Research Article

Formulation and Evaluation of Sugar Free Chewable Tablets of Montelukast Sodium

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ABSTRACT

Montelukast sodium is an anti asthmatic drug which also relives symptoms of seasonal allergies. The study was aimed to formulate sugar free Montelukast sodium as chewable tablets with better pharmaceutical and therapeutic properties and making the formulation suitable for both diabetic and non diabetic patients. The tablets were prepared by direct compression method using different disintegrants (maize starch, pregelatinized starch) and superdisintegrants (sodium starch glycolate, croscarmellose sodium and crospovidone). The prepared tablets were evaluated for various parameters like general appearance, thickness, hardness, weight variation, friability, wetting time and water absorption ratio, taste evaluation, disintegration test, drug content and *in vitro* drug release. The best formulation was subjected to stability studies for three months at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH. Post compression parameters for all formulation (F-I to F-V) were found to be within the I.P limits. Formulation F-V was considered as the best formulation based on rapid disintegration time (1.10±0.01), wetting time (30±0.54sec) and *in vitro* drug release (97.29 %) at the end of 30 min. Stability study revealed formulation F-V was stable even after stored at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH for 3 months. Hence the study concludes that formulation F-V containing crospovidone as superdisintegrant was found to be the better one which satisfied all the criteria for chewable tablets.

Keywords: Chewable tablets, Crospovidone, Direct compression, Montelukast sodium.

INTRODUCTION

Chewable tablets are an immediate release (IR) oral dosage form intended to be chewed and then swallowed by the patient rather than swallowed whole. They should be designed to have a pleasant taste and be easily chewed and swallowed.[1] Chewable tablets should be safe and easy to use in a diverse patient population, pediatric, adult or elderly patient, who is unable or unwilling to swallow intact tablets due to the size of the tablet or difficulty with swallowing. Montelukast sodium is used for chronic treatment of asthma and allergic rhinitis. Pediatric, geriatric and bedridden patients show inconvenience in swallowing conventional tablets of Montelukast sodium with lesser amounts of water. Montelukast sodium is basically a tasteless drug. [2] So some patient's does not like to consume the drug orally. Hence the work was aimed to produce a drug delivery system with better pharmaceutical and therapeutic properties and making the formulation suitable for diabetic and non-diabetic patients by formulating sugar free chewable tablets.

The tablets were prepared by direct compression method using different disintegrants (maize starch, pregelatinized starch) and super disintegrants (sodium starch glycolate, croscarmellose sodium and crospovidone). Five formulations (F-I to F-V) of Montelukast sodium chewable tablets were prepared by direct compression method and evaluated for various post compression parameters.

MATERIALS AND METHODS

Materials

Montelukast sodium was obtained from MetroChem API Pvt. Ltd, Hyderabad, India. Mannitol anhydrous was procured from Shandong Tianli Pharmaceutical Co. Ltd, China. Maize starch was procured from Universal Starch Chemical Alied, Ltd., Maharashtra, India. Pregelatinized starch was procured from DFE Pharma, Cuddalore, Tamilnadu, India. Sodium starch glycolate and Croscarmellose sodium were procured from Prachin Chemicals Pvt. Ltd, Ahmedabad, India, Crospovidone from Huangshan Bonsun Pharma Pvt. Ltd., China, Neo sucralose from Nutra Sweet Company, Jaipur, Rajasthan, India, Methyl and propyl parabens from Rasula Pharmaceuticals and Fine Chemicals Pvt. Ltd., Hyderabad, India. All other chemicals and reagents used were of analytical grade.

Methods

Preformulation Studies

Preformulation can be defined as an investigation of physical and chemical properties of drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.[3]

Organoleptic properties

The organoleptic properties like color, odor and taste of the API were evaluated. A small quantity of Montelukast sodium was taken in a butter paper and the colour was

viewed in well-illuminated place. Very less quantity of Montelukast sodium was used to assess the taste with the help of tongue as well as smelled to get odor.

Solubility test

Solubility of Montelukast sodium in water, methanol and ethanol was determined by using sonicator at room temperature. [4]

FT-IR studies

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture of drug and excipients in highest concentration was prepared and mixed with suitable quantity of potassium bromide.[5] Samples were compressed to form a transparent pellet using a hydraulic press at 10 tons pressure and scanned between 4000- 400 cm-1 in a Shimadzu FT-IR (IR Affinity-1) spectrophotometer.

