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Design, development and evaluation of fast dissolving tablets of montelukast sodium using synthetic superdisintegrants

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Abstract
Objective: This research was aimed at to design, develop and evaluate fast dissolving tablets of montelukast sodium using synthetic superdisintegrants at variable concentrations.
Methods: In the present study, the fast dissolving tablets of *Montelukast Sodium* were formulated using direct compression method incorporating microcrystalline cellulose (MCC) as direct compressible diluents after finding encouraging results of prefomulation studies. Sodium starch glycolate (SSG) and Croscarmellose sodium (CCS) were selected as synthetic superdisintegrants seeing their high swelling index. Ten formulations were prepared using varied concentrations of superdisintegrants. The investigations of these formulations were aimed to look into their influence on the disintegration time and dissolution rate of these tablets and other evaluation parameters were also evaluated.
Results: Fast dissolving tablets of montelukast sodium were prepared with croscarmellose sodium (7.5 mg) had a shorter disintegration time and gives the best pharmaceutical performance. The evaluation of formulations reflected good pre and post-compressive characteristics.
Conclusion: The result obtained in this research work clearly shows that a promising potential of fast dissolving tablets of montelukast sodium containing croscarmellose sodium as a result of faster dissolution leading to possibilities of faster onset of action in asthma attack may be beneficial.

Keywords: fast dissolving tablets, synthetic superdisintegrants, montelukast sodium, sodium strach glycolate, croscarmellose sodium

Introduction

Fast dissolving tablets (FDTs) have obtained massive need throughout the past decade and the field is getting a fast-growing field in the pharmaceutical market [1]. Recent advances in research as a result of evolution of poor methodologies into state of the art technological support, researchers have diversified the approach from conventional dosage form to novel drug delivery system (NDDS) that aims to enhance the 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 obviating the need for water during administration [2]. Despite tremendous advancements in drug delivery, the oral route 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 dosage forms [3]. Quite often people practically 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, the past decade, there has been an enhanced demand for more patient-friendly and highly 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 research laboratories 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].

Montelukast inhibits broncho-constriction due to antigen challenge. Montelukast Sodium 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

Materials

Montelukast sodium was procured from Cadila Healthcare Ltd, Ahmedabad, India. Sodium starch glycolate, Talc, Mannitol and MCC were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Croscarmellose sodium was received from S.D Fine Chemicals Ltd., Mumbai, India. Sodium saccharin, Aerosil-200 were obtained from Nice Chemicals Pvt. Ltd, Cochin, India. 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.

Formulation of fast dissolving tablets of montelukast sodium

Different formulations (F1 to F10) were prepared by direct compression technique (table-1). In this technique all the ingredients were weighed as specified in the formula (table-1). Drug, diluent, lubricant and disintegrant were passed through sieve # 80. The drug was first mixed homogeneously with diluents and disintegrant in a mortar and pestle to obtain the required degree of fineness was attained. Finally, aerosil-200 and magnesium stearate were added and mixed. The resultant blends after micromeritic evaluation, were directly compressed using 9 mm convex round punches with tablet weight 200 mg in a hand operated machine. A batch size of 50 tablets was prepared in each formulation.

Table 1: Composition of fast dissolving tablets of montelukast sodium

Ingredients (mg/tablets)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Montelukast Sodium	10	10	10	10	10	10	10	10	10	10
Croscarmellose Sodium	5	7.5	10	12.5	15	-	-	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	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

Pre-Compression Evaluation

a. Determination of Swelling Index

The swelling index value of all the superdisintegrants viz. CCS (Croscarmellose Sodium) and SSG (Sodium Starch Glycolate) were determined. The swelling index of CCS & SSG in various solvents such as distilled water, 0.1 N HCl & 0.5% w/v SLS solution in distilled water were noted [10]. The readings of swelling index are depicted in table 2.

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.

$$\theta = \tan^{-1}\frac{h}{r} \quad \text{.....1.1}$$

Where θ = angle of repose, h = height of pile, r = radius of the base of the pile4

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].

$$\text{Bulk Density} = \frac{\text{Weight of powder}}{\text{Bulk volume of powder}} \quad \text{.....1.2}$$

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume of powder}} \quad \text{.....1.3}$$

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]

$$C.I = \frac{T.D - B.D}{T.D} x100 \quad \text{.....1.4}$$

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].

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{.....1.5}$$

Post-Compression Evaluation

a. Tablet Hardness

The crushing strength (Kg/cm^3) 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 were 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.

$$\text{Percent Friability} = \frac{W_0 - W}{W_0} 100 \quad \text{.....1.6}$$

c. Uniformity of Tablet Weight

The weight variation test is run by weighing 20 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 5 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 5 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 was withdrawn from the dissolution apparatus at different time intervals and replaced with fresh dissolution medium to maintain the sink condition. These sample solutions 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].

