CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

PREPARATION AND CHARACTERIZATION OF SOLID DISPERSION CONTAINING ORALLY DISINTEGRATING TABLETS

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Article Received: February 2024 Accepted: March 2024 Published: April 2024

Abstract:
The orally disintegrating tablet of monteleukast prepared batches of tablets were evaluated for thickness, weigh variation, hardness, friability, drug content uniformity, wetting time, water absorption ratio, in vitro disintegration time and in-vitro drug release. Formulations were tested for the in-vitro drug release pattern (in pH 7.4 phosphate buffer). The various formulations containing superdisintegrants in different concentration will be examine the angle of repose, bulk density, tapped density, Compressibility index and Hausner's ratio of powder blend the results were found to be within prescribed limits and indicated good flowing property. In the present study four natural superdisintegrants and its concentration shall be during the preparation of ODTs. Superdisintegrants are primarily required for fast dissolving or disintegrantion of tablets for this purpose.

Keywords: *Solid dispersion, Oral formulations, Disintegrating tablets, Montelukast, Bronchial asthma*

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Please cite this article in press ***Karuna Sharan*** *et al,* ***Preparation And Characterization Of Solid Dispersion Containing Orally Disintegrating Tablets.,****Indo Am. J. P. Sci, 2024; 11 (4).*

INTRODUCTION:

Asthma is a chronic inflammatory disorder of the airways. This feature of asthma has implications for the diagnosis, management, and potential prevention of the disease. Bronchial asthma is a chronic inflammatory disorder of the airways associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment [1]. Oral administration has been considered as one of the most convenient and widely accepted routes of delivery for most therapeutic agents. Traditionally oral dosage forms refer to tablets, capsules and liquid preparations taken orally, swallowed and transiting the gastrointestinal tract (GIT) for post buccal absorption. The orally disintegrating tablets are synonymous with mouth fast disintegrating tablets, melt in mouth tablets, rapimelts, porous tablets, orodispersible, quick dissolving or rapidly disintegrating tablets. Their growing importance was underlined recently when European pharmacopoeia adopted the term "orodispersible tablet" as a tablet that can be placed in the mouth where it disperses rapidly, before swallowing [2-3]. A superdisintegrant is an excipient, which is added in lower concentrations to a tablet or capsule blend to aid in breakup of the compacted mass within seconds. Direct compression is defined as the process by which tablets are compressed directly from powder blends of the active ingredients and suitable excipients including fillers disintegrating agents and lubricants, which flow uniformly into a die cavity and form into a firm compact [3-4]. The main advantages of the direct compression method is that it is cost-effective when compared to all other methods, uses conventional equipment and commonly available excipients, limited number of processing steps and higher doses can be easily accommodated [5-6]. The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing orally disintegrating tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation [7]. ODT technology is relatively new to the industry and had a significant impact on patients of all ages and taste masking being an essential requirement for ODTs for commercial success. Taste-masking of bitter or with objectionable-tasting drug substances is critical for any orally-administered dosage form. Less commonly, active pharmaceutical ingredients to be incorporated are tasteless and do not require taste masking. Taste masking of bitter drugs become necessity in case of oral administration and selection of technology depends upon the bitterness of drugs and their compatibility with taste masking agents that does not affect the bioavailability of drug [8]. Methods commonly used for taste masking involves various physical and chemical method that prevent the interaction of taste bud with drugs, Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor Popular approaches in the development of taste masking in liquid dosage form include use of flavor followed by viscosity modification and if failed, by ion exchange resin [9]. In the case of ODTs, the total stay time of tablet in mouth remains few seconds (less than 60sec.) and has to disintegrate and dissolve within mouth in the salivary fluid so quick disintegration of ODTs being an important step for success of ODTs and may be achieved by different mechanism [10]. 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. The mean plasma half-life of montelukast varies from 2.7 to 5.5 hours when observed in healthy young adults. The purpose of the present study is to optimize formulation of oro dispersible tablet of as a model drug using natural superdisintegrant with direct compression method [11]. The objective of the proposed study will be develop and optimize an oral disintegrating tablet formulation of montelukast sodium which is an effective drug in the treatment of asthma and allergic disorders for paediatric patients. Montelukast sodium is the drug used in treatment of ashthmatic and allergicrhinitis; it is selective leukotrienes receptor antagonist. Oral disintegrating tablet is rapid dissolving or disintegrates without water within a few minutes in the oral cavity which may produce rapid onset of action due to the action of superdisintegrants. The oral disintegrating tablet will be prepared by using direct compression method. A various superdisintegrant agents such as croscarmilose sodium, crosspovidone and sodium starch glycolate.