Precompression Parameters

The prepared powder blend was evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The angle of repose was determined by fixed funnel method to assess the flow property.[6] Bulk density is the ratio between a given mass of the powder or granules and its bulk volume. Tapped density is the ratio between a given mass of powder or granules and the constant or fixed volume of powder or granules after tapping. Bulk and tapped density were determined using digital bulk density apparatus.[7] The compressibility index and the Hausner ratio are determined by measuring both the bulk volume and tapped volume of the powder.[8]

$$\text{Compressibility index (\%)} = \frac{\text{TD-BD}}{\text{TD}} \times 100$$

Where, TD = Tapped density, BD = Bulk density

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Formulation of Montelukast Sodium Chewable Tablets [9]

Five formulations (F-I to F-V) of Montelukast sodium chewable tablets were prepared by direct compression method as per the composition shown in Table 1.

Direct compression method

The active ingredient was passed through the sieve # 40. The other ingredients given in the formulation table were passed separately through the same sieve. All the materials (including the active ingredient) were weighed and taken in a poly bag and mixed for 10 minutes. The magnesium stearate was passed through the sieve # 60 and mixed together with the powder mixture in a polybag for 5 minutes to get a uniform blend. Finally, the powder mixture was compressed into tablets using rotary tablet compression machine of punch size 7.14mm to prepare tablets each weighing 150mg.

Table 1: Composition of Montelukast sodium Chewable Tablets

Ingredients	Quantity per Tablet (mg)				
	Formulation Code				
	F-I	F-II	F-III	F-IV	F-V
Montelukast sodium	5.00	5.00	5.00	5.00	5.00
Mannitol anhydrous	124.20	124.20	124.20	124.20	124.20
Maize starch	15.00	-	-	-	-
Pregelatinized starch	-	15.00	-	-	-
Sodium starch glycolate	-	-	15.00	-	-
Croscarmellose sodium	-	-	-	15.00	-
Crospovidone	-	-	-	-	15.00
Neo sucralose	1.50	1.50	1.50	1.50	1.50
Strawberry powder flavor	0.80	0.80	0.80	0.80	0.80
Iron oxide red	0.20	0.20	0.20	0.20	0.20
Methylparaben	1.50	1.50	1.50	1.50	1.50
Propylparaben	0.30	0.30	0.30	0.30	0.30
Magnesium stearate	1.50	1.50	1.50	1.50	1.50
Weight of each tablet(mg)	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**

Post Compression Parameters

The prepared Montelukast sodium chewable tablets were evaluated for various parameters such as General appearance, Thickness, Hardness, Weight variation, Friability, Disintegration time, Taste evaluation, Wetting time, Water absorption ratio, Assay, *In vitro* drug release studies and Stability studies.

General appearance

The tablets should be free from cracks, depressions, pinholes etc. The surface of the tablets should be smooth.

The tablets were examined externally under a biconvex lens for surface cracks, depressions and pinholes.[10]

Thickness and hardness test

Thickness of the tablet was measured by using vernier caliper. Thickness values were expressed in millimeter. Hardness (diametric crushing strength) is the force required to break a tablet across the diameter. The hardness of tablets was determined using a Monsanto hardness tester. The tablet is placed across the diameter in between the spindle and anvil. The knob is adjusted to hold the tablet in position. The pressure is increased slowly to break the tablet.[10] The value was expressed in Kg/cm^2.

Weight variation test

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. Not more than two of the tablets weight should deviate from the average weight by more than the percentage deviation and none should deviate from the average weight by more than twice that percentage deviation(±7.5%).[10]

Percentage deviation of the tablets were calculated by using the following formula

Percentage deviation =

$$\frac{\text{(Weight of tablet (mg)} - \text{Average weight of tablet (mg)}}{\text{Average weight of tablet (mg)}} \times 100$$

Friability

Friability is tested by using Roche friabilator. Friabilator is made up of a plastic drum fixed with a machine which rotates at 25 rpm for 100 revolutions. Tablet falls from 6 inches height in each turn within the apparatus.[11] The percentage friability of the tablets were calculated by the formula.

$$\text{Percentage Friability} = W1 - W2/W1 \times 100$$

Where,

W1 = Weight of tablets before testing, W2 = Weight of tablets after testing.

Taste evaluation (sensory evaluation)[12]

The taste evaluation was done by taste panelist. The method chosen was ranking test and for this purpose 10 human volunteer was selected. The dispersion of pure drug and trial formulations were given to the panelists. The intensity of bitterness was asked from panelists.

