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Research Article

PREPARATION AND EVALUATION OF MONTELUKAST ORAL DISPERSIBLE TABLETS BY DIRECT COMPRESSION METHOD

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ABSTRACT
The purpose of this research was to develop oral dispersible tablets of montelukast sodium. Montelukast sodium is most commonly used in treatment of Asthma. Oral dispersible tablets were prepared by using a direct compression method employing superdisintegrants such as low substituted hydroxyl propyl cellulose, crospovidone, croscarmellose sodium, and sodium starch glycolate. Tablets were evaluated for weight variation, thickness, hardness, friability, drug content, *in vitro* disintegration time, and drug release. Other parameters such as wetting time and drug-excipient compatibility were also evaluated. The tablets' hardness was maintained in the range of 3-4 kg and friability was <1% for all formulations. All tablet formulations disintegrated rapidly *in vitro* within 10 to 30sec. Release of drug was faster from formulations containing 7.5% crospovidone (MF11) compared to the marketed tablets. Kinetic studies indicated that all the formulations followed first order release with diffusion mechanism. Finally, it can be reasonably expected that the obtained drug dissolution rate improvement will result in an increase of its bioavailability, with the possibility of reducing drug dosage and side effects.
KEY WORDS: Montelukast sodium, super disintegrants, precompression properties and evaluation of tablets and fast dissolving tablets

INTRODUCTION

Fast disintegrating solid dosage forms have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry because of the advantages of easy administration to patients who have difficulty swallowing, more rapid drug absorption, patient convenience, and improved patient compliance[1,2]. The popularity and usefulness of the formulation resulted in the development of several related technologies and processes such as freeze drying, tablet moulding, direct compression, spray drying, rotary process and sublimation method[3,4].

Direct compression represents a simple and cost effective tablet manufacturing technique. Use of conventional equipment, commonly available excipients and limited number of processing steps are the advantages of this technique. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agents[5]. The commonly used superdisintegrants are croscarmellose sodium, crospovidone and sodium starch glycolate. In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution.

The key properties of fast disintegrating tablets (FDTs) are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires not only that excipients should have high wettability, but also that the tablet structure should have a highly porous network [3].

Montelukast sodium[6] is a leukotriene receptor antagonist (LTRA) used in maintenance treatment of asthma and to relieve symptoms of seasonal allergies and its bioavailability is 63%[7]. It is usually administered orally. It has extensive first-pass metabolism and show a very poor dissolution rates in order to overcome this problem preparation of oral dispersable tablets.

The main goal of the present investigation was to develop mountelkast oral dispersible tablets consisting of sodium starch glycolate, crospovidone, croscarmellose sodium and L-hydroxy propyl cellulose by using direct compression technique.

MATERIALS AND METHODS

Montelukast sodium was received as a gift sample from Hetero Drugs, Hyderabad India. Sodium starch glycolate, L-hydroxyl propyl cellulose croscarmellose sodium and crospovidone was obtained as gift sample from Signet Chemicals Mumbai. All other materials like, mannitol, microcrystalline cellulose, magnesium stearate, talc used was of analytical grade and procured from commercial sources.

Compatibility Studies

The compatibility of drug in the formulation was confirmed by IR spectra of pure drug and formulations were determined between 4500-450cm^{-1} using Shimadzu 160a, Kyoto, Japan by KBr Disc method.

Formulation of Oral Disintegrating Tablets of Montelukast sodium

Montelukast sodium tablets were prepared by direct compression method according formula given in table I. The drug along with the excipients was taken and observed for any aggregates or lumps which were then triturated and passed through sieve number 40. Then finally lubricants and glidants are passed through the same sieve in to the powder mass. This powder mass was then loaded in to a blender for obtaining a uniform powder blend. The mixture blends of all the formulation were subjected for pre-compression parameter[8] like bulk density, tapped density, angle of repose, compressibility index and hausner ratio. The tablets were compressed using 6.2 mm flat punch to get a tablets of 100 mg weight using MT Rimek 12 station compression machine.

Evaluation of tablets

Weight Variation

Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight. None of the tablets deviated from the average weight by more than ±5% [9].

% Weight variation = [(Average weight - Individual weight) / Average weight]*100

Friability

The friability of ten tablets was determined using Roche friabilator at 25 rpm for 4 minutes. The tests were carried out in triplicate. The friability was expressed in terms of weight loss and was calculated as the percentage (% ± SD) of the initial weight according to the following equation:

$f = W_0 - W_t / W_0 \times 100\%$

where f = friability, W_0= initial weight of tablets before the tests, and Wt = tablets weight after the tests.

