immediate-release montelukast for a better approach in ulcerative colitis.

Key words: Bilayer tablet, chitosan, eudragit L100, eudragit S100, mesalamine, montelukast, nanoparticles, ulcerative colitis

INTRODUCTION

The oral route of drug administration is commonly used due to painless and with patient-complied.[1] The oral drug delivery market was rapidly growing at nearly 10% annually, to extend product lifecycle and address the needs of an aging population.[2] In solid dosage form, bilayer tablets, which are made of two compacted layers of granulation, have drawn interest due to their effective material utilization and ability to be uniquely identified by markings and coloring.[3] Colonic drug delivery has developed as a critical field of research, particularly for treating local diseases such as inflammatory bowel disease to provide targeted treatment, minimize negative side effects, and increase therapeutic efficacy, especially in Crohn's disease and ulcerative colitis.[4] First-line therapy for the treatment of ulcerative colitis was mesalamine (mesalazine), which exhibits anti-inflammatory properties by inhibiting cyclooxygenase enzymes and causing gastrointestinal epithelial cells to express more peroxisome proliferator-activated receptor.[5] The cysteinyl leukotrienes receptor

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antagonist montelukast used for anti-inflammatory properties in models of colitis.[6] The ionic gelation technique relies on the ionic interaction between the negatively charged groups of poly anion, such as sodium tripolyphosphate, used as cross-linking agent due to its multivalent and non-toxic properties, and the positively charged primary amino groups of polymer chitosan.[7] Furthermore, Eudragit S100 and Eudragit L100 utilized as pH-dependent coating polymers[8] and essential to release in dissolution testing for colon delivery systems.[9]

MATERIALS AND METHODS

Materials

Montelukast sodium was generously provided by Saimirra Innopharm Pvt. Ltd., Chennai. Mesalamine was sourced from Hibrow Health Care Pvt. Ltd., Chennai. The remaining ingredients were sourced from the Department of Pharmacetics, PSG College of Pharmacy, Coimbatore.

Methods

Formulation of montelukast nanoparticles

Making the chitosan solution involved precisely weighing the montelukast sodium and chitosan before transferring them into a glass beaker. 50 mL of water and 0.1 mL of acetic acid were added to this chitosan, and it was stirred overnight to produce product A. Chitosan solution. Then tri-polyphosphate was added to the distilled water, kept for 30 min to obtain product B (tri-polyphosphate solution).[10] A beaker containing the product A (chitosan solution) was kept constantly stirred. The product B (tri-polyphosphate solution) was taken in a syringe and added dropwise into the chitosan solution. Finally, montelukast sodium nanoparticles were prepared.[11]

Characterization of montelukast sodium nanoparticles

Particle size, zeta potential, polydispersity index, and scanning electron microscopy (SEM) analysis of nanoparticles were analyzed.[12,13]

Entrapment efficiency

Entrapment efficiency of the montelukast sodium in the nanoparticles was assessed using ultraviolet (UV)-visible spectrophotometry to analyze the supernatant liquid post-centrifugation.

Preparation of mesalamine sustained release (SR) granules

Preparation of mesalamine (SR) granules was prepared by the direct compression method, it follows, mixing 250 mg of mesalamine with excipients of Eudragit L100: Eudragit S100 in the different ratios such as (2.5:2.5, 4:1, 3:2, 2:3, and 1:4)[14] with the help of mortar and pestle. Blend the granules to ensure homogeneity. Add lubricant such as magnesium stearate, and talc to the homogenous mixture of blend along with the disintegrant sodium starch glycolate and coloring agent (Sudan III). Then compress the granules into a tablet using a tablet compression machine [Table 1].

Preparation of montelukast nanoparticle granules

Lyophilized powder was sieved through #72 mesh. 197 mg of montelukast sodium nanoparticles (contains montelukast 10 mg) with excipients was mixed well to ensure homogeneity [Table 2].

Preparation of bilayer tablet

Bilayer tablets of mesalamine SR granules and montelukast nanoparticles were prepared by the direct compression method.