Disintegration time [13]

Place 1 tablet in each of these six tubes of the basket and one disk was added to each tube. Operate the disintegration apparatus using 900 ml of distilled water at $37^0 \pm 2^0$C. The time taken in seconds for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

Wetting time and water absorption ratio[14]

A piece of tissue paper folded twice was placed in a small petridish (internal diameter =6.5cm) containing 6 ml of water. A preweighed tablet was placed on the surface of the paper and the time required for complete wetting was then measured.The time required for the water to reach upper surface of the tablet was noted as the wetting time. The water absorption ratio (R) was determined using the following equation.

$$R = \frac{Wa - Wb}{Wb} \times 100$$

Where,

Wa - Weight of tablet before wetting, Wb-Weight of tablet after wetting.

Assay of montelukast sodium by HPLC method [15]

Chromatographic conditions

Column	:	Stainless steel column 15 cm × 4.6 mm.
Mobile phase	:	22ml buffer solution, 78 ml Methanol.
Buffer	:	Dissolve 3.85gm of ammonium acetate in 1000 ml of water and add 1ml of triethylamine. Adjust the pH to 5.5 with glacial acetic acid.
Flow rate	:	1.5 ml per minute.
Injection volume	:	10µl.
Wave length	:	240 nm.
Temperature	:	40°C.

Preparation of standard solution

0.005% w/v solution of Montelukast reference standard in methanol.

Preparation of sample solution

20 tablets were weighed and powdered. The powder equivalent to 50mg of Montelukast was dissolved in methanol. 1.0 ml of this solution was diluted to 10 ml with methanol.

Sample injection procedure

10 µl of filtered sample solution and standard solution were separately injected into HPLC system. The chromatogram was recorded and responses were measured for major peaks. The content of Montelukast in the powder mixture was calculated by using the following equation,

Content of Montelukast sodium =

$$\frac{Samplearea}{Standardarea} \times \frac{Standardweight}{Sampleweight} \times \frac{P}{100} \times Avg.Wt$$

Where,

P = Purity of Montelukast sodium, Avg. Wt = Average weight in mg

In vitro dissolution studies [16]

The *in-vitro* dissolution studies of Montelukast sodium chewable tablets were performed using dissolution apparatus USP Type II (paddle). The volume of dissolution medium (distilled water with 0.5% SLS solution) used was 900ml and the temperature was maintained at 37±0.5˚C. The speed of the paddle was set at 50rpm. One tablet was placed in each jar of dissolution apparatus. 5ml of sample from each jar was withdrawn at every 5 minutes interval upto 30 minutes and same volume of dissolution medium was replaced to each dissolution jar, so that volume of dissolution medium was maintained to 900ml. The sample was filtered and diluted with dissolution medium and the amount of Montelukast sodium released from chewable tablets was determined spectrophotometrically at 350nm using distilled water with 0.5% SLS as blank.

Stability studies [17]

Stability studies were carried out for optimized formulation (F-V) at 25±2°C/60C±5%RH and 40±2°C/75%±5%RH for 3 months. The selected clear ALU-ALU packed formulations were stored at 25±2°C/60C±5%RH and 40±2°C/75%±5%RH for 3 months and their physical appearance, average weight, thickness, hardness, friability, disintegration test, assay and *in vitro* drug release were evaluated at specified intervals of time (every month).

RESULTS AND DISCUSSION

Preformulation studies

The color of Montelukast sodium was found to be off white to pale yellow, no characteristic odor and no characteristic taste was observed in the study. Montelukast sodium showed similar color, odor and taste as per I.P specification. The solubility analysis of drug indicates that Montelukast sodium is soluble in water, freely soluble in ethanol, methanol and practically insoluble in organic solvent like acetonitrile. FT- IR spectral studies indicated that the drug is compatible with all the excipients. The FT- IR spectrum of physical mixture showed all the characteristic peaks of Montelukast sodium, thus conforming that no interaction of drug occurred with the components of formulation.

Precompression parameters

The angle of repose of all formulations were found between 25^0.60' to 29^0.30' that is well within the specification limit of 25^0- 29^0 which indicates the flow type of powder blend was excellent. Formulation F-V showed better flow property. The bulk density was found between 0.292 to 0.309 g/cm^3, tapped density was found between 0.342 to 0.367 g/cm^3. Compressibility index was found in the range of 15.4 to 16.3% which indicates the flow type of powder blend was fair. Hausner's ratio ranges between 1.17to 1.19. The above results in terms of precompression parameters revealed that the flow property of all formulation was excellent and within the acceptable limit.