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

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

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

Results & Discussion

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

Swelling Index

The swelling index of croscarmellose sodium and SSG was observed out in water, 0.1 N HCL and 0.5% SLS Solution in distilled water, respectively. From the results, it shows that CCS has the highest swelling index value i.e. 78.33 in water (table-2) than SSG in all the solvents viz. water, 0.1 N HCL and 0.5% SLS Solution and hence CCS can act as potential superdisintegrant for the development of fast dissolving tablets of Montelukast Sodium

Table 2: Swelling index for different superdisintegrants

Sr. No.	Superdisintegrant	Swelling Index (w/v) ±S.D.		
		Distilled water	0.1 N HCl	0.5% w/v SLS solution
1.	Sodium Starch Glycolate	49.49±0.87	57.16±0.41	63.04±0.78
2.	Croscarmellose Sodium	78.33±0.36	73.02±0.61	71.55±0.10

Pre-compression evaluations

The angle of repose values varied from 25.95 to 29.39 degree°. Bulk densities of various formulations varied from 0.253 to 0.293 gm/ml. The values obtained from Tapped

density, Compressibility index and Hausner's Ratio was 0.272 to 0.323, 6.757 to 10.683 and 1.073 to 1.116 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 3: Micromeritic studies of tablet blends

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	29.39±0.66	0.291±0.002	0.323±0.004	9.712±0.721	1.108±0.009
F2	27.77±0.93	0.268±0.002	0.293±0.002	8.480±0.605	1.093±0.007
F3	27.32±0.69	0.279±0.002	0.309±0.002	9.768±0.65	1.108±0.001
F4	25.95±0.71	0.288±0.008	0.319±0.005	9.620±0.742	1.107±0.009
F5	27.47±0.90	0.293±0.005	0.319±0.006	8.293±0.683	1.090±0.008
F6	27.32±0.94	0.282±0.003	0.309±0.002	8.915±0.573	1.098±0.007
F7	28.66±0.91	0.270±0.003	0.302±0.006	10.638±0.734	1.116±0.009
F8	27.32±0.94	0.269±0.003	0.299±0.004	9.863±0.578	1.109±0.007
F9	27.62±0.69	0.269±0.004	0.293±0.002	8.056±0.965	1.088±0.011
F10	26.72±0.26	0.253±0.003	0.272±005	6.757±0.662	1.073±0.008

Post Compression Evaluations

The Hardness, thickness and friability of all the tablet formulations were observed in the range of 3.17 to 3.77 kg/cm^2, 2.43 to 2.62 mm and 0.28 to 0.88% w/w respectively. Weight variation was found within the specification of the I.P.[11] limits of 7.5%. Average weight of 20 tablets of all ten formulations was found in the range of 198.97 to 203.05 mg. Drug content of all the formulations was found in the range of 98.48 to 100.42% as per limits of I.P.

Table 4: 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±0.20	0.28±0.07	200.56±0.69	98.48±0.82	2.44±0.01
F2	3.63±0.55	0.44±0.08	199.86±0.61	99.73±0.53	2.57±0.03
F3	3.57±0.35	0.43±0.07	199.70±0.69	98.57±0.94	2.53±0.03
F4	3.60±0.30	0.31±0.11	203.05±0.89	99.47±0.80	2.59±0.02
F5	3.43±0.50	0.43±0.20	202.24±0.34	99.11±0.41	2.46±0.02
F6	3.70±0.36	0.53±0.21	200.75±0.31	100.42±0.73	2.62±0.04
F7	3.70±0.62	0.80±0.28	200.37±0.45	99.20±0.93	2.58±0.03
F8	3.17±0.47	0.64±0.17	198.97±0.65	99.11±0.15	2.43±0.02
F9	3.77±0.67	0.88±0.28	201.28±0.62	100.00±0.456	2.52±0.04
F10	3.50±0.40	0.78±0.15	200.67±0.59	99.82±0.56	2.47±0.04

***In vitro* Evaluations**

The *in-vitro* disintegration time was measured by the time taken to undergo complete disintegration and was observed to be 10.33 to 39.00 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 17.67 to 69.00 sec and 13.00 to 61.33 sec. respectively, as per readings obtained from the table 5 it proves that F2 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 6

