FORMULATION AND EVALUATION OF MONTELUKAST SODIUM ORODISPERSIBLE TABLETS

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ABSTRACT: Orally disintegrating tablets (ODTs) are a modern form of tablets that when placed in the oral cavity, disperses rapidly. These tablets have advantages, particularly good applications for children and old patients who have a complication in chewing or swallowing solid dosage forms. Montelukast sodium is a drug of choice in treatment of asthma and allergic rhinitis. Drug compatibility with excipients was checked by FTIR studies. In the present work, oral dispersible tablets of Montelukast were prepared by direct compression method with a view to enhance patient's compliance. To formulate oro dispersible tablets of Montelukast for rapid dissolution of drug and absorption, which may produce rapid onset of action in the treatment of motion sickness. Drug and excipient compatability studies measured by using FTIR studies. Four formulations having different concentrations of super disintegrants were prepared. The pure drug and formulation blend was examined for angle of repose, bulk density, tapped density, Compressibility index and Hausner's ratio. These tablets were evaluated for drug content, weight variation, friability, hardness, wetting time and in vitro disintegration time. Drug content was found to be in the range of 88.91±0.29 to 93.59±0.20 %. In vitro drug release was found to be 98.50±0.30% for 60 min. The wetting time is an important criterion for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 25±0.22-32±0.20sec. Among the formulations tablets of batch F2 containing Sodium starch glycolate showed superior organoleptic properties along with excellent in-vitro disintegration time and drug release as compared to other formulations. Hence sodium starch glycolate is recommended as suitable disintegrant for the preparation of direct compression oro dispersible tablets of Montelukast sodium. It was concluded that the presence of a super disintegrant is desirable for orodispersion of tablets by direct compression method.

Keywords: Montelukast, super disintegrants, FTIR studies, direct compression technique, in-vitro drug release studies, Drug release kinetics

I. INTRODUCTION

Oro dispersible dosage forms are preferable alternative for oral medication in improving Sthe quality of life and patient acceptability. ODTs are also known as oro dispersible tablets, mouth dissolving tablets, rapimelts, melt-in-mouth tablets, fast disintegrating tablets and rapid dissolving tablets.[1]ODTs are the solid unit dosage forms/entities containing medicinal substances which disintegrate or dissolve rapidly in oral cavity usually within a few seconds even without the need of water or chewing. As the tablet disintegrates in mouth, this can enhance the clinical effect of drug through pregastric absorption from the mouth, pharynx and esophagus[2]. In such cases, bioavailability of drug is significantly enhanced by avoiding first pass hepatic metabolism than those observed with conventional tablets. ODTs also combine the advantages of both liquid and conventional tablet formulations allowing the ease of swallowing in the form of liquid.[3] The advantages of these dosage forms are continuously and increasingly being identified in both pharmaceutical industries as well as in academia. The objective of present work is to highlight the development of ODTs, their significance, ideal characteristics, various techniques and aspects related to design and formulation, marketed preparations and future prospectives.[4] FDTs as a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed under the mouth, ODTs are known by various names such as "fast-melting, fast-dissolving, mouth melts, mouth dissolving, quick disintegrating, porous tablets, rapimelts or oro dispersible tablets."Wide range of drugs can be considered as a suitable candidate for such dosage forms. Various researchers have developed orally disintegrating

dosage forms for different categories of drugs used in clinical therapy in which rapid peak plasma concentration is required to achieve the desired pharmacological response.[5] oral dispersible tablets of Montelukast were prepared by direct compression method with a view to enhance patient's compliance. To formulate oro dispersible tablets of Montelukast for rapid dissolution of drug and absorption, which may produce rapid onset of action in the treatment of motion sickness.

II.MATERIALS AND METHODS

montelukast was collected as a gift sample from Hetero labs, Hyderabad and various excipients and polymers were purchased from AR chemicals, Hyderabad.

2.1 METHODOLOGY

Fourier Transform Infrared Spectroscopy (FTIR)[10]

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a dosage form. The use of FTIR technique allows pointing out the implication of the different functional groups of drug and excipients by analysing the significant changes in the shape and position of the absorbance bands. In this method individual samples as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a mortar and compressed into disc by applying pressure of 5 tons for 5 mins in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm-1 in FTIR spectrophotometer. Then the characteristics peaks were obtained of all sample as well as mixtures.

