



Design, development and evaluation of fast dissolving tablets of Montelukast sodium using natural Superdisintegrants

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Abstract

Objective: The main aim of this work was to design, develop and evaluate fast dissolving tablets of Montelukast Sodium using natural superdisintegrants at variable concentrations.

Methods: In the present study, the fast dissolving tablets of *Montelukast Sodium* were prepared by direct compression method using microcrystalline cellulose (MCC) as direct compressible diluent after the satisfactory results of pre-formulation studies. Potato Starch and Ispaghula Husk were selected as natural superdisintegrants on the basis of high swelling index. Ten formulations were prepared using different concentrations of superdisintegrants and were investigated for their effect on the disintegration time and dissolution rate profiles of drug incorporated in the tablets, and other evaluation parameters were also studied.

Results: Fast dissolving tablets of Montelukast sodium were prepared using Potato starch (15 mg) had a shorter disintegration time and showed the best pharmaceutical performance. The formulations showed desired pre and post-compressive characteristics.

Conclusion: The results obtained in this research work clearly that a promising potential of fast dissolving tablets of Montelukast sodium containing Potato starch as fast onset of action in asthma attack.

Keywords: Fast dissolving tablets, mouth dissolving tablets, montelukast sodium, ispaghula husk, potato starch

Introduction

Fast dissolving tablets (FDTs) have obtained massive need throughout the past decade and the field is getting a fast-growing in the pharmaceutical market [1]. Recent advances in novel drug delivery (NDDS) aims to enhance the stability, safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. FDT's are swallowed in the mouth, allowed to disperse in the saliva. They start releasing the drug when they come in contact with the saliva, thus eliminating the need for water during administration [2]. Despite tremendous advancements in drug delivery, the oral route still remains the perfect route for the administration of therapeutic agents because of the low cost of therapy, self-medication, ease of administration, pain avoidance, accurate dosage, versatility, leading to high levels of patient compliance. Tablets and capsules are the most popular oral dosage forms [3]. Quite often people practical experience annoyance in consuming conventional dosage forms such as tablet when water is not readily available, within the instance of the motion sickness (kinetosis) and sudden episodes of coughing throughout the typical cold, infectious illness and bronchitis. For this reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [4]. Therefore, for the past decade, there has been an enhanced demand for more patient-friendly and patient-compliant dosage forms. Thus, the massive need for the growth of FDT's, a new technology has been increasing enormously. Since the development cost of a new drug molecule has been very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved

safety and efficacy together with reduced dosing frequency [5]. To fulfill the medical needs and to overcome these drawbacks, rapidly dissolving tablets have emerged as different solid unit dosage forms. All these are innovative kinds of tablets that disintegrate in saliva within a couple of seconds [6]. They even fulfill the prerequisite of being stable, safe and efficacious.

Montelukast inhibits broncho-constriction due to antigen challenge. Montelukast Sodium (sodium 2-[1-((1R)-1-(3-[(E)-2-(7-chloroquinolin-2-yl) ethenyl] phenyl)-3-[2-(2-hydroxypropan-2-yl) phenyl] propyl] sulfanyl) methyl] cyclopropyl] acetate) is the selective leukotriene receptor antagonist of the cysteinyl leukotriene CysLT 1 receptor. The cysteinyl leukotrienes (LTC 4, LTD 4, and LTE 4) are products of arachidonic acid metabolism that are released from various cells, including mast cells and eosinophils [7]. Drug bind to cysteinyl leukotriene receptors (CysLT) found in the human airway. Binding of cysteinyl leukotrienes to leukotriene receptors has been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process, factors that contribute to the signs and symptoms of asthma. Montelukast sodium binding to the CysLT 1 receptor is high-affinity and selective, preferring the CysLT 1 receptor to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or beta-adrenergic receptor. Montelukast inhibits physiological actions of LTD 4 at the CysLT 1 receptors, without any agonist activity [8]. Montelukast Sodium is a drug which was chosen as the best drug candidate for fast dissolving formulation because it fulfills all the required ideal characteristics for FDT's. Montelukast Sodium has various

characteristics which are required for the FDT formulation like good stability & solubility in water, having low dose then 50 mg, having smaller molecular weight & having a shorter half-life. In this study, our main goal was to achieve the fast onset of action in the asthmatic attack. Montelukast Sodium is desired to depict the quick onset of action in the serious asthmatic attack. My work aims to determine the right superdisintegrant and also their optimum concentration which gives the maximum release of the drug.