Postcompression parameters

The general appearance of all formulations (F-I to F-V) were examined. The color of the tablets was found to be brick red and round shape. The surface was found to be smooth with no cracks, depressions and pinholes.

The thickness of tablets was measured and were found in the range between 3.20±0.032 mm to 3.22±0.032 mm. All the formulation possessed uniform thickness. The hardness of the tablet were found in the range between 6.05±0.21 kg/cm^2 to 6.65±0.17 kg/cm^2. The prepared tablets possessed good mechanical strength with sufficient hardness. The thickness and hardness of marketed sample was found to be 2.81±0.16 mm and 7.00±0.1 kg/cm^2 respectively. All formulations of Montelukast sodium chewable tablets passed the weight variation test since the values are within the acceptable variation limit (±7.5%) of the tablet. Similarly percentage friability values of the prepared Montelukast sodium chewable tablets showed less than 1% weight loss that is highly within the acceptable limit. Hence all the tablets passed the friability test. Montelukast sodium chewable tablets were evaluated for various parameters and the results are given in Table 2.

Disintegration time of Montelukast sodium chewable tablets were found between 1.10±0.01 to 5.21±0.015 minutes. Specification limit of disintegration time for uncoated tablet from I.P is NMT 15 minutes. Disintegration time of all formulations were found within the time as specified in the I.P and hence passed the disintegration test. The disintegration time of formulation-V containing crospovidone showed rapid disintegration (1.10±0.01 min) compared with other formulations. Tasteless of the drug was changed in all formulations by using sugar free sweetening agent. All the formulations possessed sweet taste. The content of Montelukast sodium in the chewable tablets were found in the range between 100.53 to 102.08%. The acceptable limit of Montelukast content as per I.P is 90 to 110%. The results revealed that the content of Montelukast sodium was within the acceptable limits in all the formulations. Wetting time of all formulations were found between 30 to 73 seconds. Formulation V containing crospovidone as superdisintegrant showed least wetting time (30 sec). Water absorption ratio of all formulations were found between 70% to 96%. Montelukast sodium release was studied in 0.5% SLS solution for upto 30 minutes. The drug release of formulation F-I, F-II was found to be 67.07±0.45% and 72.66±0.98% at 30 minutes. The drug release of formulation F-III, F-IV and F-V was found to be 89.15±0.01%, 90.13±0.99% and 97.29±0.99% respectively. The acceptable *in vitro* dissolution limit for Montelukast sodium as per IP is NLT 80% of drug release at 30 minutes. Formulations F-III, F-IV and F-V passed the *in vitro* drug release studies.

Table 2: Evaluation of Montelukast sodium Chewable Tablets

Formulation code	Thickness (mm)	Hardness (kg /cm^2)	Weight variation (mg)	Friability (%)
F-I	3.22±0.018	6.05±0.21	153.60±1.82	0.011±0.006
F-II	3.20±0.032	6.42±0.14	149.20±1.59	0.012±0.008
F-III	3.21±0.027	6.20±0.56	155.10±1.42	0.012±0.004
F-IV	3.20±0.041	6.65±0.17	151.90±1.78	0.014±0.009
F-V	3.22±0.032	6.15±0.56	150.80±1.29	0.013±0.012
Marketed sample	2.81±0.16	7.00±0.1	153.01±2.32	0.012±0.05

All the values are expressed as mean ± SD, n=3

Table 3: Postcompression Parameters

Formulation Code	Disintegration test (min)	Wetting time (Sec)	Water absorption ratio (%)	Drug content (%)	In vitro drug release at the end of 30 min (%)
F-I	5.21±0.015	73±0.57	70.18±0.57	100.70±1.50	67.07±0.45
F-II	5.07±0.064	70±0.57	86.88±0.56	100.53±1.45	72.66±0.98
F-III	4.39±0.005	65±0.41	90.80±0.59	100.89±2.86	89.15±0.01
F-IV	3.23±0.057	49±.53	93.2±0.57	101.52±1.24	90.13±0.99
F-V	1.10±0.01	30±0.54	96.80±0.58	102.08±1.45	97.29±0.99
Marketed sample	2.42±0.025	39±0.43	92.14±0.57	100.70±1.50	88.01±0.83

All the values are expressed as mean ± SD, n=3

Among the three formulations, formulation F-V containing crospovidone as superdisintegrant showed highest dissolution rates at the end of 30 minutes. They may be due to easy swelling ability and wicking capacity of crospovidone when compared to other disintegrants. The order of enhancement of the dissolution rate with various disintegrants and superdisintegrants was found to be crospovidone > croscarmellose sodium > sodium starch glycolate > pregelatinized starch > maize starch. Montelukast sodium chewable tablets were evaluated for various parameters and the results are given in Table 3. The dissolution profiles of Montelukast sodium chewable tablets were shown in Fig 1.

