Development of Orally Disintegrating Tablet containing Montelukast for Paediatric Patients

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Abstract: The oral route is most accepted way for the management of therapeutic agents because of the low cost of treatment and simplicity of management guide to high levels of patient importance. The pre-compression parameters showed that the powder blends had sufficient flow properties thickness was uniform and compression force was applied while punching the tablets. The uniformity in weight resulting in effective die cavity filling and hardness known to have longer deviation resulted in differences in disintegration time. The friability values were consistent and disintegration test, wetting time and dispersion time was less than 90 sec. The result was indicated that the formulation disperses within a minute and followed the need of purpose. Formulation MODTs3 has the best dissolution profile of 99.99 % at 30 min. The in vitro dissolution studies were fitted to zero order, first order and Korsmeyer-Peppas equations. The addition of solid dispersion containing drug and mannitol (1:3) ratio has water wicking and swelling properties which lead to rapid disintegration of drugs, which in turn, leads to the more rapid dissolution of drugs. The combination of agents have more disintegrating property due to rapid water uptake and dispersion time which lead to rapid release of drug and made the dissolution faster. The results of the release kinetics study showed that all the formulations obeyed first order drug release profile more closely, i.e., the release rate depended upon the initial concentration of drug.

Keywords: Solubility enhancement, Solid dispersion, Orally Disintegrating Tablet, Montelukast, Paediatric Patients

Introduction: Bronchial Asthma is a chronic inflammatory disorder of the airways characterized by bronchial hyper-responsiveness and reversible airflow obstruction causing cough, wheeze, chest tightness and shortness of breath [1]. The oral route of drug administration has been used most preferably for both conventional as well as for novel drug delivery because of the ease of administration and widespread acceptance by patients [2]. The term "direct compression" is employed to describe the procedure by which tablets are manufactured directly from the powder blends of active pharmaceutical ingredient/s and appropriate excipients [3]. Orally disintegrating tablets (ODTs) offer several advantages over the conventional oral dosage forms particularly in terms of patient compliance [4]. One negative aspect of solid oral dosage forms is dysphagia (difficulty in swallowing) and chewing in some patients particularly in geriatric and paediatric patients [5]. Orally disintegrating tablets (ODT) are well established dosage forms that disintegrate in the oral cavity leaving an easy-to-swallow residue. ODT's disintegrate rapidly in saliva without the need of water, within few seconds to minute [6]. Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid-dosage forms. The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar [7]. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules [8]. Many patients express difficulty in swallowing tablets and hard gelatin capsules, resulting in noncompliance and ineffective therapy [9]. To overcome this weakness, scientists have developed innovative drug delivery systems known as fast dissolving tablets [10]. The fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed up on the tongue" [11]. Their characteristic advantages such as administration without water,

patient compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market [12]. 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. Montelukast is a leukotriene receptor antagonist used as part of an asthma therapy regimen, to prevent exercise induced bronchoconstriction, and to treat seasonal allergic rhinitis [9]. Montelukast is a leukotriene receptor antagonist that demonstrates a marked affinity and selectivity to the cysteinyl leukotriene receptor type-1 in preference to many other crucial airway receptors like the prostanoid, cholinergic, or beta-adrenergic receptors. **T**he mean plasma half-life of montelukast varies from 2.7 to 5.5 hours when observed in healthy young adults. The plasma clearance documented for montelukast is an average of 45 mL/min when observed in healthy adults [13]. The proposed study is prepared and characterizes the oro-dispersible tablet containing monteleukast solid dispersion (MSDs) formulation with using natural superdisintegrant with direct compression.

Material and methods: Monteleukast, superdisintegrants {sodium starch glycolate (SSG), crosscarmellose sodium (CCS), crosspovidone (CP), and microcrystalline cellulose (MCC)} which were used alone and in combination, diluents: lactose, granulated lactose, and mannitol, along with lubricant and glidants.

Analytical and valiudation studies: The drug samples will be use for determination of absorption maxima (λmax) in various solvents i.e. phosphate buffer pH 6.8 solution. The analytical method evaluated with preparation of calibration curve. The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer (Shimadzu, UV-1800, A11454500755/UV-1800, Shimadzu Corporation, Kyoto, Japan).

