Research Article

Formulation and *In-Vitro* Evaluation of Montelukast Oral Disintegrating (5 Mg) Tablets: Effects of Diluents

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ABSTRACT

The aim of the present study was to prepare oral disintegrating tablets (ODT) by using relatively a simple direct compression technique with high mechanical strength while keeping the attributes of fast disintegration and dissolution to improve the bioavailability of the drug. Mannitol and microcrystalline cellulose (MCC) were studied as diluents in the same quantity for manufacture of montelukast sodium tablet using crospovidone as super disintegrants and sodium bicarbonate as wicking agent. The blend was examined for angle of repose, bulk and tapped density, compressibility index, and Hausner's ratio. The drug-excipients interaction was investigated by FTIR. After compression hardness, friability, disintegration and dissolution, all the formulations batches were analyzed. It was found that microcrystalline cellulose was suitable diluent for tablets considering hardness, friability and disintegration time. Ten formulations F1 to F10 were prepared by central composite methods (Two level factorial designs) for the selection of optimum concentration of disintegrant and diluents. The overall results showed that crospovidone was the best super-disintegrant for showing the shortest disintegration time while MCC was the good diluent in preparing montelukast oro-dispersible tablet and this suggested the possibility of utilizing the selected best formula (F2 and F4) in the preparation of oro-dispersible tablet as a new dosage form for oral administration.

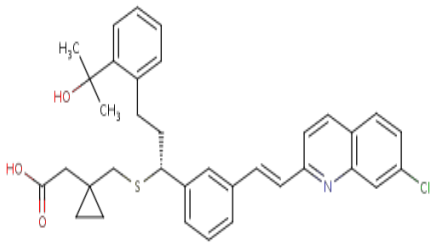
Keywords: Montelukast sodium, central composite method, direct compression, oral disintegrating tablets.

INTRODUCTION

An orally disintegrating tablet or oro-dispersible tablet (ODT) is a drug dosage form available for a limited range of over-the-counter (OTC) and prescription medications. ODTs differ from traditional tablets in that they are designed to be dissolved on the tongue rather than swallowed whole. The ODT serves as an alternative dosage form for patients who experience dysphagia (difficulty in swallowing). Common among all age groups, dysphagia is observed in about 35% of the general population, as well as up to 60% of the elderly institutionalized population[1, 2] and 18-22% of all patients in long-term care facilities.[3] An additional reason to use ODTs is the convenience of a tablet that can be taken without water.

Montelukast sodium is an orally active compound and binds with high affinity and selectivity to the Cysteinyl leukotriene receptor 1 (CysLT1). Montelukast sodium inhibits physiologic actions of Leukotriene D4 (LTD4) at the CysLT1 receptor without any agonist activity. The chemical name of this compound is [R-(E)]-1-[[[1-[3-[2-(7-chloro-2quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1-methyl ethyl) phenyl] propyl] thio] methyl] cyclo propane acetic acid, monosodium salt and the structural formula is as follow:

Montelukast sodium is a hygroscopic, optically active, and white to off-white powder. It is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.



In order to achieve targeted content uniformity of the tablets and to facilitate tablet handling during manufacture, the tablet size should be kept above 2-3 mm and weigh above 50 mg. Many potent drugs have low dose. In such cases diluents provide the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size. Usually the range of diluent may vary from 5-80%.

Diluent in direct compression formulation has a dual role. It increases bulk of the dosage form and also it promotes binding of the constituent particles of the formulation. Hence, selection of diluent is important in tablets produced by direct compression method.[4] Diluent properties can significantly affect disintegration time as well as tablet hardness. Solubility of the diluent in a formulation has shown to affect the rate and mechanism of tablet disintegration. Water-soluble diluents tend to dissolve rather than disintegrate, while water-insoluble diluents produce rapid disintegration. Addition of one or more effective disintegrants combined with suitable amount of a water-insoluble material produce fast disintegrating tablets with good physical resistance

(hardness) and maintain optimal disintegration even at low compression force.[5]

The selection of diluents is based on the consideration that it should be pharmacologically inert, compatible with other ingredients, have consistent physical and chemical characteristics, neither promote nor contribute to segregation of the granulation or powder blend to which they are added and should be able to be milled (size reduction) if necessary in order to match the particle size distribution of the active pharmaceutical ingredient.