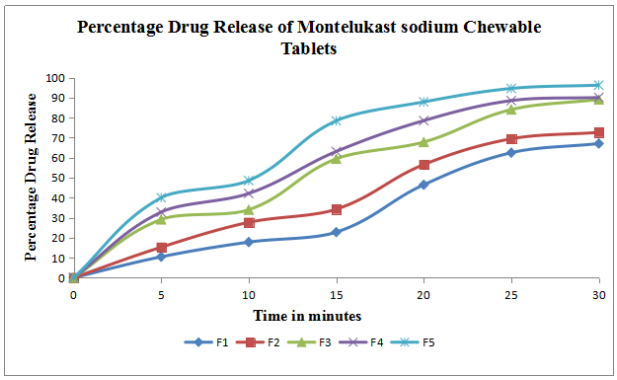

Fig 1: *In Vitro* Drug Release Profiles of Montelukast sodium Chewable Tablets

Formulation F-V containing crospovidone as superdisintegrant was taken as optimized formulation based on rapid disintegration time (1.10 min), wetting time (30 sec) and *in vitro* dissolution profiles (97.29 %) at the end of 30 min. The dissolution profile of optimized formulation (F-V) was compared with marketed Montelukast sodium chewable tablet. The percentage drug release of marketed sample and optimized formulation (F-V) was found to be 88.01±0.83 % and 97.29 ±0.99 % at 30 minutes. The drug release of optimized formulation of Montelukast sodium chewable tablets was found to be greater than that of marketed product. The comparative drug release profiles are shown in Table 4 and fig 2.

Table 4: Comparative *In Vitro* Release Data of Montelukast sodium Marketed Tablet and Optimized Formulation (F-V)

Time (min.)	Percentage Drug Release (%)	
	Formulation F-V	Marketed tablet
5	39.99±0.56	30.09±0.11
10	48.55±0.59	43.30±0.55
15	78.45±0.64	59.47±0.90
20	87.92±0.88	68.33±1.01
25	94.65±1.00	77.57±0.62
30	97.29±0.99	88.01±0.83

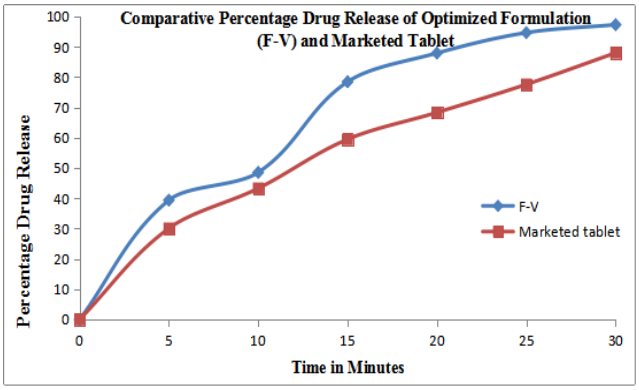

Figure 2: Comparative *In Vitro* Drug Release Profiles of Montelukast sodium Marketed Tablet and Optimized Formulation (F-V)

Stability results revealed that there were no significant changes found in physical appearance, weight, thickness, hardness, friability, disintegration time, drug content and *in vitro* drug release during the period of 3 months even after stored at 25±2°C/ 60%±5%RH and 40±2°C/ 75%±5%RH. Stability study revealed formulation F-V was stable even after stored at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH for 3 months.

CONCLUSION

From this study, the overall results revealed that the formulation F-V containing crospovidone as superdisintegrant was found to be better one which satisfied all the criteria for chewable tablets and also showed better drug release than marketed tablet. The work concludes that Montelukast sodium chewable tablets could be successfully formulated by direct compression method using crospovidone as superdisintegrant which may improve the patient compliance, convenience in administration, therapeutic efficiency, better mouth feel making the formulation suitable for geriatric, bed ridden, diabetic and non diabetic patients.

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