Materials and Methods

Montelukast sodium was procured from Cadila Healthcare Ltd, Ahmedabad, India. Talc, Mannitol and MCC were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Potato starch was procured from M/s Titan biotech limited, Bhiwadi, India. Ispaghula husk was received from Sat-Isabgol, Sidhpur, India. Sodium saccharin & Aerosil-200 were obtained from Nice Chemicals Pvt. Ltd, Cochin, India and Magnesium stearate was procured from Central Drug House (P) LTD, New Delhi, India. Orange Flavor was obtained as gift sample from Synmedic Laboratories, Faridabad, India.

Table 1: Formulation of Montelukast Sodium tablets containing different concentration of Natural superdisintegrants

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Montelukast Sodium	10	10	10	10	10	10	10	10	10	10
Potato Starch	5	7.5	10	12.5	15	-	-	-	-	-
Ispaghula husk	-	-	-	-	-	5	7.5	10	12.5	15
MCC	100	100	100	100	100	100	100	100	100	100
Talc	4	4	4	4	4	4	4	4	4	4
Mannitol	74	71.5	69	66.5	64	74	71.5	69	66.5	64
Mag. Stearate	4	4	4	4	4	4	4	4	4	4
Sodium Saccharin	1	1	1	1	1	1	1	1	1	1
Aerosil-200	1	1	1	1	1	1	1	1	1	1
Orange Flavor	1	1	1	1	1	1	1	1	1	1
Total Weight	200	200	200	200	200	200	200	200	200	200

a. Determination of Swelling Index

The swelling index value of all the superdisintegrants viz. Potato starch and Ispaghula Husk were determined. The swelling index of Potato starch & Ispaghula husk in various solvents such as distilled water, 0.1N HCl & 0.5% w/v Sodium Lauryl Sulphate (SLS) solution in distilled water were noted [10].

b. Angle of Repose

A glass funnel was held in place with a clamp on a ring and graph paper was placed on a flat horizontal surface. Approximately 2 g of powder blend is transferred into the funnel, keeping the orifice of the funnel blocked by the thumb. After pouring powder the thumb was removed from the orifice maintained about a 6.4 mm gap between the bottom of the funnel stem and top of the powder pile. When the powder is emptied from the funnel, the height of the pile and radius of the base was measured by the ruler [11]. The angle of repose was calculated by using following eqn. 1.1 and results obtained are depicted in table-3.

$$\theta = \tan^{-1} \frac{h}{r} \dots\dots\dots 1.1$$

Where θ = angle of repose, h = height of pile, r = radius of the base of the pile

c. Bulk Density and Tapped Density

Both bulk density (BD) and tapped density (TD) were

determined. A suitable amount of powder blend from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 100 mL measuring cylinder. After observing its initial volume, the cylinder is tapped 100 times manually. The tapping was continued until no further change in volume was noted. Volume after tapping was noted. BD and TD were calculated by using following eqn.1.2 & 1.3 respectively and results obtained are noted in table-3 [11].

$$\text{BulkDensity} = \frac{\text{Weightofpowder}}{\text{Bulkvolumeofpowder}} \dots\dots\dots 1.2$$

$$\text{TappedDensity} = \frac{\text{Weightofpowder}}{\text{Tappedvolumeofpowder}} \dots\dots\dots 1.3$$

d. Compressibility Index

It is a simple index that can be determined on small quantities of powder. Compressibility index values of powder blend were calculated according to the following equation 1.4 and results obtained are depicted in table-3 [12].

$$C. I = \frac{T.D-B.D}{T.D} \times 100 \dots\dots\dots 1.4$$

e. Hausner's Ratio

It is the ratio of tapped to bulk density and was calculated by using the following eqn. 1.5 and calculated the values of Hausner's ratio for each batch and results obtained are depicted in table-3 [12].

$$\text{Hausner's Ratio} = \frac{\text{Tappeddensity}}{\text{Bulkdensity}} \dots\dots\dots 1.5$$

Post-Compression Evaluation

a. Tablet Hardness

The crushing strength (Kg/cm³) of prepared tablets was determined by using Monsanto hardness tester. The hardness tests were performed for each batches of prepared formulation in triplicate manner [12]. The average hardness and standard deviation was determined and results obtained are shown in table-4

b. Friability

Friability test was done by Roche's Friabilator. Twenty tablets were weight (W_o) and revolved at 25 rpm & operated for 100 revolutions. The tablets were dusted and reweighed (W) after completion of 100 revolutions. The percentage friability was calculated using following eqn. 1.6 & obtained reading are shown in table-4.