The objectives of the current studies were to select the right and appropriate diluent for tablets formulation, to prepare the oral disintegrating tablet by using direct compression method and to evaluate the effect of different diluents on pharmaceutical parameter of the formulation.

MATERIALS AND METHODS

Materials

Montelukast sodium was gifted by MSN Pharmachem Pvt. Ltd**,** India. All others chemicals that were used during the study includes microcrystalline celluloses of Fluka-Biochemika Germany, sodium bicarbonate/HPMC pharmacoat 606 of Labchem Products, crospovidone of BASF Chemicals. Mannitol, aspartame / sucralose, cherry flavour and magnesium stearate were a gift from Julphar pharmaceutical, Ras al Khaimah, UAE. All other materials and reagents were of analytical or pharmaceutical grade, and used as received.

Equipment

The entire experiment was carried by using the equipment that includes dissolution apparatus (Labindia-D5 8000), UV/Visible spectrophotometer (Make – Shimadzu; Model –UV-1700; Made – Japan), analytical balance (Mettler Toledo; Model – PB-153S -Switzerland), disintegration apparatus (Veego-VTD-D), tablet compression machine (Cadmac D3; Germany), FTIR spectrophotometer (Agilent Technologies, Cary 630 FTIR), tablet hardness tester (Pharmatron Dr. Schleuniger; Model –8M), digital vernier caliper (Mitutoyo –Japan), tablet friability test apparatus (Veego, VFT-2D)

METHODS

Design and development of formulation

Initially a draft for Oro-dispersed tablets was design by keeping the standard range and limit of different excipients as per USP and BP. Two (2) level factorial designs were selected in the preparation of orally disintegrating formulations of montelukast sodium (5 mg/tablet) by sodium bicarbonate and crospovidone by keeping two responses disintegration and friability encountered for optimization of formulation. These two ingredients were used in different proportions by using two diluents i.e. mannitol and microcrystalline cellulose in two separate formulas having average weight of 150 mg/tablet and prepared total 10 different batches separately. The pre and post formulation studies were performed for all the batches.

Both types of tablets (10 batches for each) were prepared by direct compression method with variable quantities of crospovidone and sodium bicarbonate. Accurately weighed all ingredients were passed through mesh # 40 manually. Montelukast sodium, microcrystalline cellulose/ mannitol, sodium bicarbonate and crospovidone were mixed in a poly bag for five to ten minutes than cherry flavor, aspartame and magnesium stearate were added and mixed. The mixing time was set based on the uniformity of the parameter of unitary dose. The lubricated blend was compressed on 7.0 mm round plain concave shaped punches at theoretical weight of 150 mg ± 7.5%. Flat-faced tablets were prepared by using a Cadmac D3 tablet compression machine, containing a seven (7) dies, and 7 pairs of plane punches of 7 mm diameter each. About 100 tablets from each formulation were produced.

Pre-formulation studies

Pre-formulation studies provide a frame work for the drug combination with pharmaceutical excipients in the dosage form and aid in collecting information needed to describe the nature of the drug substance. Therefore, the following pre-formulation studies were performed, while developing orally disintegrating tablets (ODTs) of Montelukast Sodium.

Angle of repose [6, 7]

The frictional forces in a loose powder, can be measured by the angle of repose, it is an indication of the flow properties of the powder. The angle of repose was calculated by measuring the height and the base of the heap of powder formed, according to the USP:

$$\text{Tan}(\alpha) = \frac{\text{height}}{0.5 \times \text{base}}$$

Where α = represents the angle of repose, the height in cm, and the radius/ base in cm.