Preformulation study: The drug were characterized by organoleptic properties, microscopic examination by using phase contrast microscope. The physical characteristics of drug samples i.e. density, particle size, flow properties, compatibility, solubility in various dissolution medias, partition coefficient and drug-excipients compatibility by UV Spectroscopy, FTIR etc.

Formulation of Orally Disintegrating Tablets: These types of formulations solid dosage forms as tablets of model drugs have to be prepared by different methods (Direct compression).

Solid dispersion method using sugar derivative as mannitol: The solid dispersion of drug was prepared by weighed amount of drug was dissolved in ethanol and mannitol in different ratios (1:1, 1:2, 1:3 w/w) was added to this drug solution (in ethanol) and mixed on Vortex shaker (Electro Lab, India) for one hour. The solvent was evaporated in hot air oven at 45°C until dry. The solid dispersion was collected and ground using mortar and pestle and then sieved through mesh #18. This dried solid dispersion was used for further evaluation study.

Evaluation of monteleukast solid dispersion (MSD1 – MSD3)

Physical appearance: All the batches of monteleukast physical mixture and solid dispersions were evaluated for color and appearance.

Solubility studies: The solubility of drug was determined in distilled water, 0.1N HCI, ASA pH 6.8 and phosphate buffer pH 7.4. A accurate weighed 25 mg drug was kept in conical flask and required quantity upto 50 ml were kept in burrete. Now start the addition of 5 drops to conical flask containing drug. The conical flask regularly shaking and the amount of dissolution media noted, at which the drug was solubilized and kept for shaking at 37^{o}C for 24 h in orbital shaking machine. Aliquots were filtered through whatman filter paper and the solubility of drug was calculated with unit mg/ ml.

Differential Scanning Calorimetry (DSC): Pure drug (Monteleukast (ML), solid dispersion (5-10 mg) was heated in hermetically sealed aluminium pans with a heating rate of 10°C/min under nitrogen atmosphere (flow rate 20 ml/min) and thermograph were recorded using differential scanning calorimeter (Perkin-Elmer DSC7, USA).

SEM studies: The physical mixture and solid dispersions were evaluated for their physical structural changes in the surface topography of the drug particles by scanning electron microscopy (SEM) technique.

Percent practical yield: Percent practical yield was calculated to know about percent yield or efficiency of the any method thus it helps in selection of appropriate method of

production. Physical mixture / Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation:

$$PY\ \% = \frac{\text{Practical mass}}{\text{Theoretical mass (drug + carrier)}} * 100$$

Formulation of Monteleukast Orally Disintegrating Tablets: Monteleukast Orally Disintegrating Tablets (formulas MODTs1- MODTs3) were prepared by direct compression method according to the formulas given in **(Table 6.1)**. The content of optimized effective formulation was MODTs3, which containing drug: mannitol (1:3) ratio solid dispersion. The equivalent amount of drug 25mg presents in solid dispersion MSD3 about 100 mg total weight powder. The procedure is as follows: All the ingredients (except lubricants and glidant) were passed through sieve mesh #40 meshes separately. Then weighed and mixed in geometrical order for about 10 min. Then lubricants and glidant were added to the mixture and mixed for about 2 min. Finally an accurate weight of the blend was compressed into tablets of 200 mg using 8 mm punch tablet compressing machine.

Table 1: Preparation of MSD3 containing Monteleukast Orally Disintegrating Tablets

Ingredients (in mg)	MODTs1	MODTs2	MODTs3
Solid dispersion equivalent to 25 mg (MSD3)	100	100	100
SSG (Sodium starch glycollate)	20	40	30
Ac-Di-Sol	40	20	30
Crosspovidone (5%)	10	10	10
Spray dried lactose	150	50	75
Microcrystalline Cellulose PH 102	0	100	75
Magnesium stearate	15	15	15
Purified talc	15	15	15
Total amount (g)	350	350	350

Evaluation of Monteleukast Orally Disintegrating Tablets: The prepared **FMODs** will be evaluated for thickness of tablets, uniformity of weight, hardness, friability, disintegration time, water uptake percent, swelling studies, rupture test, drug content, in-vitro drug release study.