$$\text{Percent Friability} = \frac{w_0-w}{w_0} \times 100 \dots\dots\dots 1.6$$

c. Uniformity of Tablet Weight

The weight variation test is run by weighing 220 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight. The weight variation test was performed for each batch of prepared formulation in triplicate manner and results obtained are presented in table-4.

d. Uniformity of Drug Content

For the drug content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of Montelukast Sodium was dissolved in 10 mL of 0.5% w/v SLS solution and liquid was filtered using whattman filter paper and diluted by taking 1mL from above

solution and volume makeup up to 10µg/ml. The Montelukast Sodium content was determined by measuring the absorbance at 346 nm using UV spectrophotometer. The results obtained are depicted in table-4.

e. Tablet Thickness

Ten tablets from each batch of formulations were selected randomly and thickness of tablets was measured using vernier caliper. The average value of thickness was calculated and shown in table-4 [11].

f. In-vitro disintegration time

Six tablets of each formulation were used to determine disintegration time. Phosphate buffer pH 6.8 was used as a disintegration medium and temperature was maintained at 37±0.5°C and readings were noted in table 3 and histogram is plotted in fig. 1 [11].

g. In-vitro dispersion time

In-vitro dispersion time was measured by dropping a tablet in a beaker containing 50 mL of phosphate buffer pH 6.8. Three tablets from each formulation were randomly selected and in-vitro dispersion time was performed. The readings were noted in table-5 and histogram is plotted in fig. 1 [11].

h. Wetting time

Wetting time for each formulation (F1-F10) was determined. For determination of wetting time a tablet was placed in a small petri-dish containing 6 ml of colored solution eosin solution. Three trials for each formulation were carried out and the standard deviation was also determined. The readings were noted in table 3 and histogram is plotted in fig. 1 [12].

i. In-vitro percent drug release

In-vitro release of prepared Montelukast sodium fast dissolving tablets F1-F10 were determined by using USP type II dissolution apparatus in 900 mL of 0.5% w/w SLS solution in distilled water at constant temperature of 37±0.5°C at 50 rpm. One mL of sample solutions were withdrawn from the dissolution apparatus at different time intervals and replaced with fresh dissolution medium to maintain the sink condition. These sample solution were filtered and the absorbance of these solutions was measured

by using a double beam UV spectrophotometer at 346 nm against fresh solutions 0.5% w/v SLS solution in distilled water as blank. All the studies were conducted in triplicate and percent drug release was calculated by using the following eqn. 1.7 and 1.8. The readings were depicted in table-6. The histogram is shown in 2 [11].

$$\text{Percent drug release} = K \times \text{Absorbance} \dots\dots 1.7$$

Where K can be calculated by using the following eqn. 4.9 as follows:

$$K = \frac{\text{Standard Conc.} \times \text{Vol. of Dissolution media} \times \text{Dilution factor} \times 100}{\text{Standard Absorbance} \times \text{dose} \times 1000} \dots\dots 1.8$$

Results & Discussion

In the present study, Montelukast sodium fast dissolving tablets were prepared in ten formulations with varying concentration of superdisintegrants i.e. Potato starch and Ispaghula husk.

Swelling Index

The swelling index Potato starch and Ispaghula husk was observed out in water, 0.1 N HCL and 0.5% SLS Solution in distilled water, respectively. From the results, it shows that ispaghula husk has the highest swelling index value i.e. 87.13 in water than potato starch in all the solvents viz. water, 0.1 N HCL and 0.5% SLS Solution and hence ispaghula husk can act as potential superdisintegrant for the development of fast dissolving tablets of Montelukast Sodium.

Pre-compression evaluations

The angle of repose values varied from 27.92 to 30.54 & 7.32 to 8.79%. Bulk densities of various formulations varied from 0.248 to 0.293 g/cc The values obtained from Tapped density and Hausner's Ratio was 0.270 to 0.319, and 1.079 to 1.096 respectively and found be in range for the preparation of tablets. From these values, it was evident that these blends had good flow properties and excellent compressibility.