Bulk Density[8]

Accurately weigh 50 g of individual powder and mixture of powder separately and transfer it to a 100 mL graduated cylinder. The powders was carefully leveled without compacting and read as the unsettled apparent volume (V_o)

$$\text{Bulk density } (\rho\text{bulk}) = \frac{\text{Mass of powder}}{\text{Apparent Volume (Vo)}}$$

Tapped Density[8]

In the same way of bulk density, powder individually and in combination 50 g was accurately weighed and transferred to a 100 mL graduated cylinder. The cylinder containing the sample was tapped; according to minimal number of taps required by the USP that is 500. The final tapped volume (V_t) was then measured to the nearest graduated units.

$$\text{Tapped Density (ρ tapped)} = \frac{\text{Mass of powder}}{\text{Tapped Volume (Vt)}}$$

Compressibility Index (Carr's Index) [8]

Powder flowability is measured by Carr's index by using bulk and tapped densities and it is expressed in percentage.

$$\text{Compressibility or Carr index} = \frac{\text{Vo} - \text{Vt}}{\text{Vo}} \text{ X } 100$$

Hausner Ratio[9,10]

It is an indirect index to measure the ease of powder flow. Compressibility index and Hausner ratio are closely related, simple, fast and popular methods to predict the characteristics of powder.

$$\text{Hausner Ratio} = \frac{\text{ρ tapped}}{\text{ρ bulk}}$$

Drug-excipients compatibility studies using FTIR

The compatibility studies were done to analyze the possibility of interaction between drug and Excipient. FTIR spectroscopy was performed for pure drug and the individual excipients separately and for the blended mixture of drug and excipients. This study was done for all the 10 blended formulation batches. The presences of characteristic peaks for the respective functional group in the compound were observed for each batch.

Post-formulation studies

Weight variation

The uniformity of the weight of the tablets is one of the important parameter because in general it is considered as the uniformity of the contents, as one tablet contains the label claim amount of active pharmaceutical ingredient and variation or difference of tablet weight will result in variation in amount of active pharmaceutical ingredient in each tablet. Twenty (20) tablets of each batch were weighed individually for performing the weight variation test and then calculating the mean and range.

Hardness and thickness[11]

The pharmacopeias do not directly define the limit for hardness, thickness and diameter/ length which are actually related to the packaging aspect of dosage form. Tablet hardness and thickness have a strong relationship with each other and thickness is controlled with the help of hardness; so generally the thickness of the tablets should be within ±5% variation.

Friability Test[12-15]

Friability test is useful to assess that the dosage form during transportation from manufacturer till its delivery to patient is able to withstand the jerks and jolts that it may come across. According to the procedure defined in both USP and BP, the friability testing of uncoated tablets were carried out. The test was conducted on a friabilator which is rotated at 25 rpm for four minutes, works on the same principal defined in both pharmacopeias.

Wetting Time

Based on tablet size, a recommended volume of 0.1% (w/v) dye solution was added into 10 mL petri dishes. The ODT was carefully placed on the surface of the dye solution and finally the total wetting time was measured.[16,17] The time required for the dye solution to diffuse through the tablet to reach the center of the upper surface of the tablet was noted for each batch.

Disintegration Test

This is very important test as it provides the in-vitro simulation of drug disintegration and dispersion after intake. The in-vitro disintegration time test is a significant characteristic required for orally disintegrating tablets. For ODT dosage forms it must be within a minute.

Dissolution Test

It is an in-vitro test that measures the rate at which the drug passes into solution form. It provides the in- vitro simulation for bioavailability studies. In this test total amount of drug in solution form is measured as a function of time.[18]

$$\% \text{ Dissolution} = \frac{Absorbance\ of\ Sample}{Absorbance\ of\ Standard} \text{ X } \frac{Wt.of\ Standard}{Dilution} \text{ X } \frac{Dilution}{Wt.of\ Sample} \text{ X } 100$$

$$= \frac{\text{Calculated amount}}{\text{Claimed amount (5 mg)}} \text{ X } 100$$

Drug content (Assay) for Montelukast Sodium tablet

Standard and sample solutions of montelukast sodium were prepared in methanol in ratio of 25mg / 100mL. Drug content was analyzed spectrophotometrically at λ = 254 nm.