Result and Discussion

Analytical Study: Monteleukast drug was analytic validated by UV spectrophotometric methods and drug was estimated in the dissolution medium ASS pH 6.8 phosphate buffer solutions. The calibration curves in the dissolution medium ASS pH 6.8 phosphate buffer solution prepared with drug solutions of known concentrations. The absorbance of each solution was measured separately at 350 nm, for ASS pH 6.8 phosphate buffer solution of drug **(Figure 1)**.

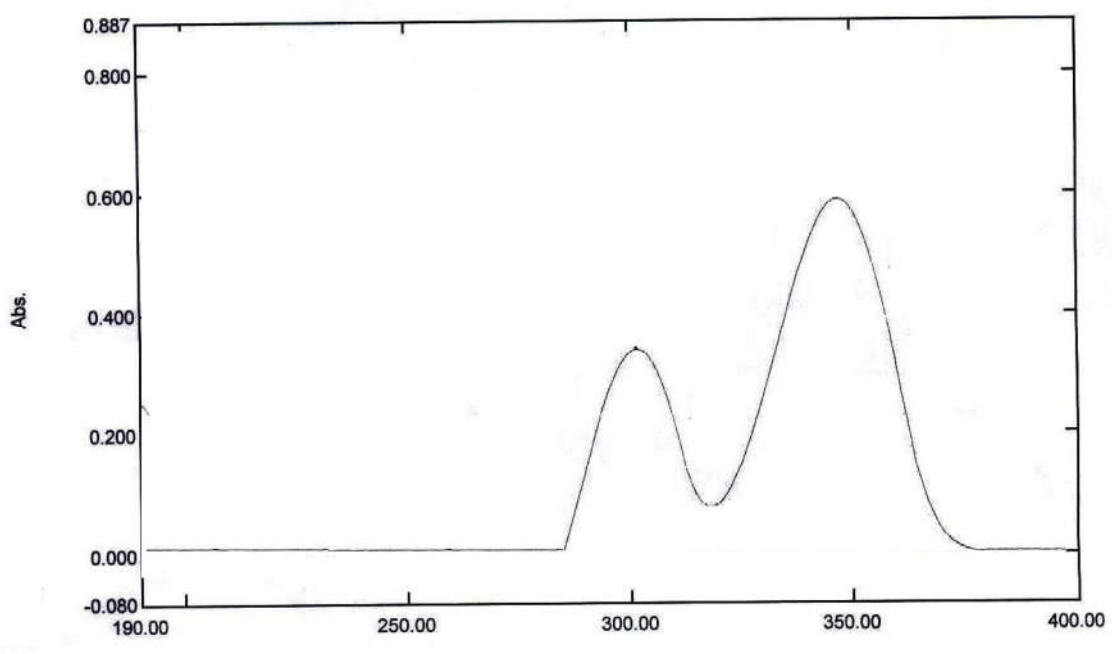

Figure 1: Absorption maxima (λ-max) of drug in phosphate buffer ASS (pH 6.8) solution

The absorbance was measured and standard curve was plotted between absorbance vs. concentration. The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to be greater than 0.99. The curves were found to be recti-linear in the concentration range **5 µg / ml to 20 µg / ml** for the drug **(Figure 2)**.