Table-1: Formulation table

S.No	Ingredient	F1	F2	F3	F4
1	Montelukast sodium	10	10	10	10
2	Sodium starch glycolate	5	10	-	-
3	Crospovidone XL	-	-	5	10
4	Lactose	80	75	80	75
5	Magnesium stearate	3	3	3	3
6	Talc	2	2	2	2
7	Total wt	100	100	100	100

Preparation method

Direct compression technique

Montelukast sodium fast dissolving tablets were prepared by direct compression method by using superdisintegrants like Crospovidone, Sodium Starch Glycolate and Lactose as a diluent, Magnesium Stearate, Talc used as a lubricant and glidents. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order after sufficient mixing of drug as well as other components and compressed into tablets of 100mg using 6mm round flat punches on 12-station rotary tablet machine.

EVALUATION STUDIES [11,12,13]

a) Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

b) Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured.

Tapped density = weight of sample taken / tapped volume

Where,

V_o = initial volume

V_f = final volume.

Compressibility index

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's ratio

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

Hausner's ratio = Tapped density / Bulk density

Angle of repose

The flow characteristics are measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\tan\theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Evaluation of tablet

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage.

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Drug Content

The drug content was determined by triturating tablets in a mortar and pestle. The 100 mg of sample powder was dissolved in 6.8 phosphate buffer. The solution was filtered through Whattmann filter paper. The filtrate was analyzed by U.V. spectrophotometer (LAB INDIA) at 282 nm.

In Vitro Disintegration Test

The disintegration time of tablets was determined by using Disintegration test apparatus (scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly

was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.

***In- Vitro* Release study**

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for remaining period of time. Temperature maintained at 37±1° C. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. The solution was filtered through Whattmann filter paper. The filtrate was analyzed by U.V. spectrophotometer (Lab India) at 282 nm. The drug release was plotted against time to determine the release profile of various batches.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared disintegration tablets of Montelukast sodium were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 90 days.

III.RESULTS & DISCUSSION

Drug - excipient compatibility studies (FT-IR)

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).