RESULTS AND DISCUSSIONS

Prior to the development of any dosage form, it is essential that certain fundamental physical and chemical properties of drug powder should be determined. This information may help in subsequent event and approaches in formulation development. The micromeritics studies such as bulk density (BD) and tapped density (TD), compressibility index (Carr's index), Hauser's ratio (H), and angle of repose were performed in order to determine the best excipients to be used in the formulation development of montelukast sodium orally dispersed tablets.

For direct compression, the flowability of the powder blend is very important. Therefore, two methods were used for powder flowability measurements. First was the bulk density and tapped density of the powder blends to calculate the Hausner ratio and Carr's index. The second was to determine the angle of repose (Table 1).

Table 1: Comparison of Physical Characteristics of Powder Blends having microcrystalline cellulose and Mannitol

Formula No	Bulk density		Tapped density		Carr's index		Hausner Ratio		Angle of repose	
	MCC*	M*	MCC	M	MCC	M	MCC	M	MCC	M
F1	0.555	0.499	0.665	0.623	16.54	19.90	1.20	1.248	32.3	33.9
F2	0.496	0.596	0.540	0.650	8.148	9.18	1.09	1.089	27.63	30.0
F3	0.595	0.578	0.788	0.656	23.51	11.89	1.32	1.135	36.81	35.81
F4	0.598	0.497	0.668	0.567	10.479	13.51	1.11	1.141	29.3	32.5
F5	0.560	0.523	0.693	0.611	19.19	14.403	1.24	1.168	31.81	33.81
F6	0.499	0.497	0.595	0.575	19.56	13.565	1.19	1.157	38.3	37.9
F7	0.509	0.501	0.630	0.670	14.44	25.224	1.23	1.337	32.62	38.12
F8	0.495	0.491	0.595	0.565	16.81	13.097	1.20	1.151	35.73	36.73
F9	0.590	0.587	0.693	0.613	14.86	4.241	1.17	1.044	36.7	38.7
F10	0.551	0.551	0.675	0.635	18.37	13.228	1.23	1.152	34.63	35.60

*MCC =Microcrystalline cellulose; *M = Mannitol; Angle of Repose = Excellent = 25-30; Carr's index = Excellent = ≤ 10

Table 1 showed that the physicochemical properties such as carr's index, angle of repose, bulk and tapped density and hausner ratio are significantly different for powder blends prepared with same ratio and compositions of all other components of the formulation except these two diluents, microcrystalline cellulose and Mannitol.

Mannitol has poor flow properties as compare to the microcrystalline cellulose it need high concentration of lubricant that can creates other formulation problems.[19] Microcrystalline cellulose (MCC) is highly compressible and most widely used direct-compression tablet diluent. It gives hard tablets, at low compression pressures. It also exhibits binding properties and possesses disintegrants activity and thus promotes fast tablet disintegration.[19]

FTIR spectroscopy was performed for pure drug and the individual excipients separately and also for the blended mixture of drug and excipients. The presence of characteristic peaks for the respective functional group in the compound were observed for pure drug, excipients, and its physical mixture, as illustrated in below Fig.1

Montelukast sodium pure drug shows the bond vibrations at 3396 cm^{-1} (COOH stretching), 3057 cm^{-1} (aromatic C–H stretching), 2925 cm^{-1} (aliphatic C–H stretching), and 1710 cm^{-1} (C–O stretching). From the physical mixtures of drug and excipients, there were no major shifting as well as no loss of any functional peaks between the spectra of drug, excipients and its physical mixtures. It was concluded that there was no interference of the functional group that indicating compatibility between adjuvants (Fig. 1).