MATERIAL AND METHODS:

Analytical and validation studies: The analytical study of drug sample was used for determination of absorption maxima (λmax) in phosphate buffer pH 6.8 solution. 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). The calibration curve of drug monteleukast was dissolved in dissolution medium artificial saliva solution (ASA phosphate buffer pH 6.8) to get concentration of 10 µg / ml, 20 µg / ml upto 50 µg / ml respectively. The absorbance of each solution was measured separately at 347 nm, for artificial saline salivary solution pH 6.8 respectively for drug.

Formulation of olid dispersion: 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 solid dispersions mixture 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 amount of 25 mg drug was kept in conical flask and required quantity of solvent upto 50 ml were kept in burette. 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 37ºC 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.

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 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.

Evaluation of ODT: The prepared **MODTs** 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.

Thickness and diameter: Ten tablets from each formulation were taken randomly and their thickness was measured with a digital vernier caliper**.**

Weight variation: Twenty tablets were selected randomly from each formulation and weighed individually. The individual weights were compared with the average weight for the weight variation.

Hardness: The test is done using hardness tester (Erweka TBH 320) and the hardness was expressed in kg/cm^2 as a force required crushing the tablets. The mean of six determinations was used ± SD 10.

Friability: Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was calculated using equation:

$$\textbf{\% Friability} = \frac{\textbf{Initial weight – Final weight}}{\textbf{Initial weight}} \times \textbf{100}$$

Drug Content Uniformity: One tablet of the all formulation was placed in 100 ml volumetric flask, 50 ml of ASS (pH 6.8) was added, shaked by mechanical means for 30 min., ASS (pH 6.8) added to volume, filtered, diluted suitably, and finally the quantity of monteleukast in the tablet was measured spectrophotometrically at λmax of 237 nm.

In Vitro Disintegration Test: The artificial saliva solution (ASS) was prepared of 0.426 g disodium hydrogen orthophosohate, 1.680 g Sodium bicarbonate, 0.147 g calcium chloride, 1N hydrochloric acid to adjust pH to 6.8, and distilled water up to 1L. The in vitro disintegration test was done for all formulation at 37°C using artificial saliva solution (ASS) as a dissolution medium for the test.

Disintegration apparatus with a basket rack assembly containing six open ended tubes and 10-mesh screen on the bottom was used. A tablet was placed in each tube of the basket and the time required for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

Wetting time and Water absorption ratio: The evaluation of such parameters, the method was slightly modified by using artificial saliva solution as a medium. A piece of tissue paper folded twice was placed in a small Petri-dish (internal diameter = 6.5 cm) containing 10 ml of ASS and 0.05% w/v amaranth solution (coloring agent). A tablet was placed on the tissue paper and the time required for complete wetting of the tablets was recorded as wetting time. The mean of three determinations was used ± SD 13. The same procedure of wetting time test was followed for determining the water absorption ratio (WAR) and it was determined according to the equation:

$$WAR = [(Wa - Wb) / Wb] \times 100$$

where, Wb and Wa were the weights of the tablets before and after the test.

In Vitro dissolution studies: In vitro dissolution studies were performed for the formulation containing monteleukast (25mg) by using type I (Basket) dissolution apparatus at 100 rpm, and 900 ml of ASS (pH 6.8) was used as a dissolution medium. Temperature of dissolution medium was maintained at 37±0.5°C. Five ml aliquot of the dissolution medium was withdrawn at specific time intervals and replaced by fresh ASS (pH 6.8) solution. The aliquot was filtered and diluted suitably and then analyzed spectrophoto-metrically at the λmax of 234 nm.

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 347 nm, for ASS pH 6.8 phosphate buffer solution of drug **(Figure 1)**. 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 **10 µg / ml to 50 µg / ml** for the drug.

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
HPMC	20	40	30
Crosslinked sodium carboxymethylcellulose	40	20	30
Crosspovidone (5%)	10	10	10
Dried lactose	50	15	25
Avicel PH 102 (MCC)	0	35	25
Magnesium stearate	15	15	15
Purified talc	15	15	15
Total amount (g)	250	250	250

Table 2: Solubility study of monteleukast solid dispersion

S. No	Medium	Solubility (mg/ml)±SD*		
		Solid dispersion		
		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	ASS 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

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]
MODTs1	18.01±0.002	1.17±0.011	26.1±0.001
MODTs2	17.04±0.011	1.17±0.001	29.1±0.001
MODTs3	18.03±0.013	1.15±0.028	28.8±0.002

n = 3 (mean ± Standard deviation)

Table 4: Physical characterization of orally disintegrating tablets (MODTs1 – MODTs3)