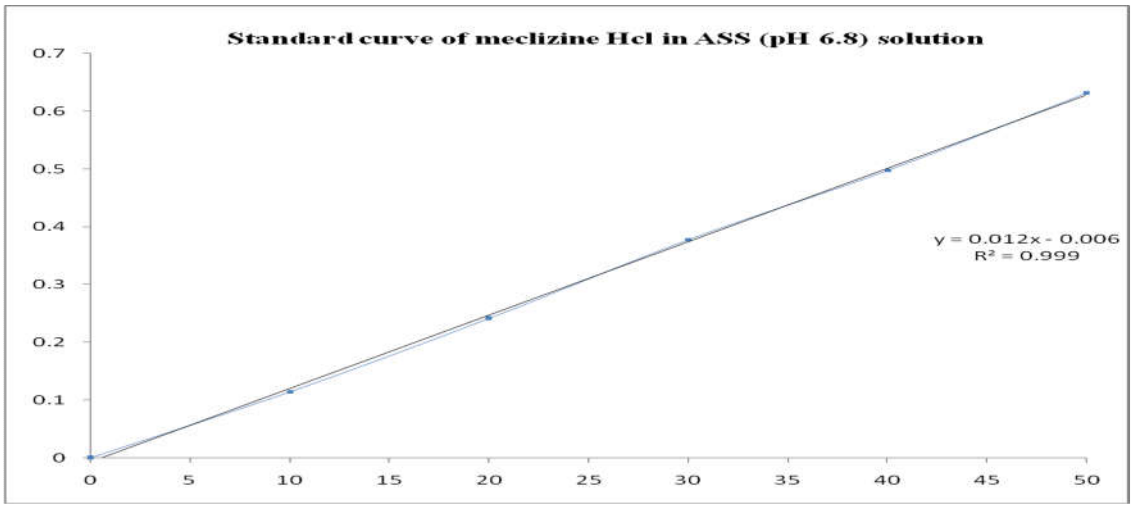

Figure 2: Standard curve of drug in ASS (pH 6.8) solution (350 nm)

Preformulation Studies: Preformulation studies are important task for development of dosage forms of model drug substances. The overall objective of preformulation studies is to produce information constructive to the formulator in development of stable and bioavailable dosage forms. Drug was found to be White to off white powder, specific odorless, tasteless in nature. The microscopic examination of the drug sample was crystalline powder. The drug powder bulk and tapped densities to be 0.591 gm / cm^3 and 0.728 gm / cm^3, respectively. The particle size of unmilled powder was 93 µm. The flow of unmilled drug powder was good to excellent flow characteristics. The solubility of drug was very less soluble in all dissolution media. The partition coefficient of monteleukast was found to be 2.42 and the value of partition coefficient of drug showed that the drug was lipophilic in nature. The Infrared spectra were obtained using an FTIR spectrometer. The blend was filled in amber color glass vials and stopped with grey rubber stoppers followed by aluminium seal. IR spectrum of monteleukast **Figure 3 and 4** is characterized by 2420cm-1 (–NH3– stretch), 2300cm-1 (CH2–CH2), 1450cm-1 (C = C stretch), 1080-1 (C–N stretch), 910 cm-1 (C–Cl stretch). No significant alterations in

the IR bands of the pure drug were detected in the physical mixture.and passed through sieve # 40, mixed well.