% Friability of Tablets less than 1% are considered acceptable[10].

Thickness

The thickness were measured by using vernier calliper and values were tabulated. Three tablets of each batch were measured.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shock while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the same tablets from each formulation was determined. The mean and standard deviation values were also calculated[11].

Drug Content

Twenty tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 10 mg of Montelukast sodium was transferred into a 100 ml standard flask and volume made up with 0.5% Sodium lauryl sulphate and absorbance of the resulting solution was observed at 240 nm.

***In-vitro* Disintegration time**

The disintegration time was measured using disintegration test apparatus. Place one tablet in each of the 6 tubes of the basket and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37°±1°C as the immersion liquid. The assembly should be raised and lowered between 100 cycles per minute. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

Wetting Time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. The wetting time was measured by a modification of the described procedure by Rawas-Qalaji et al[12]. The tablet was placed at the center of two layers of absorbent paper fitted into a rounded plastic dish with a diameter of 12 cm. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded.

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6 mL of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R, was determined using following equation[13]

R= Wa - Wb / Wb × 100

Where, Wa= weight of tablet after absorption, Wb= Initial weight of the tablet.

***Invitro* Dissolution Studies**

The dissolution rate of montelukast sodium from the oral dispersable tablet was studied in 900ml of water containing 0.5% sodium laurlyl sulphate using Electrolab TDT-08L USP dissolution test apparatus with paddle stirrer at 50 rpm. A temperature of 37°C $\pm$ 0.5°C was maintained throughout the study. One tablet containing 10 mg of montelukast sodium was used in each test. Samples of dissolution media (5 ml) were withdrawn at time interval 2, 5, 10, 20, 30, 40, 50 and 60 min, and assayed for montelukast sodium at 240nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh dissolution fluid. The dissolution experiments were conducted in triplicate.

Similarity factor

Several methods are available for the comparative analysis of dissolution profile. A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles[14]. The difference factor (f_1) calculates the percent difference between the two curves at each time point and is a measure of the relative error between the two curves:

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100$$

where n is the number of time points, R_t is the dissolution value of the reference t batch at time t, and T_t is the dissolution value of the test batch t at time t.

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measure of the similarity in the percent dissolution between the two curves.

$$f_2 = 50 \times \log\left\{ \sqrt{\left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]} \times 100 \right\}$$

The specific procedure to determine difference and similarity factors is as follows (FDA). The dissolution profiles of the two products, the test product and reference products should be determined. Using the mean dissolution values from both curves at each time interval, calculate the difference factor (f_1) and the similarity factor (f_2) using above two equations. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves and thus, of the performance of the test and reference products. This model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. As further suggestions for the general approach, the following recommendations should also be considered: The dissolution measurements of the selected and market formulation should be made under exactly the same conditions and same time interval like 2, 5 and 10 min.

Stability studies

The optimized formulation (MF11) was wrapped in aluminum foils and kept in petri dish at 40±2°C/75±2% RH and analyzed for disintegration time, wetting time and *in-vitro* dissolutions study for a period of three months.

RESULTS AND DISCUSSION

In the present study montelukast sodium oral dispersible tablets were prepared by using croscarmellose sodium, crospovidone, l- hydroxypropyl cellulose and sodium starch glycolate as a disintegrants. FT-IR studies of montelukast sodium absorption bands at 3420 cm^{-1} sodium starch glycolate containing tablet formulations, absorption bands at 3380 cm^{-1} L-hydroxy propyl cellulose having tablet