Formulation code	Tablet Thickness (mm)		Weight Variation (%)	Hardness (kg/cm ^{2})	Friability w/w (%)
	Diameter	Height			
MODTs1	8.01±0.001	2.11±0.002	2.1±0.011	3.6±0.12	0.614±0.005
MODTs2	8.02±0.002	2.04±0.011	2.2±0.031	4.1±0.19	0.515±0.002
MODTs3	8.01±0.001	2.01±0.011	2.1±0.002	4.9±0.21	0.493±0.002

n = 3 (mean ± Standard deviation)

Table 5: Physical characterization of orally disintegrating tablets (MODTs1 – MODTs3)

Formulation code	Drug Content (%)	Disintegration Time (sec)	Wetting time (sec)	Water absorption ratio (%)	Dispersion Time (sec)
MODTs1	99.2±0.10	51±0.01	21.01±0.09	28.11±1.02	33±0.02
MODTs2	99.1±0.05	42±0.03	16.22±0.03	23.61±1.13	31±0.01
MODTs3	99.8±0.01	31±0.03	11.00±0.03	19.31±1.42	32±0.02

n = 3 (mean ± Standard deviation)

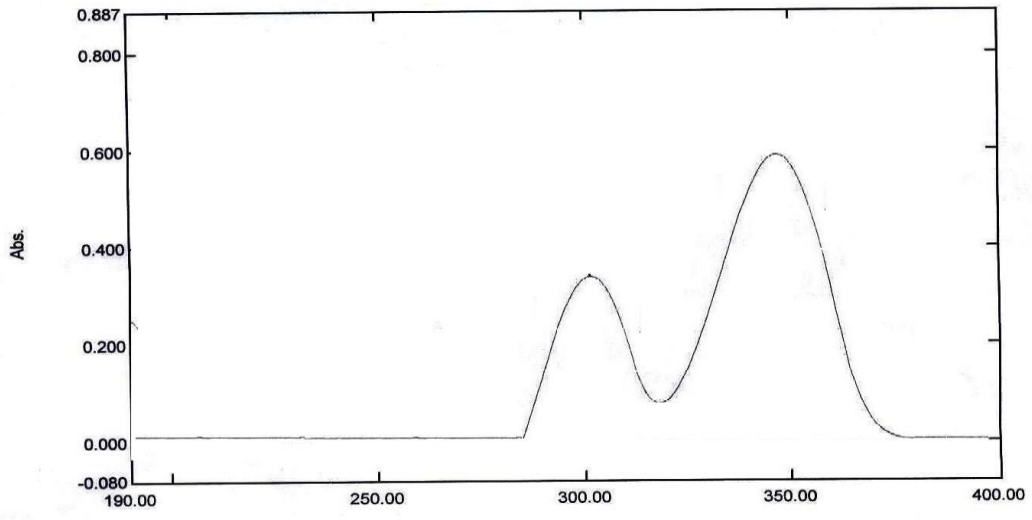

Figure 1: Absorption maxima (λ-max) of drug in phosphate buffer ASS (pH 6.8) solution