Table 2: Micromeritic and post- compression studies of tablet blends and tablets

Micromeritic details of pre-compressed of F1 to F10					
Formulation Code	Angle of repose (degree) (n=3)	Bulk density (g/mL) (n=3)	Tapped density (g/mL) (n=3)	Compressibility index (%) (n=3)	Hausner's ratio (n=3)
F1	28.95 ±0.92	0.270±0.003	0.296±0.005	8.566±0.725	1.094±0.009
F2	28.80±1.17	0.282±0.003	0.308±0.004	8.452±0.097	1.092±0.001
F3	27.92±0.89	0.282±0.003	0.305±0.002	7.506±0.586	1.081±0.007
F4	28.22±0.92	0.282±0.003	0.308±0.004	8.452±0.097	1.092±0.001
F5	30.54±0.85	0.293±0.005	0.319±0.006	8.293±0.683	1.090±0.008
F6	28.07±0.68	0.248±0.003	0.270±0.003	8.262±0.0546	1.090±0.006
F7	28.95±1.01	0.293±0.005	0.319±0.006	8.293±0.683	1.090±0.008
F8	29.97±0.665	0.270±0.017	0.295±0.016	8.473±0.793	1.093±0.009
F9	29.25±0.44	0.278±0.003	0.305±0.002	8.791±0.566	1.096±0.007
F10	28.66±1.11	0.259±0.004	0.279±0.005	7.328±0.602	1.079±0.007
Post-Compression evaluation M.S Tablets					
Formulation Code	Hardness (Kg/cm ²) (n=3)	Friability (%) (n=3)	Weight Variation test (mg) (n=3)	Drug content (%) (n=3)	Thickness (mm) (n=3)
F1	3.50±0.40	0.65±0.17	204.21±0.28	99.11±0.56	2.50±0.02
F2	3.63±0.31	0.49±0.11	200.17±0.81	98.40±0.71	2.54±0.03
F3	3.37±0.47	0.97±0.22	203.46±0.57	98.57±0.94	2.45±0.06
F4	3.57±0.35	0.46±0.22	200.50±0.77	99.11±0.86	2.53±0.05
F5	3.40±0.46	0.66±0.10	200.97±0.77	98.48±0.56	2.43±0.03
F6	3.53±0.32	0.63±0.28	201.59±0.82	99.47±0.27	2.55±0.01
F7	3.47±0.75	0.61±0.06	201.25±0.86	99.20±0.93	2.47±0.03
F8	3.50±0.40	0.63±0.12	198.47±0.71	98.57±0.86	2.51±0.07
F9	3.60±0.56	0.65±0.13	200.51±0.65	98.33±0.73	2.51±0.05
F10	3.17±0.40	0.67±0.20	197.54±0.69	99.82±0.56	2.50±0.05

Post Compression Evaluations

The Hardness, thickness and friability of all the tablet formulations were observed in the range of 3.17 to 3.63 kg/cm², 2.43 to 2.54 mm and 0.46 to 0.97% w/w, respectively. Weight variation was found within the specification of the IP limits of 7.5%. Average weight of 20 tablets of all ten formulations was found in the range of 198.47 to 204.21 mg. Drug content of all the formulations was found in the range of 98.33 to 99.82% as per limits of I.P.

In vitro Evaluations

The *in-vitro* disintegration time was measured by the time taken to undergo complete disintegration and was observed to be 9.67 to 89.33 sec. The rapid disintegration may be due to the rapid uptake of water from the medium, swelling and bursting effect. *In-vitro* dispersion time and wetting time was found in the range of 18.33 to 189.00 sec and 10.00 to 178.67 sec. respectively, as per readings obtained from the table 3 it proves that F5 have the least disintegration time as well as

dispersion time which facilitate the faster dispersion in the mouth. *In vitro* dissolution studies of various formulations at different time intervals are reported in table 3

Table 3: Value of *In-vitro* Disintegration Time, *In-vitro* Dispersion Time and Wetting Time

Formulation Code	<i>In-vitro</i> Disintegration Time (Sec.) n=3	<i>In-vitro</i> Dispersion time (Sec.) n=3	Wetting Time (Sec.) n=3
F1	36.00±1.0	18.67±0.58	16.67±0.58
F2	17.33±0.58	27.67±1.15	15.33±0.58
F3	15.67±2.08	23.33±2.08	14.00±1.0
F4	15.33±1.15	23.33±0.58	11.33±1.15
F5	9.67±1.15	18.33±1.53	10.00±1.0
F6	89.33±0.58	189.00±2.0	178.67±0.58
F7	70.67±0.58	151.67±2.08	142.00±2.0
F8	24.33±1.53	55.67±0.58	43.67±0.58
F9	24.33±1.53	35.00±1.0	27.00±1.0
F10	20.67±1.53	19.33±1.53	11.00±2.65

Table 4: Cumulative % drug release of formulations developed using Potato starch superdisintegrant at varied time