formulations, absorption bands at 3400 cm^{-1} and cross povidone containing tablet formulations, absorption bands at 3370 cm^{-1} indicates OH group. Hence there was no chemical and physical interactions between drug and excipients showed in Figure.1. The values of pre-compression parameters evaluated were within prescribed limit and indicated good free flowing property as showed in table.2. Bulk density was found in the range 0.28 to 0.35 g/sqcm and tapped density in the range of 0.34 to 0.40 g/sqcm. Using these two density factors hausner`s ratio and compressibility index were calculated. The powder blend of all formulations had hausner`s ratio less than 1.21 which indicates better flow property and compressibility index between 18.18 to 20.16 which indicates good flowability property. The flowability property of the powder blend was also evidenced with angle of repose between 28.4^0 to 33.3^0 which is below 40^0 indicating good flow ability. Hardness, friability, weight variation, *in-vitro* wetting time and *in-vitro* disintegration time are shown in table 3. The hardness was found to be in the range of 3.4 to 5kg/cm^2 for all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations the friability values are less than 1% and meet the IP limits. All the tablets passed weight variation test as the percentage weight variation was within the pharmacopoeial limits. The percentages drug contents of all the tablets were found to be between 93.1 to 99.3 of which was within the acceptable limits. The results of *in-vitro* wetting time and *in-vitro* disintegration time of all the tablets were found to be within the prescribe limits and satisfy the criteria of oral dispersible tablets. The *in-vitro* wetting time was found to be in the range of 13 to 40 seconds while the *in-vitro* disintegration time was founds in the range of 8 to 40 seconds respectively. It was observed that when croscarmellose sodium is used as disintegrant, the tablets disintegrates rapidly within less time due to easy swelling ability of croscarmellose sodium when compared to other tablets prepared by using crospovidone and sodium starch glycolate. Among the formulation of tablets the batch containing croscarmellose sodium 7.5% was found to be the best as compare to other formulations as this formulation showed good hardness, good friability and wetting time (21sec) and disintegration time of (12.5sec), which is an ideal characteristic of an dispersible type tablet . The cumulative percentage of the drug released for formulation MF-11 found by the dissolution studies shows the better drug release of 98% within 10 min indicates good bioavailability of the drug from these formulations. The dissolution data of montelukast sodium tablets are given in Table 4 and Figure 2. Croscarmellose sodium 7.5% when comes in contact with water gets inflated immediately burst out there by releasing the drug in the short duration of time. Similarity factor 'f_2' (85.3) and dissimilarity factor 'f_1'(2.1) between dissolution profiles of the rapidly disintegrating tablet formulation MF11 and the marketed formulation indicated that the two dissolution profiles were similar. The selected formulation showed no significant variations for the in-vitro disintegration time, wetting time and *invitro* drug release pattern above mentioned parameters and it was stable for the specified time period.

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Table-1 FORMUALTION COMPOSITION OF MONTELUKAST SODIUM ORAL DISPERSIBLE TABLETS

Ingredients(mg)	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9	MF10	MF11	MF12
Montelukast sodium	10	10	10	10	10	10	10	10	10	10	10	10
Sodium starch glycolate	5	7.5	12.5	-	-	-	-	-	-	-	-	-
L-hydroxy propyl cellulose	-	-	-	5	7.5	12.5	-	-	-	-	-	-
Cross povidone	-	-	-	-	-	-	5	7.5	12.5	-	-	-
Crosscarmellose sodium	-	-	-	-	-	-	-	-	-	5	7.5	12.5
Orange flavour	1	1	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Micro crystalline cellulose	79.5	77	72	79.5	77	72	79.5	77	72	79.5	77	72
Total weight (mg)	100	100	100	100	100	100	100	100	100	100	100	100

Table-2 PRE-COMPRESSION PARAMETERS OF MONTELUKAST SODIUM (Mean±SD n=3)

Formulations	Bulk density	Tapped density	Carr"s index	Angle of repose^0	Hausneers ratio
MF-1	7.6±0.1	6.3±0.1	19.3±0.82	28.4±.005	1.19±.008
MF-2	8.0±0.1	6.7±0.2	18.8±0.79	28.4±.005	1.18±.007
MF-3	7.7±0.2	6.5±0.3	18.8±.979	32.4±.004	1.18±.009
MF-4	7.6±0.1	6.4±0.1	18.7±1.71	30.0±.005	1.18±.017
MF-5	8.7±0.3	7.2±0.2	21.3±1.85	31.7±.006	1.21±.018
MF-6	7.6±0.1	6.2±0.3	21.2±0.83	33.3±.004	1.21±.008
MF-7	8.1±0.7	6.7±0.4	20.3±1.02	29.1±.009	1.20±.010
MF-8	8.7±0.1	7.2±0.2	19.7±1.67	29.7±.005	1.19±.016
MF-9	8.0±0.4	6.7±0.1	19.3±0.16	31.8±.005	1.19±.006
MF-10	7.4±0.3	6.2±0.1	20.4±2.78	32.4±.004	1.20±.027
MF-11	7.0±0.2	5.9±0.1	19.1±2.12	29.7±.006	1.19±.021
MF-12	7.4±0.1	6.1±0.1	21.3±3.17	32.3±.004	1.21±.031

Table-3 EVALUATION OF MONTELUKAST SODIUM ORAL DISPERSIBLE TABLETS CONTAINING SUPERDISINTEGRANTS (Mean±SD n=3)