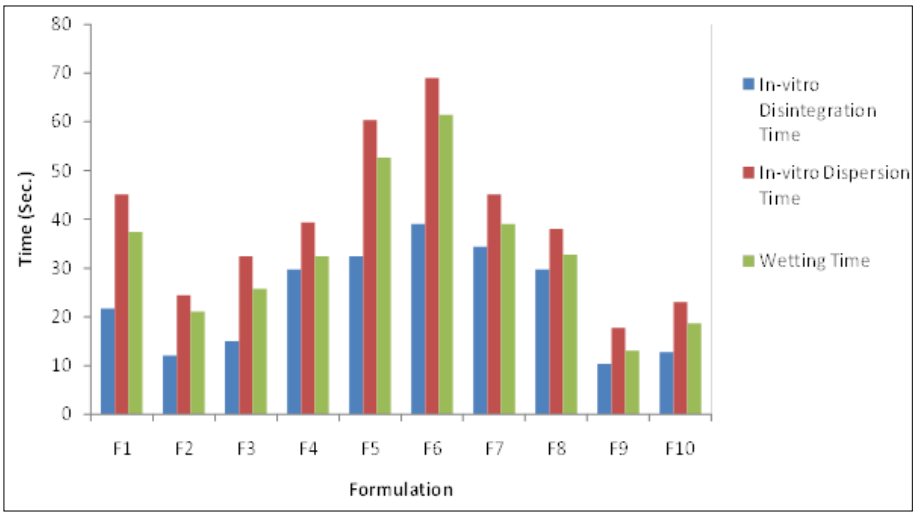

Fig 4: Histogram shows *In-vitro* disintegration time (sec.), *In-vitro* dispersion time (sec.) and Wetting Time of various formulations

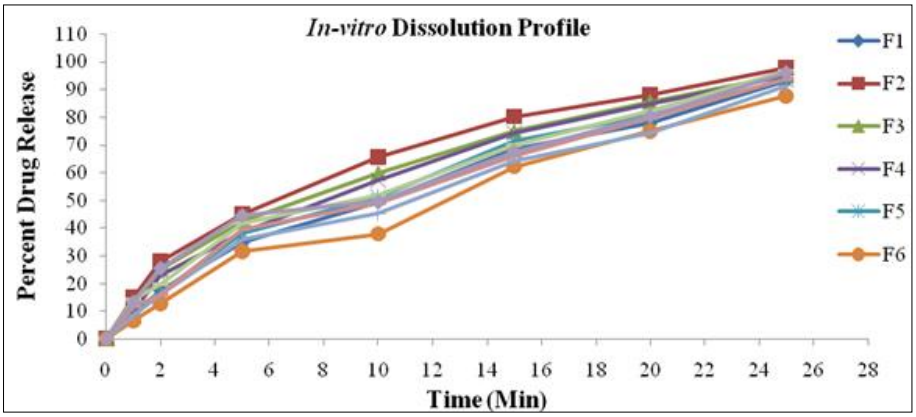

Fig 4: Histogram of *In-vitro* dissolution study of various formulations of Montelukast Sodium Tablet

The formulation F2 showed the maximum dissolution rate of 97.86%±0.92 drug release in 25 min, whereas the marketed tablet (Montair) formulation released up to 63.52%±0.40 in 25 min. (Fig. 5) From the overall observations, formulation F2 containing 7.5 mg CCS was considered to be the best formulation, which releases up to 97.86%±0.92 of the drug in 25 min.

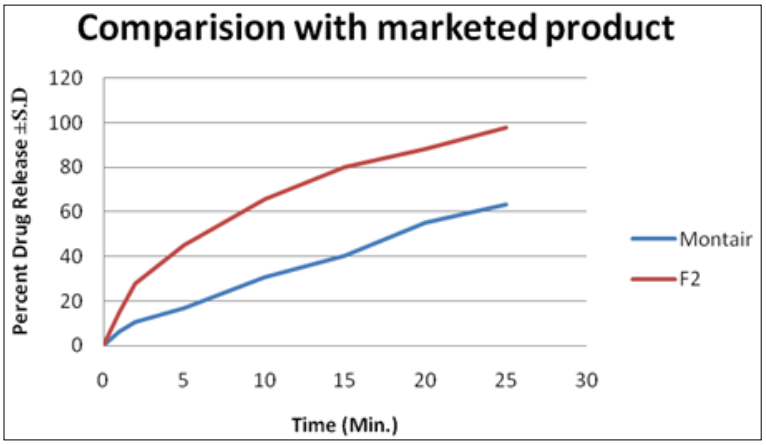

Fig 5: Histogram of *In-vitro* dissolution comparision of F2 with marketed product.