After analysis of physiochemical parameters of powder blends, orally disintegrating tablets were formulated with microcrystalline celluloses and mannitol in combination of different ratio of two disintegrants, sodium bicarbonate and crospovidone.

The quali-quantitative composition of the optimize formulations were developed and prepared according to centrally composite method (2^2 factorial) by using "Design Expert (v.9)" soft-wear. The influence of excipients on the pharmaceutical properties of tablets was evaluated. Hardness, friability and disintegration time were chosen for this factorial study. In the proposed study the focus was on the qualitative factors of the type of filler and the type of disintegrants on the quality control properties of tablets.

By evaluating the effect of microcrystalline cellulose and mannitol as filler in tablets was indicated that microcrystalline cellulose alone can produce a good strength in the tables (NLT 4KP) whereas the mannitol (alone) is not a good filler for the direct compression tablets (Table2). Tablets friability was significantly higher ($p \leq 0.05$) for formulations prepared with mannitol in relation to formulations containing microcrystalline cellulose (Fig. 2).So the concern of the study was to obtain ODT with high mechanical strength while caring the quality of fast disintegration and dissolution to improve the availability of the drug in the systemic circulation.

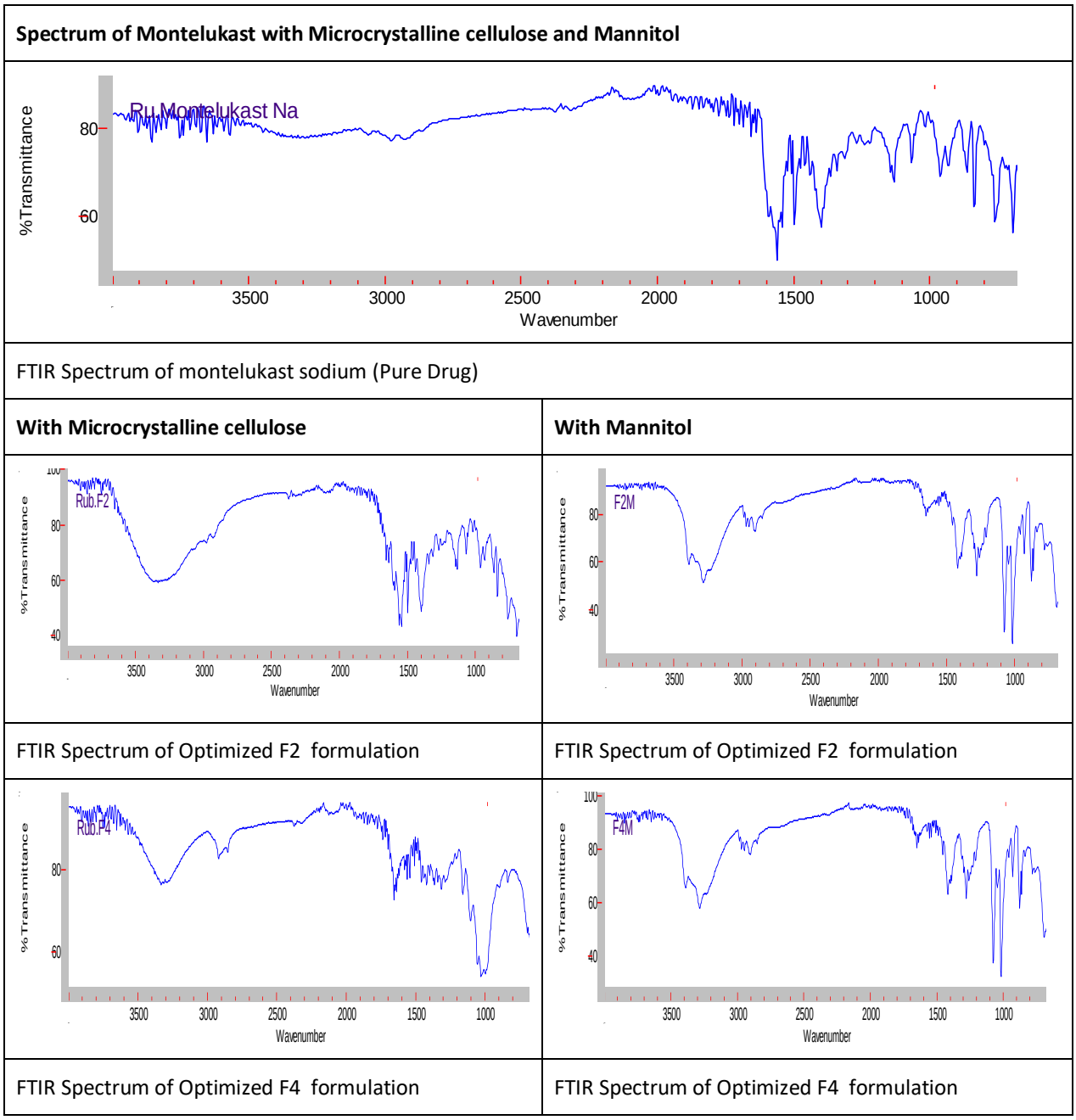


Figure 1: Comparison of spectrum of Montelukast sodium with microcrystalline cellulose and mannitol

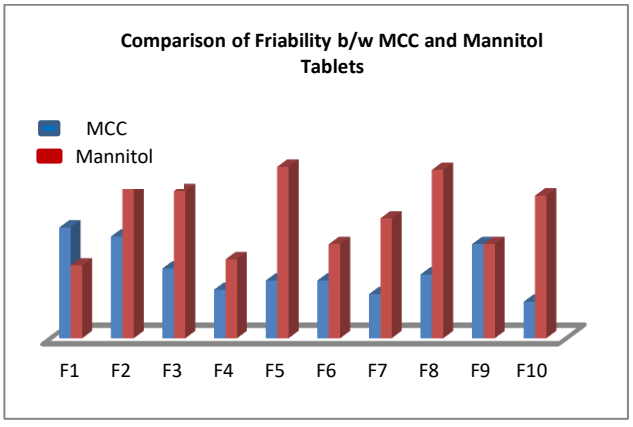


Figure 2: Comparison of friability of tablets containing MCC and Mannitol