First punching layer

Mesalamine was taken and mixed with polymers of Eudragit S-100 and Eudragit L-100, and other excipients were

Table 1: Formulation of mesalamine SR layer

S. No.	Ingredients	F1	F2	F3	F4	F5
1.	Mesalamine (mg)	250	250	250	250	250
2.	Eudragit L100: Eudragit S 100 (mg)	2.5:2.5	4:1	3:2	2:3	1:4
3.	Magnesium stearate (mg)	5	5	5	5	5
4.	Talc (mg)	4.8	4.8	4.8	4.8	4.8
5.	Sodium starch glycolate (mg)	5	5	5	5	5
6.	Sudan III (mg)	0.2	0.2	0.2	0.2	0.2

SR: Sustained release

Table 2: Formulation of montelukast nanoparticles immediate release layer

S. No.	Ingredients	F1	F2	F3	F4	F5
1.	Montelukast nanoparticles (mg)	197	197	197	197	197
2.	Starch (mg)	5	5	5	5	5
3.	Sodium starch glycolate (mg)	1	2	3	4	5
4.	Lactose (mg)	197	196	195	194	193
5.	Magnesium stearate (mg)	2.5	2.5	2.5	2.5	2.5
6.	Talc (mg)	2.5	2.5	2.5	2.5	2.5

punched to produce a tablet, which considered the first punch layer.

Second punching layer

The montelukast sodium nanoparticles, granules, and excipients were bought to the second step of punching.[15]

Evaluation of bilayer tablet

Weight variation

The prepared bilayer tablet was evaluated for weight variation by weighing 20 tablets in accordance with the IP Standard procedure.

Thickness

The tablet's thickness was measured with a vernier caliper.

Hardness

The crushing strength of 10 tablets was assessed using a digital hardness tester. A tablet hardness of approximately 5–7 kg/cm^2 is considered sufficient for mechanical stability.[16]

Friability

The friability of the tablets was assessed using a Roche friabilator.[17]

Drug content

The solution was analyzed for drug content using a UV-visible spectrophotometer at 212 nm and 289 nm for mesalamine and montelukast sodium, respectively.[18]

Disintegration test (DT)

The bilayer tablets of 12 numbers were taken for study and analyzed by DT apparatus with water as the medium at 37 ± 0.4°C.

In vitro drug release studies

The *in vitro* dissolution studies for the bilayer tablet were performed using a USP II dissolution apparatus. The dissolution medium used was 900 ml pH 1.2 buffer for the first 2 h, pH 6.8 phosphate buffer for the next 3 h, and pH 7.4 buffer for the remaining 4 h. The medium was maintained at 37 ± 0.4°C. Aliquots were withdrawn hourly, filtered, and analyzed using UV spectrophotometry.[19]

Release kinetics

To find the release pattern using the DD solver, the release kinetics of the prepared bilayer tablet were fitted into a variety of kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas. The r^2 and n-values were calculated for the linear curve for the plots.[20]

RESULTS

Formulation of montelukast nanoparticles

Nanoparticle of montelukast was prepared ionic gelation method chitosan and Tripoly phosphate (TPP).

Characterization of montelukast sodium nanoparticles

The particle size, zeta potential, and Poly dispersity index (PDI) of montelukast sodium were found to be 201 nm, 29 mV, and 0.382, respectively, as determined by Malvern Zetasizer after appropriate dispersion with water. The nanoparticles were further analyzed using SEM, which confirmed their irregular shape of particles as shown in [Figure 1].

Entrapment efficiency

The entrapment efficiency of montelukast nanoparticles was determined using a UV-visible spectrophotometer and found to be 85.6%.

Preparation of bilayer tablet

Bilayer tablets of mesalamine SR granules and montelukast nanoparticles were prepared by the direct compression method with the first punching of mesalamine and the second pinching of montelukast.

Evaluation of bilayer tablets

Weight variation, friability, hardness, thickness, drug content, and DT were mentioned in [Table 3].

