ORIGINAL ARTICLE

Formulation and Evaluation of Wax Matrix Fast Dissolving Mini-tablets of Montelukast Sodium

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Abstract

Aim: To prepare montelukast sodium mini-tablets that have sweet taste and dissolve quickly, using wax type matrix forming agents such as carnauba wax, rice bran wax, glyceryl monostearate, and polyethylene glycol 4000. **Materials and Methods:** Mini-tablets were prepared by direct compression technique after the blends of wax matrix formers and drug with other excipients was evaluated for characteristics such as flow properties. The tablets were evaluated for parameters such as thickness, hardness, friability, disintegration time, dissolution time, and mouthfeel. **Results and Discussion:** The blends of waxes showed satisfactory properties of flow and were directly compressed to tablets with desirable physical properties. The tablets disintegrated within 2 min and had an acceptable mouthfeel. **Conclusion:** The wax matrix substances can be successfully used for the formulation of mini-tablets with a pleasant taste and mouthfeel.

Key words: Wax matrix, fast dissolving tablets, mini-tablets, montelukast sodium, rice bran wax

INTRODUCTION

Oral solid unit dosage forms such as tablets and capsules are difficult to swallow and require the aid of liquid-like water for swallowing. They sometimes are unpleasant in odor and taste. While catering to patients such as elderly, children, mentally retarded, nauseated, and are more comfortable if the dosage form can be taken without water. Hence, a tablet that has pleasant taste and dissolves in mouth rapidly even if water is not taken concomitantly is becoming more popular.[1-7]

Mini-tablets are multiple unit dosage forms developed to retain advantages of formulations such as pellets that include uniformity of drug release, less tendency of dose dumping, greater patience compliance. However, mini-tablets score more advantages such as improved mechanical strength, more dose loading capacity, and uniformity of size and shape. Mini-tablets have a diameter in the range of 2 mm and can be presented filled in capsules such as pellets or separately which serves an advantage of dose variation with the age and clinical condition of the patient.[8]

Montelukast sodium, a leukotriene receptor antagonist, blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor CysLT1 in lungs and bronchial tubes to decrease bronchoconstriction and inflammation. It is used in treatment of asthma and for symptomatic relief from seasonal allergies. Montelukast sodium is a hygroscopic, optically active, white to off-white powder, freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile with a melting point 135.5°C and half-life 2.2-5.5 h.[9]

The objective, therefore, is to formulate a tablet that fits in the size range of mini-tablets, allows variation of drug dose, and is pleasant in taste so that it can be taken without water and has greater patient acceptance.

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MATERIALS AND METHODS

Montelukast sodium was obtained as a gift sample from Zim Laboratories, Nagpur, pharmaceutical grade mannitol, sodium starch glycolate, crospovidone, microcrystalline cellulose, saccharin sodium, glyceryl monostearate, magnesium stearate, talc were obtained from HiMedia, Mumbai, polyethylene glycol (PEG) 4000, PEG 6000, carnauba wax and PEG 500 were obtained from Research Laboratories, Mumbai, Maharashtra, India. Rice bran wax was procured from Maheshwari Rice Mills, Gondia. Solvents were obtained from SD fine chemicals and were distilled before use.

Purification of crude rice bran wax to get food-grade rice bran wax[10]

The purification of rice bran wax involves a two-step process commencing from the removal of residual oil with the help of solvent *n*-hexane followed by isopropanol. The defatted wax is then bleached with sodium borohydride to yield a white compound which can be used further. About 100 g of crude rice bran wax was refluxed with about 1 L of *n*-hexane at about 50°C for 3 h. The mixture was cooled to about 20°C and was filtered and dried. This dried wax about 50 g was then refluxed with about 500 ml of isopropyl alcohol at about 80°C for 3 h and was then cooled to about 20°C and the residue was filtered. Most of the oil content is removed by *n*-hexane washing and remaining polar oils and lipids are washed in the isopropyl alcohol washing to yield a brownish wax which is harder to feel.