All the 10 formulations of each diluent met pharmacopoeial specifications for weight variation, fell in the range from (Mean ±SD) 138.35 ± 0.39 to 151.05 ± 0.73 mg with lower limit of 138.75 mg and upper limit of 161.25 mg and higher percentage of drug release, minimum of 75.5% and maximum of 97.14% after 15 min. of dissolution from MCC tablets and 95.90-107.81% from mannitol tablets (Table 2)but the disintegration time in case of mannitol is more better with 7.99 second minimum and 15.94 seconds maximum time as compare to the formulation having microcrystalline cellulose that is between 11.0 -36.00 seconds (Table 2). In the present project the targeted time for disintegration was 30 second to get faster disintegration as per desire requirement of the study. This is an essential parameter for Oro-dispersed tablets where trying to keep the

disintegration time less than one minute (< 1) as it could be the rate-determining step in the process of drug dissolution and absorption.

The wetting time is one of the vital parameter to predict how much of fluid is enough for breaking of tablets when put on to the tongue (volume of normal saliva = 0.25–0.35ml/min). The wetting time is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water. Wetting time test was performed on triplicate of each formulation and was found to be in the range of 20 to 45 second for both types of tablets. This approach also helps to calculate and adjust the in-vitro disintegration time of a tablet. A lower wetting time implies a quicker disintegration of the tablet. The content assay was carried out for all batches of formulation and it was found well within the acceptance limits defined by the USP (NLT 90% and NMT 110%).