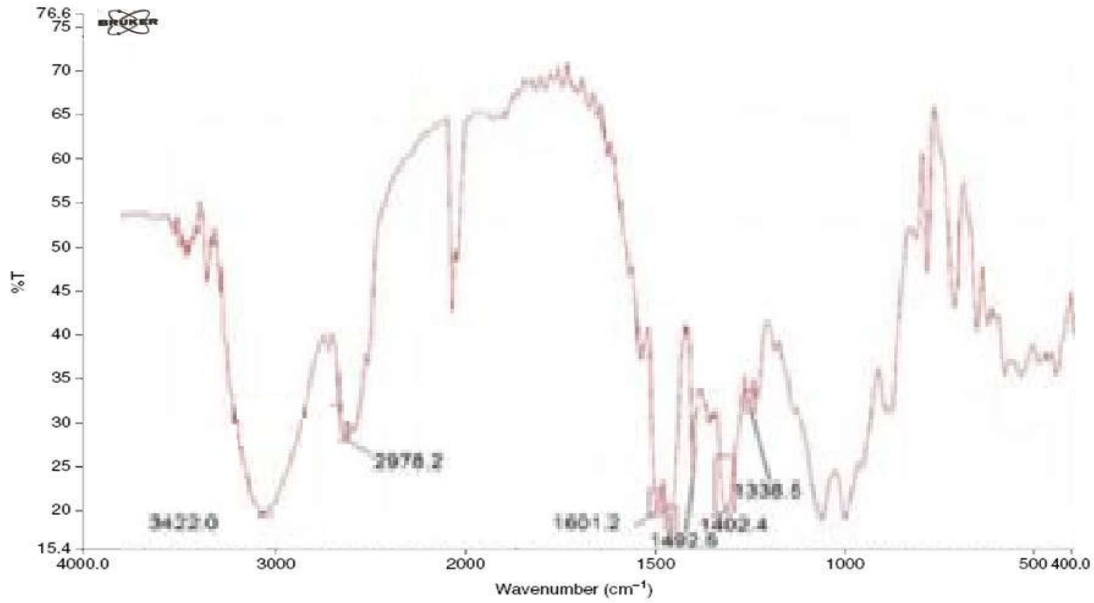

Figure 3: The I. R. Spectrum of drug sample (S1)

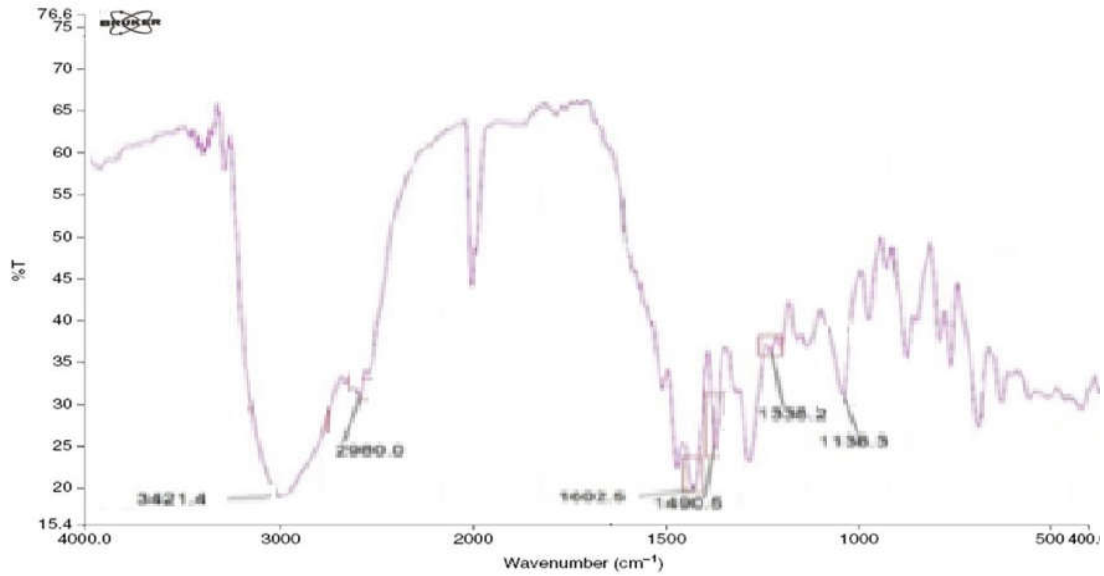

Figure 4: The I. R. Spectrum of drug and all excipients (S2)

Characterization of drug solid dispersion: The physical appearance and color of prepared solid dispersion powders was granular product in appearance and off-white in

color. The solubility studies were conducted in different media for all the prepared solid dispersions and compared with pure drug. From the solubility studies, it was found that as the increase in pH of the media increased the solubility i.e. MSDs showed greater solubility in ASS phosphate buffer pH 6.8. The solubility data of different formulations showed in **Table 2**. From the results, solid dispersions with 1:3 ratio with mannitol showed grater solubility when compared to other, by increasing the carrier concentration the solubility also increased proportionally. From all the above formulations, MSD3 formulation showed highest solubility in ASS phosphate buffer pH 6.8. The percent practical yield obtained for formulation MSD1, MSD2 were 90.12 - 98.23% respectively. The DSC thermogram of mannitol showed sharp endothermic peak at 171.12°C and monteleukast mannitol solid dispersion shows two endothermic peaks corresponding to the melting point of drug and mannitol indicating no chemical interaction between them **(Figure 5 – 6)**. The SEM photographs describes that monteleukast are small crystalline structure but its original one was totally amorphous and no sign of crystallinity was observed in SEM photographs **(Figure 7)**.