Bleaching of the defatted wax

The color is due to the presence of resinous matter which can be removed by bleaching. The defatted wax about 50 g is refluxed with isopropyl alcohol at about 80°C in a two-neck round-bottomed flask fitted with a rubber cork. When the desired temperature is reached, the wax is bleached by drop-wise addition of 10% solution of sodium borohydride. The process yields a separate layer of resinous matter, being more polar in nature, separates and the wax remains in the molten state. The mixture is filtered when hot to separate resinous matter and the white wax separates as solid crystals from the filtrate upon cooling.

The rice bran wax was evaluated for its content and quality. By same procedure, carnauba wax was also purified and bleached.

Preparation of blends

Four different wax matrix formers were used, namely, PEG 4000, glyceryl monostearate, carnauba wax (purified and bleached), and rice bran wax (purified and bleached) in different batches and their influence on the tablet properties was compared. The wax matrix former was passed through a sieve no. 30 (ASTM). The drug and the other excipients were added after being passed through sieve no. 80 (ASTM) to the wax matrix former [Table 1].

Precompression evaluation of blends and mini-tablets[11-16]

The blends were evaluated for their compressibility by measuring the angle of repose, Carr's index, and Hauser's ratio.

Angle of repose

It is determined by allowing a powder to flow through a funnel and fall freely onto a surface. Further addition of powder is stopped as soon as the pile touches the tip of the funnel. A circle is drawn around the pile without disturbing it. The height and diameter of the resulting cone are measured. The same procedure is repeated three times and the average value is taken. Angle of repose is calculated using the following equation [Table 2]:

$$\tan \theta = h/r$$

where h = height of the powder cone; r = radius of the powder.

Table 1: Formulation of mini-tablets

Ingredients	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Montelukast sodium	200 mg	200 mg	200 mg	200 mg
Carnauba wax	2 g	-	-	-
PEG 4000	-	2 g	-	-
GMS	-	-	2 g	-
Rice bran wax	-	-	-	2 g
Sodium saccharin	100 mg	100 mg	100 mg	100 mg
Mannitol	100 mg	100 mg	100 mg	100 mg
Peppermint oil	0.1 ml	0.1 ml	0.1 ml	0.1 ml
Microcrystalline cellulose	100 mg	100 mg	100 mg	100 mg
SSG	100 mg	100 mg	100 mg	100 mg

PEG: Polyethylene glycol, SSG: Sodium starch glycolate, GMS: Glyceryl monostearate

Bulk density

Unless otherwise specified, pass a quantity of material sufficient to complete the test through a 1.00 mm (no. 18 ASTM) screen to break up agglomerates that may have formed during storage. Into a dry 250 ml cylinder introduce approximately 100 g of the test sample (M) weighed with 0.1% accuracy, without compacting. If it is not possible to use 100 g, the amount of the test sample and the volume of the cylinder may be modified. Select a sample mass having an untapped apparent volume of 150-250 ml. A 100 ml cylinder is used for apparent volumes between 50 and 100 ml. Fill the cylinder carefully. Carefully level the powder without compacting, if necessary, and read the unsettled apparent volume (V_o). Calculate the bulk density, in g/ml, using the formula:

$$\text{Bulkdensity} = \frac{M}{V_0}$$

Tapped density

Accurately weighed quantity of powder is introduced into a measuring cylinder. Mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester at a nominal rate of 300 drops/min. Tap the cylinder 500 times and measure the tapped volume (V_a). Repeat the operation for an additional 750 tappings and again measure the tapped volume as (V_b).

If the difference between V_a and V_b is <2%, V_b is the final tapped volume (V_f). If the difference is higher, repeat the tapings for an additional 1250 times, and then the tapped density can be calculated using the following formula (United States Pharmacopoeia, 2004):

$$\text{Tapped density} = \frac{M}{V_f}$$

where M = weight of the sample taken; V_f = final tapped volume.