Table 2: Evaluation of Oral dispersible Tablets

Formula No	Hardness NLT 4KP		Friability NMT 1%		Disintegration Time (sec)		Dissolution % At 15min	
	MCC*	M*	MCC	M	MCC	M	MCC	M
F1	4.70	4.28	0.73	0.48	11.0	15.94	75.5	96.55
F2	**5.17**	2.46	0.67	1.07	19.00	7.99	97.14	107.81
F3	7.43	2.57	0.46	0.97	24.00	8.45	79.80	98.91
F4	**6.07**	**2.6**	0.32	0.52	36.00	8.96	96.38	107.81
F5	6.03	2.23	0.38	1.13	28.00	12.18	78.90	95.90
F6	7.30	3.1	0.38	0.62	28.00	8.69	83.76	96.76
F7	5.03	2.61	0.29	0.79	33.00	11.77	82.95	100.71
F8	6.30	2.4	0.42	1.11	25.0	7.83	84.52	100.9
F9	7.43	2.83	0.62	0.62	18.0	10.35	84.86	101.67
F10	5.20	3.13	0.24	0.94	30.0	10.39	86.38	100.48

Hardness and friability are not the official tests but as per USP it's come under the physical tests that are applicable for the design and development of tablet formulations. These are used to determine the need for pressure adjustments on the tableting machine. Hardness can affect the disintegration. So if the tablet is too hard, it may not disintegrate in the required period of time. And if the tablet is too soft, it will not withstand the handling subsequently. The tablets must show good mechanical strength with sufficient hardness in order to handle shipping and transportation. Hardness or breaking force of tablets for all batches was found in the range from 4.7±0.05 to 7.43±0.03 Kp that comprised on MCC and 2.23±0.12 to4.28 ±0.14Kp which contained mannitol (Table 2) (Fig. 2). This result is also supported by the work of Radosław (2011).[20] The result indicated that the hardness and tensile strength of tablets formulated using the cellulose based filler, microcrystalline cellulose was found to be higher than tablets formulated using the sugar based filler including Mannitol. This was related to the better binding properties of microcrystalline cellulose (MCC) component. This statement is also supported by the work done by Umeh et al., 2013.[21]

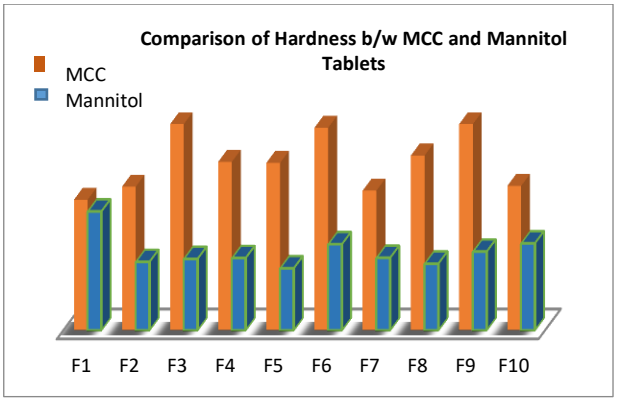


Figure 3: Estimation and Comparison of hardness between tablets consisting on MCC and Mannitol

CONCLUSION

Fast disintegrating dissolving tablets (FDDTs), a more recent innovation, have gained a great deal of attention particularly for use in various patient groups such as the paediatric, geriatric, travelling patients and patients having dysphagia. The orally disintegrating tablets of montelukast sodium were prepared by using two different diluents and evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. Post-compression parameters such as weight variation, hardness, friability, disintegration time and dissolution analysis were evaluated. Tablets containing Mannitol as filler showed a fast DT of below 30 seconds with low

hardness of 2.23Kp whereas microcrystalline cellulose showed higher DT but < 1 min and harder than mannitol tablets. For tablets containing mannitol, osmotic agents were found to result in faster disintegration of the tablets, while for tablets formulated with microcrystalline cellulose, the super-disintegrants resulted in faster disintegration.

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