Formulations	Weight variation (mg)	Thickness in (mm)	Hardness	Friability % w/w	Drug content	Wetting time (sec)	Water absorption ratio	Disintegration Time(sec)
MF1	99.1±1.0	2.8±0.1	3.7±0.2	0.35±.005	88.1±0.1	40.2±5.5	153.8±1.2	40.1±0.4
MF2	99.3±1.5	3.1±0.2	3.9±0.1	0.92±.004	97.0±0.1	38.3±3.0	171.1±1.5	22.3±1.2
MF3	97.3±2.1	3.2±0.2	3.8±0.1	0.63±.005	94.1±0.1	32.8±2.5	140.5±2.0	25.2±1.5
MF4	101.1±1.5	3.1±0.1	3.4±0.3	0.60±.005	99.2±0.1	33.4±2.0	201.1±1.5	28.2±1.5
MF5	98.4±1.2	3.0±0.1	3.8±0.1	0.33±.002	97.1±0.1	32.5±2.5	163.3±1.0	23.7±2.0
MF6	100.1±1.0	3.1±0.2	3.5±0.2	0.96±.006	91.3±.0.2	29.6±1.8	197.1±1.1	17.5±1.8
MF7	98.7±2.5	3.1±0.1	3.8±0.1	0.64±.004	93.2±0.1	36.7±1.2	155.7±0.9	27.1±2.5
MF8	100.1±3.2	3.0±0.1	3.6±0.2	0.31±.005	94.3±0.1	29.4±2.0	163.6±1.3	19.1±1.8
MF9	99.8±2.0	3.0±0.1	3.8±0.1	0.65±.004	85.6±0.2	23.5±1.2	184.8±0.8	18.8±1.5
MF10	99.3±1.5	2.8±0.3	3.8±0.1	0.34±.003	86.3±0.1	38.4±3.0	147.1±1.7	15.7±1.8
MF11	99.9±1.0	3.0±0.1	3.3±0.3	0.63±.003	98.3±0.1	21.4±2.1	200.2±1.6	12.5±2.2
MF12	97.4±2.5	2.9±0.1	3.8±0.1	0.63±.004	94.6±0.1	26.5±2.1	198.2±1.0	20.5±3.0

Table-4 DISSOLUTION PARAMETERS OF MONTELUKAST SODIUM ORAL DISPERSIBLE TABLETS

Formulations	k^{-1}	t ½	r	DP_{10}
MF1	0.09	7.5	0.929	66.7±5.0
MF2	0.05	11.5	0.977	83.1±2.1
MF3	0.09	7.0	0.959	88.5±6.0
MF4	0.09	7.2	0.974	86.3±1.1
MF5	0.11	5.8	0.962	87.7±1.3
MF6	0.07	8.8	0.852	86.7±3.3
MF7	0.07	9.7	0.967	67.5±0.9
MF8	0.10	6.8	0.925	76.3±2.4
MF9	0.06	10.0	0.778	82.7±1.2
MF10	0.04	14.3	0.724	85.9±2.8
MF11	0.12	5.6	0.822	98.0±1.4
MF12	0.07	9.7	0.793	89.5±2.2
Marketed formulation	0.11	6.0	0.822	95.9±1.4

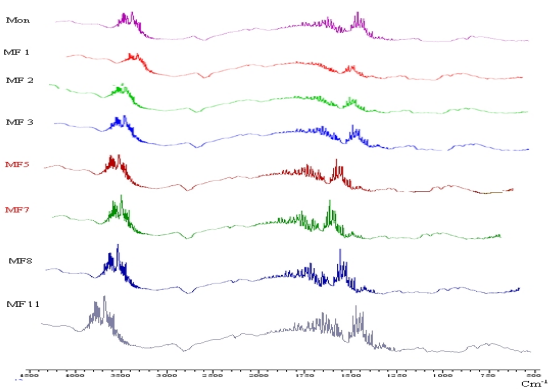

Figure-1 FT-IR Spectra of montelukast and its oral dispersible tablets

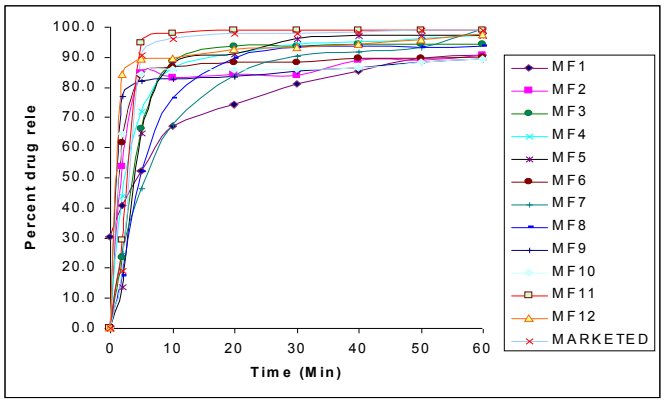

Figure-2 Dissolution profiles of montelukast oral dispersible tablets