Table 2: Solubility study of taste masking of monteleukast by solid dispersion

S. No	Medium	Solubility (mg/ml)±SD*		
		MSD1	MSD2	MSD3
1	Distilled water	1.351±0.51	1.568±0.11	1.480±0.11
2	0.1N HCI,	0.708±0.17	0.822±0.15	0.991±0.13
3	ASA pH 6.8 Phosphate buffer	1.521±0.28	1.711±0.31	1.999±0.17
4	Phosphate buffer pH 7.4	1.432±0.17	1.611±0.18	1.718±0.11

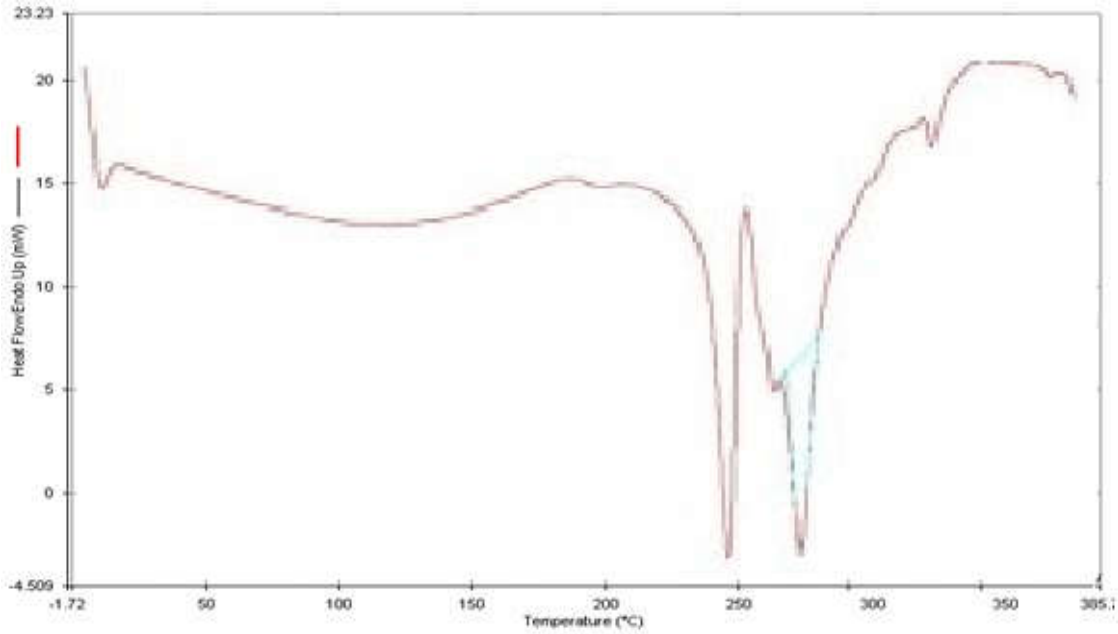

Figure 5: DSC of drug sample (S1)