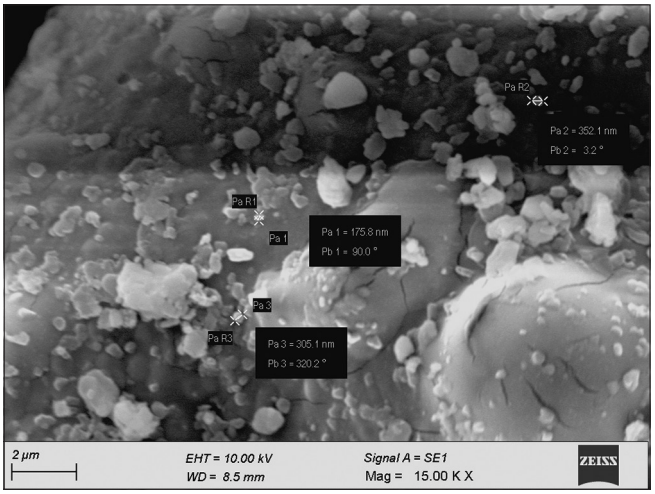

Figure 1: Scanning electron microscopy analysis of montelukast sodium nanoparticles

Table 3: Evaluation of bilayer tablets

Formulation	Weight variation (mg)#	Hardness (kg/cm²)#	Friability (%)#	Thickness (mm)#	Drug content (%)		DT (min)
					212 nm	289 nm	
F1	673.4±3.1	4±0.62	0.68	5.17±0.13	89.55	90.12	34
F2	667.4±3.1	3±0.42	0.48	5.13±0.80	87.50	95.14	32
F3	670.6±3.2	3±0.25	0.48	5.21±0.32	93.12	96.00	36
F4	673.4±3.0	4±0.34	0.22	5.12±0.17	92.88	94.70	33
F5	675.2±3.4	4±0.62	0.28	5.11±0.11	96.30	98.12	34

DT: Disintegration test. #*n*=3 ± Standard deviation

In vitro drug release studies

In vitro dissolution study of formulation F1, F2, F3, F4, and F5 performed for 9 h using pH 1.2, pH 6.8 and pH 7.4 as dissolution media and montelukast sodium almost all the formulation shows release of 70% within 2 h [Figure 2]. F5 was selected as the best formulation which showed drug release 82.16% in 9 h for mesalamine [Figure 3] due to its Eudragit S 100 effect and 98.6% in 3.5 h for montelukast sodium nanoparticles due to its increased solubility property, reduced particle size with use of sodium starch glycolate.

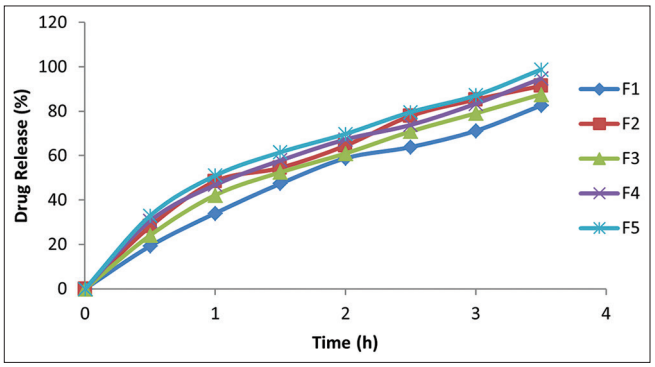

Figure 2: *In vitro* drug release of montelukast sodium

Release kinetic studies

The F5 formulation, mesalamine demonstrates a SR pattern, supported by an R^2 value of 0.9015 for zero-order kinetics, a Higuchi's plot value of 0.7501, and a Korsmeyer-Peppas *n*-value of 1.058 (*n* = higher than 1), so super Case II transport, which suggests the drug mechanism involves either relaxation or erosion characteristic of SR systems. Montelukast sodium follows first-order kinetics, with an R^2 value of 0.9838, a Higuchi's plot value of 0.9960, and a Korsmeyer-Peppas *n* = 0.542 (*n* = > 0.5 but lesser than 1), so anomalous non-Fickian transport. These findings suggest that the drug release mechanism involves both diffusion and relaxation (erosion).