S. No.	Time (min.)	Cumulative % drug release ± SD (n=3)				
		F1	F2	F3	F4	F5
1.	0	0	0	0	0	0
2.	1	9.43±0.69	10.43±0.35	11.83±0.69	15.04±0.60	16.04±0.39
3.	2	14.04±0.92	15.44±0.92	17.65±0.92	20.45±0.60	20.45±0.60
4.	5	28.07±0.92	33.29±0.92	34.69±0.92	38.90±0.92	39.71±0.60
5.	10	38.90±0.92	42.71±0.60	43.72±0.92	46.12±0.92	47.73±0.92
6.	15	54.75±0.60	56.55±0.60	61.36±0.60	66.38±0.92	68.38±0.92
7.	20	73.40±0.60	77.61±0.60	79.21±0.92	82.22±0.92	84.83±0.60
8.	25	79.81±0.92	90.04±0.92	91.84±0.69	95.25±0.92	97.66±0.69

Cumulative % drug release of formulations developed using Ispaghulasuperdisintegrant at varied time

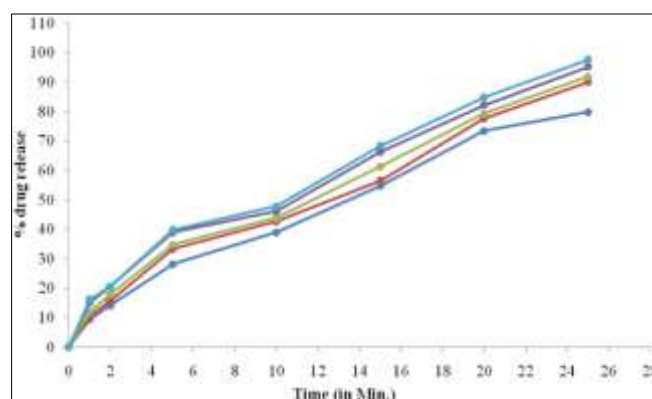


Fig 1: Cumulative % drug release from formulations containing potato starch

Table 5: Cumulative % drug release of formulations developed using Ispaghula husk superdisintegrant at varied time

S. No.	Time (min.)	Cumulative % drug release ± SD (n=3)				
		F6	F7	F8	F9	F10
1.	0	0	0	0	0	0
2.	1	7.62±0.92	9.63±0.60	11.03±0.35	13.44±0.92	15.24±0.35
3.	2	16.04±0.92	19.25±0.60	21.06±0.60	24.26±1.25	26.47±0.60
4.	5	36.50±0.92	38.10±0.92	40.11±0.92	41.51±1.20	45.32±0.92
5.	10	44.72±0.35	47.73±0.92	52.34±0.60	54.34±0.69	59.56±0.60
6.	15	58.76±0.35	62.57±0.60	64.77±0.35	66.78±0.60	67.78±0.92
7.	20	70.99±0.60	72.19±0.60	75.00±0.92	77.01±0.60	78.61±0.92
8.	25	82.22±0.92	83.82±0.92	86.03±1.20	89.04±0.60	91.84±0.92

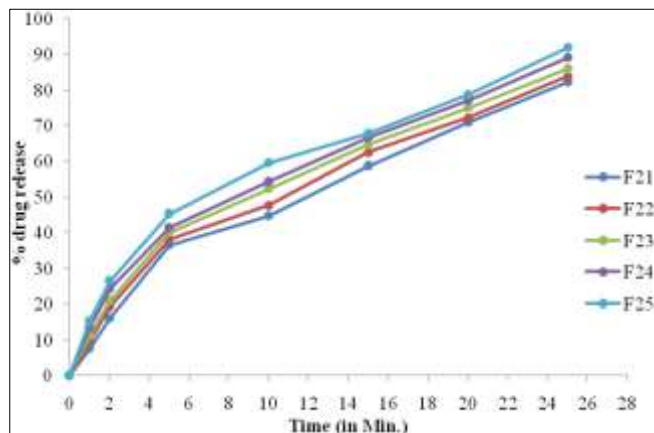


Fig 2: Cumulative % drug release from formulations containing Ispaghula as superdisintegrant

The formulation F5 showed the maximum dissolution rate of 97.66% drug release in 25 min, whereas the marketed tablet (Montair) formulation released up to 63.52% in 25 min. (Fig. 5) From the overall observations, formulation F5 containing 15 mg potato starch was considered to be the best formulation, which releases up to 97.66% of the drug in 25 min.

Conclusion

The fast dissolving tablets of montelukast sodium can be successfully prepared by containing potato starch as superdisintegrant. The prepared tablets show the better disintegration and dissolution behaviors. The *in-vitro* drug release was 97.66% in 25 min. All the post and pre evaluations data were found to be within range as per I.P. specifications. The conc. of potato starch also influences the disintegration time and dissolution data. This research work clearly shows that fast dissolving tablet of montelukast sodium containing potato starch have promising potential for fast onset of action in asthma attack.

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