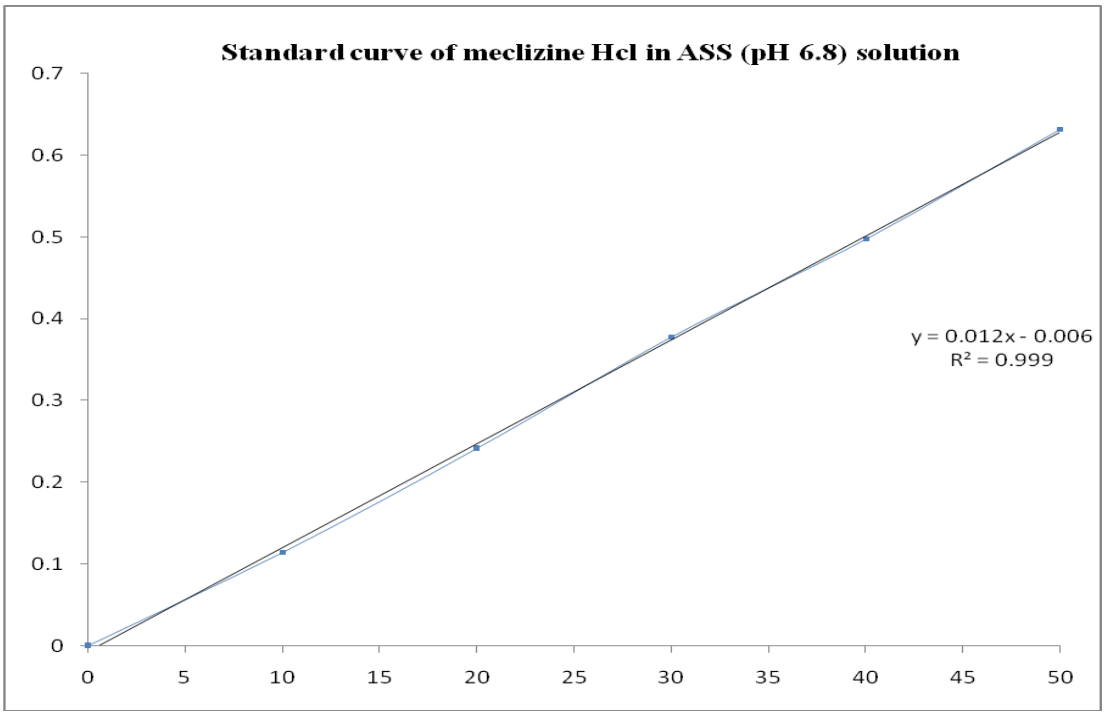

Figure 2: Standard curve of drug in ASS (pH 6.8) solution (347 nm)

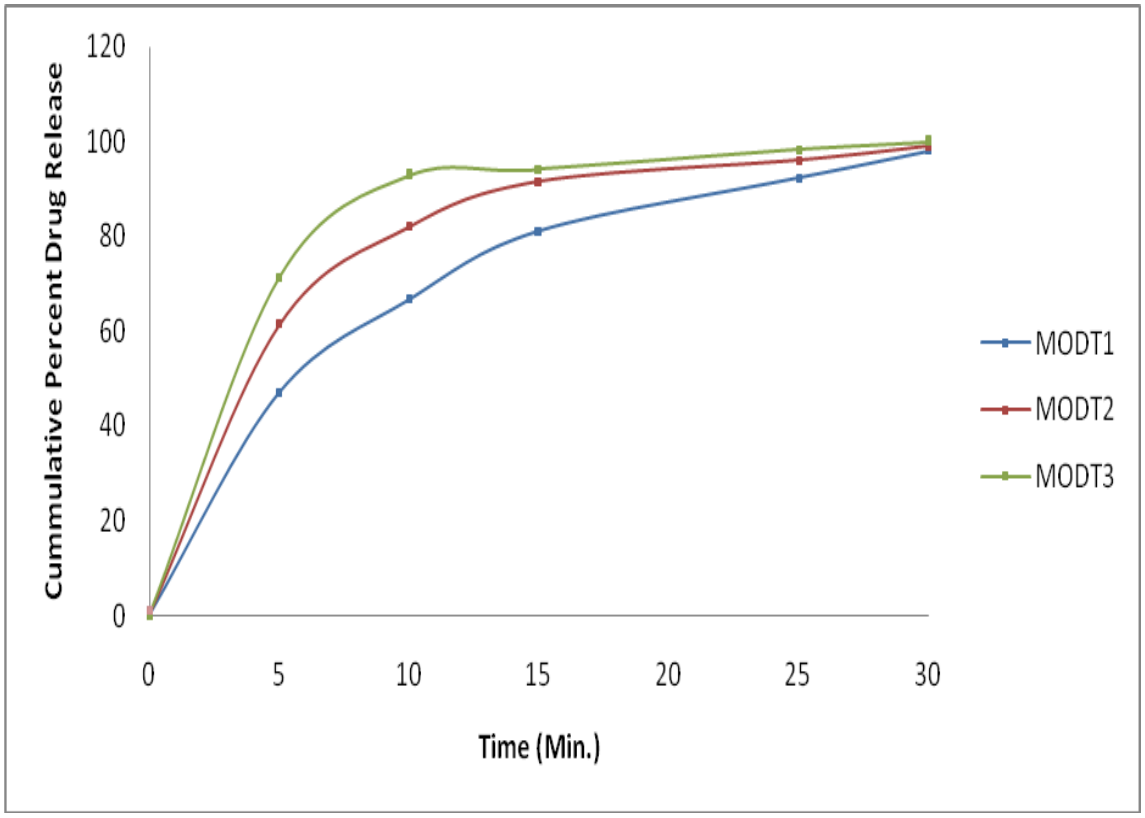

Figure 3: Zero-order plots of orally disintegrating tablets (MODTs1 – MODTs3)

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.

Evaluation of ODTs: 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 **(Table 1)**. 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. 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.

SUMMARY AND CONCLUSION:

The proposed study is prepared and characterizes the oro-dispersible tablet containing monteleukast solid dispersion (MSDs) formulation with using natural superdisintegrant with direct compression. 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 HPMC, Crosslinked sodium carboxymethylcellulose, crosspovidone (CP), 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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