Carr's index and Hausner ratio

The compressibility index of granules can be determined using The Carr's compressibility index and can be calculated by the formula: $\text{Compressibility index} = \frac{(\rho_t - \rho_o)}{\rho_t} \times 100$

Hausner's ratio is calculated as:

$$\text{Hausner's ratio} = \frac{\rho_o}{\rho_t}$$

The compressibility index is evaluated for the interpretation of the flow of the granules. The relationship is presented in Table 3.

Size distribution of mixture was checked and the blends were compressed in Cemach make R&D press at 5 tons pressure.

Evaluation of mini-tablets

The mini-tablets were evaluated for parameters such as weight variation, thickness, hardness, friability, disintegration time, dissolution time, taste, and mouthfeel.

Tablet thickness

Thickness was measured using Vernier caliper.

Weight variation

Randomly selected 20 tablets from the lot were weighted individually to check for weight variation. Weight variation specification as per IP is shown in Table 4.

Friability

Preweighed tablets were placed in the Roche friabilator for 100 revolutions. At the end of test, tablets were dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

% Friability = 1– (loss in weight/initial weight) × 100

Limit - <1%

Table 2: Interpretation of angle of repose

Repose angle (°)	Flowability
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very poor
>66	Very very poor

Table 3: Interpretation of Carr's index and Hausner's ratio

Carr's index	Flowability	Hausner ratio
10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
<40	Very very poor	>1.60

Table 4: Weight variation test specifications as per IP

Average weight of tablet	% deviation
80 mg or less	±10
>80 mg but <250 mg	±7.5
250 mg or more	±5

Table 5: Physicochemical properties of wax matrix substances

Physicochemical properties	Carnauba wax	Rice bran wax	Glyceryl monostearate	PEG 4000
Melting point[a]	84°C	81°C	56°C	54°C
Acid value[b]	10	1.8	6	-
Saponification value[b]	85	81	158	-
Iodine value[b]	10	8.1	3	-

[a]USP29 NF24 general chapters <741>, [b]USP29 NF24 general chapters <401>. PEG: Polyethylene glycol, USP: United states pharmacopoeia

Table 6: Flow property of formulations from angle of repose

Formulations	Angle of repose (q)	Flowability
F1	24°58′	Excellent
F2	25°23′	Excellent
F3	29°23′	Excellent
F4	29°16′	Excellent

Hardness test

Tablet hardness was measured with Monsanto hardness tester. A tablet was placed in the hardness tester and load required to crush the tablet was measured. The force is measured in kg and the hardness of about 5-8 kg/cm^2 was considered to be satisfactory for uncoated tablets.

Wetting time

Five circular tissue papers of 10 cm diameter were placed in a petri dish with a diameter of 10 cm. Ten millimeters of water containing eosin was added to petri dish. A mini-tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet was noted as a wetting time.

Disintegration time

A modified disintegration test apparatus is used where the mesh of the disintegration test apparatus is replaced by mesh size 30 (ASTM) that does not allow intact tablets to pass.

Taste/mouth sensation

Taste evaluation is done by a panel of 5 members using time intensity method. Sample equivalent to 10 mg, i.e., dose of drug is put in mouth for 10 s and record taste instantly and then after 10 s, 1, 2, 4, and 5 min. Volunteers' opinion for the taste is rated by giving different score values, i.e., 0 = good, 1 = tasteless, 2 = slightly bitter, 3 = bitter, 4 = awful.

Dissolution test

The dissolution method for oral disintegrating tablets was the same as that of conventional tablets. USP 2 paddle apparatus is most suitable and common choice for dissolution test of oral disintegrating tablets, where the paddle speed is 50 rpm is used.

RESULTS AND DISCUSSION

Rice bran wax and carnauba wax were evaluated for their physicochemical properties as per the methods specified in literature and the results are recorded [Table 5].

The formulation blends were considerably different in their physical and flow properties. The flow properties and packing properties of the blends show desirable characteristics for compression [Table 6].

Evaluation of granules

From the precompression parameters, it is clear that the granules are shown in Table 7.