Conclusion

The fast dissolving tablets of montelukast sodium can be successfully prepared by containing Croscarmellose sodium as superdisintegrant. The prepared tablets show the better disintegration and dissolution behaviors. The *in-vitro* drug release was 97.86% in 25 min. All the post and pre evaluations data were found to be within range as per I.P. specifications. The conc. of croscarmellose sodium also influences the disintegration time and dissolution data. This research work clearly shows that fast dissolving tablet of montelukast sodium congaing croscarmellose sodium have promising potential for fast onset of action in asthma attack.

Table 6: *In-vitro* dissolution of study of various formulations of M.S Tablet

Sr. No.	Time (min.)	Cumulative % drug release ± SD (n=3)										
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	Marketed Formulation
1	0	0	0	0	0	0	0	0	0	0	0	0
2	1	8.62±0.35	14.84±0.35	10.63±0.35	10.03±0.69	8.42±0.60	6.42±0.92	8.42±0.60	11.43±0.60	14.24±0.92	13.24±0.60	6.47±0.51
3	2	17.45±0.60	27.87±0.92	25.07±0.92	22.66±0.92	16.64±0.92	12.83±0.92	15.84±0.92	16.04±0.92	19.65±0.92	25.47±0.35	10.49±1.0
4	5	34.69±0.92	44.92±0.92	42.51±0.92	38.30±0.69	38.10±0.92	31.68±0.92	35.70±0.92	39.51±0.92	41.71±0.92	44.52±0.60	16.87±0.47
5	10	49.33±0.60	65.57±1.20	59.76±0.92	57.15±0.60	51.14±1.59	37.9±0.60	45.12±0.60	48.93±0.92	51.74±0.60	49.53±0.92	30.61±0.85
6	15	68.38±0.92	80.21±0.92	74.8±0.69	74.2±0.92	71.19±0.92	62.17±0.92	64.17±0.92	65.78±0.92	69.79±0.60	67.58±0.92	40.27±0.55
7	20	77.81±0.92	88.24±1.25	85.43±0.60	84.63±0.92	80.61±0.60	75.00±0.92	74.40±0.92	79.61±0.69	82.22±0.92	80.41±0.92	55.17±0.60
8	25	93.05±1.25	97.86±0.92	95.25±0.92	94.85±0.92	93.45±0.92	87.83±0.60	91.24±0.35	93.65±0.92	96.66±0.92	96.06±0.69	63.52±0.40

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References

1. Dave V, Yadav S, Sharma S, Vishwakarma P, Ali N. Novel approach of aceclofenac fast dissolving tablet. PMID: 25553683, PubMed. Pak J Pharm Sci. 2015; 28(1):37-41.
2. Patidar Ashish, Mishra P, Main P, Harsoliya MS, Agrawal S. A review on- recent advancement in the

development of rapid disintegrating tablet; Indian journal of life sciences and pharma research. 2011; 1(1):7-16.
3. Tejvir Kaur, Bhawandeep Gill, Sandeep Kumar, Gupta GD. Mouth dissolving tablets: A novel approach to drug delivery: International Journal of Current Pharmaceutical Research. 2011; 3(1):1-7.
4. Sagar A Konapure, Prafulla S Chaudhari, Rajesh J Oswal, Sandip S Kshirsagar, Rishikesh V Antre, Trushal V Chorage, *et al*. Mouth dissolving tablets – An innovative technology, international journal of applied biology and pharmaceutical technology. 2001; 2(1):496-502
5. Jaysukh JH, Dhaval AR, Kantilal RV. Orally Disintegrating Tablets: A Review. Tropical Journal of Pharmaceutical Research. 2009; 8(2):161-172.
6. Sharma S. New generation of tablet: fast dissolving tablet. Pharmaceutical Reviews, 2008, 6(1). www.doaj.org.
7. https://www.drugs.com/mmx/montelukast-sodium.html
8. Tripathi KD. Essentials of medical pharmacology, Jaypee Brother Medical Publisher (p) LTD, 5th edition, New Delhi, Page No. 222-223.
9. British Pharmacopoeia, Published by HMSO London, 1988, 2:A-140.
10. Cooper J, Gunn C. Power flow and compaction, In: Caroter SJ, edn. Tutorial pharmacy, New Delhi, India. CBS publishers and distributors, 1986, 211-233.
11. Indian Pharmacopoeia, Published by ministry of health and family welfare, Govt. of India, New Delhi, 2014.
12. Lachman L, Lieberman HA, L Kanig JL. The theory and practice of industrial pharmacy. 3rd edition, Varghese Publishing House, 1990, 317.