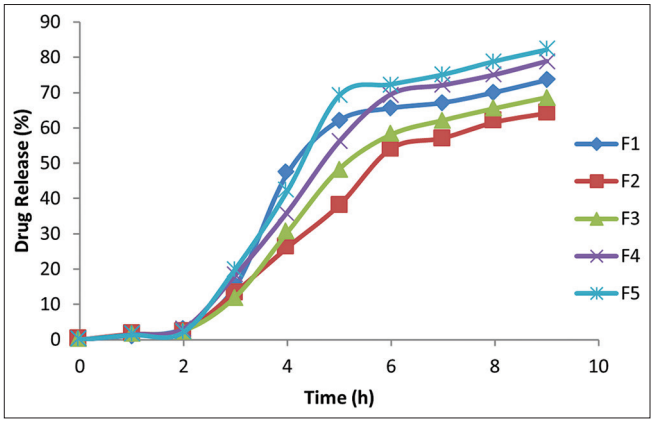

Figure 3: *In vitro* drug release of mesalamine

DISCUSSION

Montelukast sodium with a low PDI value suggests a uniform particle size distribution, while an appropriate zeta potential indicates stable nanoparticles, reducing the risk of aggregation. The formulated tablets of formulation (F1-F5) shows consistent weight ranges from 667.4 mg to 675.2 mg, with the hardness of 3–4 kg/cm². The friability was found to be below 1% which indicates that all the formulation has good physical stability. The thickness ranges from 5.11 mm to 5.21 mm, ensures uniform size of the tablet and drug content montelukast was 98.12% and mesalamine was 96.3% indicates, the drug was widely distributed in the formulation. These parameters explain that all the formulation met required pharmaceutical standards for tablet evaluation. DT and dissolution tests were pivotal in assessing the performance of the bilayer tablets. The mesalamine sustained layer does not disintegrate in acidic media, which may due to the presence of Eudragit polymers. These polymers ensuring that the tablets remain intact until they reach the intestine to release the drug in a steady state concentration. The dissolution study revealed that Formulation F5 achieved the highest mesalamine drug release, about 82.16% within 9 h when compared to all other formulations, and the release of montelukast sodium was 98.76% within 3.5 h when compared to all other formulations. The release kinetics of formulation F5 for mesalamine followed a zero-order pattern, while montelukast followed a first-order pattern based on its R^2 value. A zero-order release was ideal for SR formulation, and drug was released at a constant rate independent of its remaining concentration in the dosage form. In contrast, a first-order release corresponds to immediate release

formulations, where the drug release rate depends on its remaining drug concentration on the dosage form. In the F5 formulation, mesalamine demonstrates a SR pattern with R^2 value of 0.9035 for zero-order kinetics, a Higuchi plot value of 0.7501, and a Korsmeyer-Peppas value of 1.058, which suggests the drug mechanism involves both relaxation and erosion. Montelukast sodium follows first-order kinetics with R^2 value of 0.9838, a Higuchi plot value of 0.9960, and a Korsmeyer-Peppas "*n*" value of 0.542. These findings suggest that the drug release mechanism involves a non-swellable matrix system.

CONCLUSION

The development of the single bilayer tablet effectively integrates the benefits of both sustained and immediate drug release mechanisms for the treatment of ulcerative colitis. The SR layer, with its zero-order release profile, ensures a steady and SR of mesalamine, potentially it may enhance therapeutic efficacy and minimizing side effects associated with variable drug levels. In contrast, the immediate-release layer of montelukast sodium nanoparticles in the second layer with first-order release kinetics, provide rapid relief, addressing acute symptoms of the condition. The meticulous optimization of formulation parameters, including drug entrapment, particle size, and polymer ratios, resulted in a well-characterized bilayer tablet that meets essential quality standards. This approach may be a more effective and convenient treatment for ulcerative colitis by combining the benefits of sustained as well as immediate drug delivery in a single dosage form.

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