Evaluation of mini-tablets

The thickness and hardness of the tablets were measured during compression regularly. The tablets were subjected to weight variation, friability, and assayed for drug content and the results are reported in Table 8. Carnauba wax and rice bran wax are from natural origin and showed good compressibility under moderate pressures. The tablet weight is adjusted such that each tablet contains about 1 mg of active principle.

The wetting time for mini-tablets is more for carnauba wax and rice bran wax owing to the presence of high molecular weight fatty components along with polar components present in less proportion. The modified dissolution apparatus did not allow the passage of intact mini-tablets during the test, but the tablets disintegrated readily owing to the presence of superdisintegrants [Table 9 and Figure 1].

Dissolution profile

The dissolution profile of the formulations endorsed the influence of nature of ingredients used as matrix formers. The rate of drug dissolution is slower where carnauba wax and rice bran wax were used, but the rate of drug retardation is not pronounced as the tablets disintegrate quickly upon exposure to dissolution media [Table 10 and Figure 2].

Table 7: Flow properties of formulation by Carr's index and Hausner's ratio

Formulations	Bulk density	Tapped density (g/cm³)	Compressibility (%)	Hausner ratio	Flowability
F1	0.3946	0.4969	20.58764	1.25925	Passable
F2	0.3716	0.4928	24.59416	1.326157	Passable
F3	0.3715	0.4925	24.56853	1.325707	Passable
F4	0.3986	0.5168	22.87152	1.296538	Passable

Table 8: Quality control tests of mini-tablets

FC	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Drug content (%)	Weight variation test
F1	3.9	3.12	0.54	98.22	Pass
F2	3.1	3.23	0.62	99.33	Pass
F3	3.2	3.42	0.74	98.18	Pass
F4	3.8	3.12	0.58	98.35	Pass

Table 9: Wetting time and dissolution time of mini-tablets

Formulation code	Wetting time (s)	*In vitro* disintegration time (min)
F1	60	1.10
F2	15	1.30
F3	15	1.30
F4	25	1.30

Table 10: Average cumulative % drug release

Time (min)	Average % cumulative drug release of different batches (*n*=6)			
	F1	F2	F3	F4
2	31.51±1.16	41.8±2.6	44.26±2.18	34.96±1.98
4	52.82±0.97	60.02±2.2	65.55±1.26	63.01±2.61
6	70.54±1.18	88.61±1.59	90.26±1.35	75.69±3.02
8	82.86±1.44	98.55±0.59	98.52±0.61	86.32±1.43
10	93.04±0.81			92.1±1.06
12	98.41±0.52			97.68±1.42

Table 11: Mouthfeel of mini-tablet formulation

FC	Mouthfeel
F1	0
F2	0
F3	0
F4	0

Mouthfeel

The average rating given by volunteers to all four formulations in recorded which is indicated the acceptability of natural waxes which are cheap in formulations which are more popular for their organoleptic properties [Table 11].

Figure 1: Mini-tablets of montelukast sodium

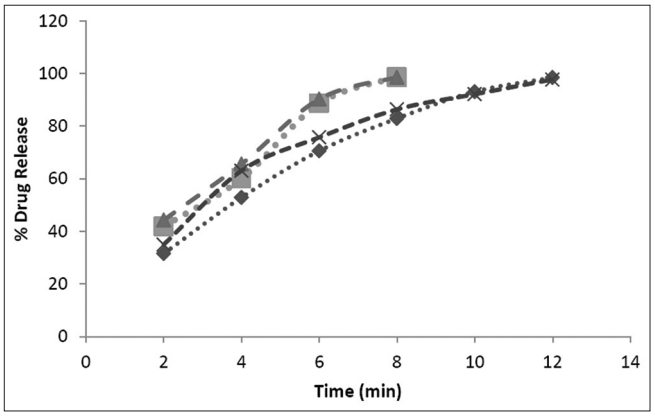

Figure 2: Drug-release profile of mini-tablet formulation

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