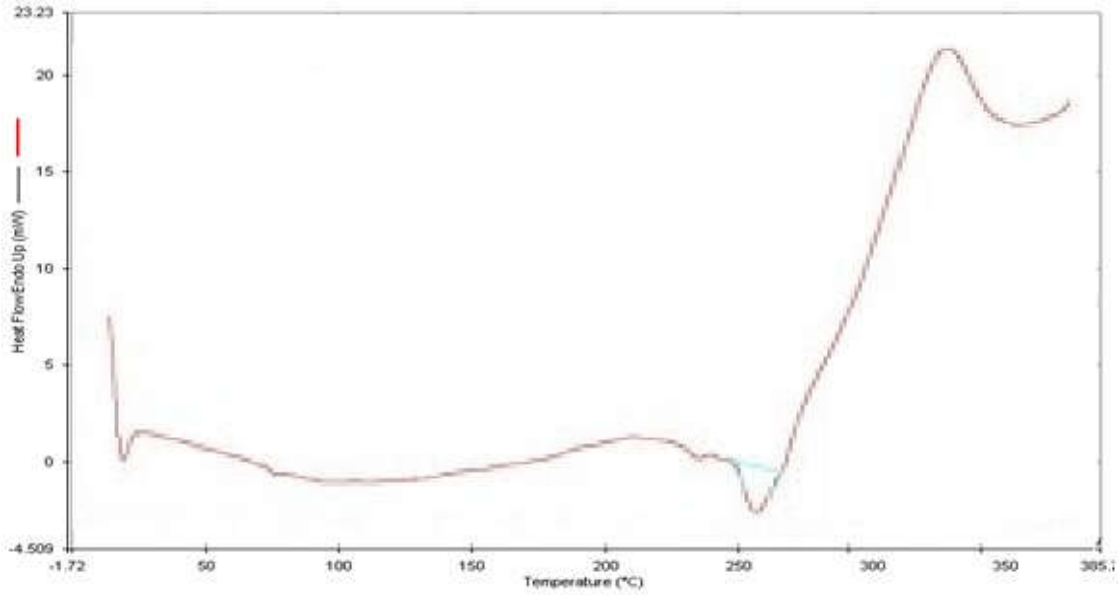

Figure 6: DSC of drug and all excipients (S2)

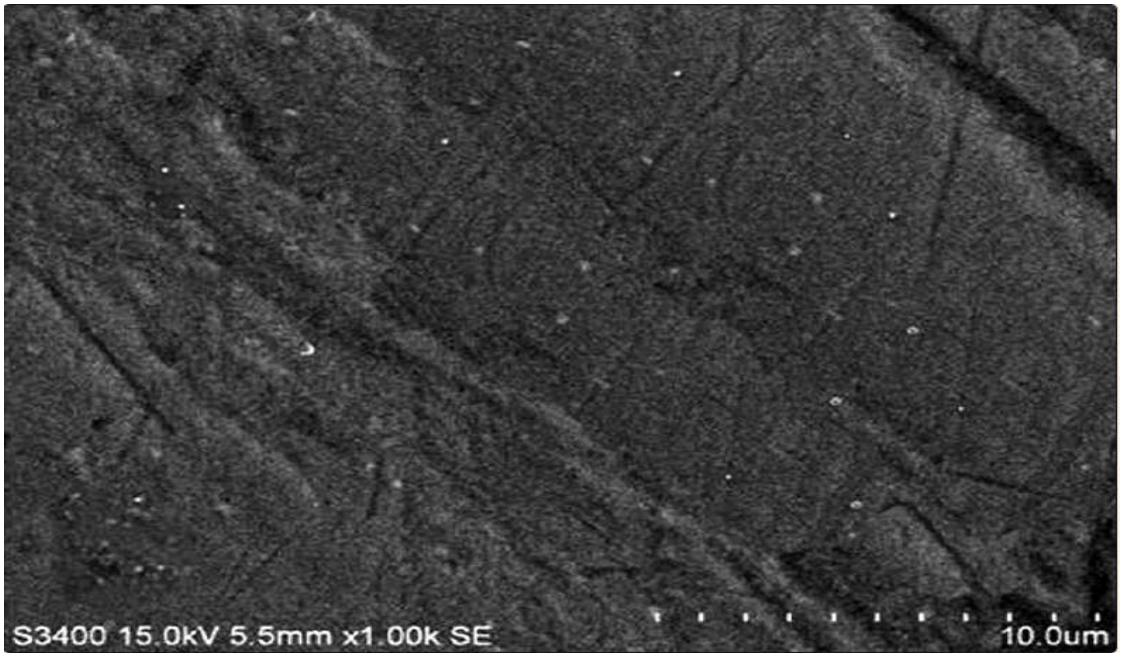

Figure 7: SEM photograph of drug solid dispersion (MSD3)

Evaluation of Orodispersible Tablets:

Monteleukast containing solid dispersion powder were direct compressed to formulate orodispersible Tablets. The pre-compression parameters showed that the powder blends had sufficient flow properties as per the approved limits. The thickness of the tablets was uniform in each batch. This showed that uniform compression force was applied while punching the tablets. The uniformity in weight is related to the improvement in powder flow properties through the addition of talc and magnesium stearate, resulting in effective die cavity filling. The MODTs were generally expected to have hardness of 3 to 3.5 kg/cm^2, since harder tablets are known to have longer disintegration times. The hardness was monitored at regular intervals during punching to keep the hardness value at a uniform level. A deviation from the hardness will result in differences in disintegration time. The tablets were highly stable to any external stress that might be involved during transportation and packaging: the friability values were consistent with the USP limit of < 1 %. The results of the disintegration test, wetting time and dispersion time was less than 60 sec., which mimics the disintegration taking place in mouth, correlated with the results of the USP disintegration test. The result was indicated that the formulation will be disperse within a minute and followed the need of purpose **(Table 3)**. Formulation

MODTs3 has the best dissolution profile of 94.38 % at 30 min. Results of in vitro dissolution studies were fitted to zero order, first order and Korsmeyer-Peppas equations. The values of r^2 ranged from 0.862 to 0.978 (first order plot) for different formulations. The values of slope of Korsmeyer-Peppas plots ranged from 0.949 to 0.774. Addition of solid dispersion containing drug and mannitol (1:3) ratio has water wicking and swelling properties which lead to rapid disintegration of drugs, which in turn, leads to the more rapid dissolution of drugs. Microcrystalline cellulose and mannitol in higher ratio act as superdispersible property and solubility enhancing agent. The combination of agents have more disintegrating property due to rapid water uptake and dispersion time which lead to rapid release of drug and made the dissolution faster. The results of the release kinetics study showed that all the formulations obeyed first order drug release profile more closely, i.e., the release rate depended upon the initial concentration of drug. The slope values of the Korsmeyer-Peppas plot showed that the mechanism was non-fickian or supercase II transport mechanism.

Table 3: Flow properties of granules of orally disintegrating blends (MODTs1 – MODTs3)

Formulation code	Carr's index [n] (%)	Hausner's ratio [n]	Angle of repose (θ) [n]	Tablet Thickness (mm)		Weight Variation (%)	Hardness (kg/cm ^{2})	Friability w/w (%)	Drug Content (%)	Disintegration Time (sec)	Wetting time (sec)	Water absorption ratio (%)	Dispersion Time (sec)
				Diameter	Height								
MODTs1	18.01 ±0.002	1.17± 0.011	26.1 ±0.001	8.01 ±0.001	2.11 ±0.002	2.1± 0.011	3.6± 0.12	0.614±0.005	99.2 ±0.10	51±0.01	21.01±0.09	28.11±1.02	33 ±0.02
MODTs2	17.04 ±0.011	1.17± 0.001	29.1 ±0.001	8.02 ±0.002	2.04 ±0.011	2.2± 0.031	4.1± 0.19	0.515±0.002	99.1 ±0.05	42±0.03	16.22±0.03	23.61±1.13	31 ±0.01
MODTs3	18.03 ±0.013	1.15± 0.028	28.8 ±0.002	8.01 ±0.001	2.01 ±0.011	2.1± 0.002	4.9± 0.21	0.493±0.002	99.8 ±0.01	31±0.03	11.00±0.03	19.31±1.42	32 ±0.02

n = 3 (mean ± Standard deviation)

Summary and Conclusion: The superdisintegrants and its concentration shall be during the preparation of MODTs with monteleukast by using direct compression via employing different excipients in different ratio including: superdisintegrants {sodium starch glycolate (SSG), Ac-Di-Sol, crosspovidone (CP), Spray dried lactose and microcrystalline cellulose (MCC)} which were used alone and in various combination and mannitol, along with lubricant and glidants. The prepared MODTs with a short disintegration time, sufficient mechanical strength, better patient compliance, and acceptable stability profile by employing different methods of preparation and studying different variables affecting pre and post-compression parameters.

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