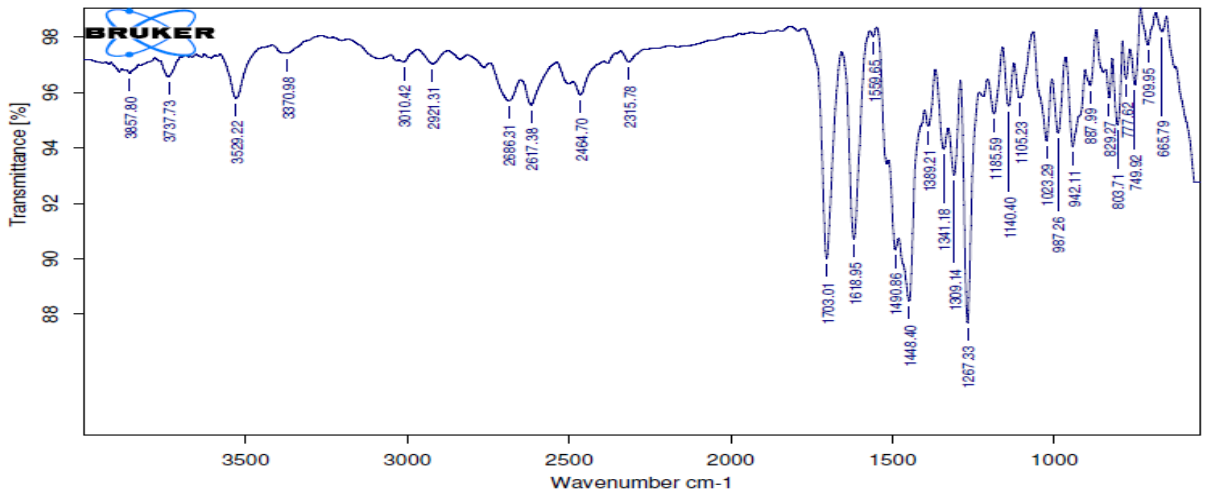

Fig-1: FT-IR Sample for Montelukast

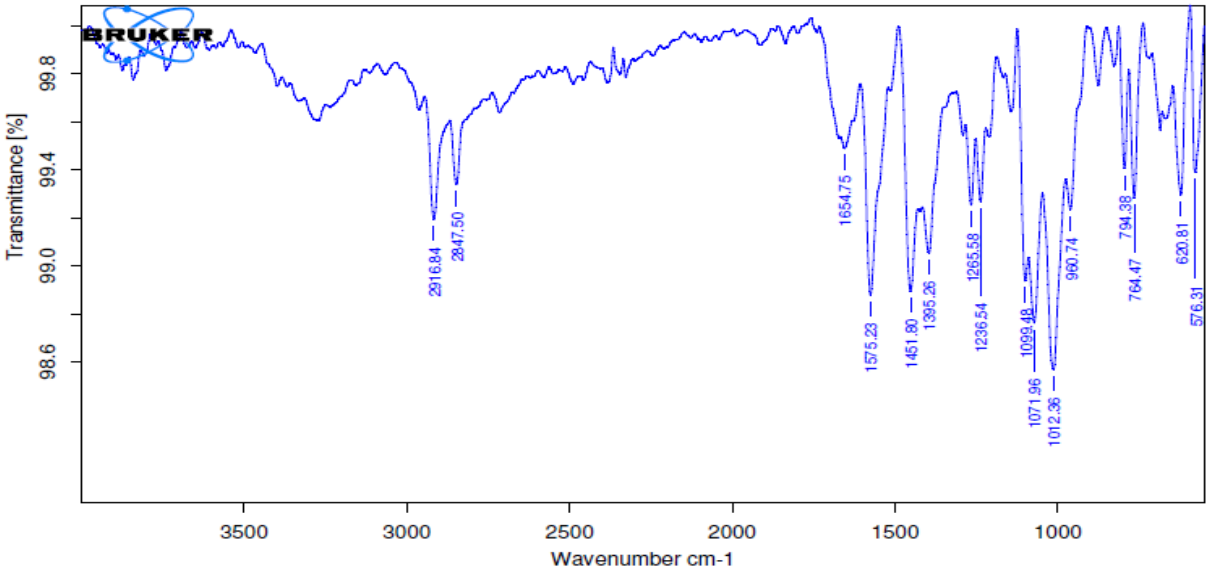

Fig-2: FT-IR Sample for physical mixture of drug and Sodium starch glycolate

In the present study, it has been observed that there is no chemical interaction between Montelukast and the superdisintegrants used. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. This further confirms the integrity of pure drug and compatibility of them with excipients.

Evaluation studies

Pre compression parameters

a) Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.305±0.22 to 0.321±0.30.

b) Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.419±0.20 to 0.432±0.22.

c) Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 28 to31^0

c) Compressibility index: Compressibility index was carried out, it found between 10% to 28.63±0.36% indicating the powder blend have the required flow property for compression.

d) Characterization of Formulation

Table-2: Pre compression parameters of montelukast oro dissolving tablets

S. no	**Bulk density**	**Tapped density**	**Compressibility index**	**Hausner ratio**	**Angle of repose(0)**
F1	0.312 ±0.32	0.426±0.28	26.76±0.32	1.36±0.18	31^0c
F2	0.321±0.30	0.432±0.22	25.69±0.35	1.34±0.22	28^0c
F3	0.318±0.28	0.429±0.32	25.87±0.30	1.34±0.28	30^0c
F4	0.299±0.26	0.419±0.20	28.63±0.36	1.40±0.30	28^0c

Evaluation parameters

Table-3: Evaluation Parameters for Montelukast oro dispersible tablets

Parameter	**F1**	**F2**	**F3**	**F4**
Weight variation	100±0.28	100±0.31	99±0.28	98±0.32
Thickness (mm)	2.3±0.52	2.2±0.48	1.8±0.50	1.5±0.53
Hardness (kg/cm^2)	3.35±0.32	3.40±0.34	3.38±0.38	3.42±0.26
Friability (%)	0.56±0.48	0.58±0.50	0.59±0.52	0.49±0.54
Disintegration time	28±0.11	26±0.13	29±0.16	30±0.18
Drug content	91.02±0.18	93.59±0.20	89.69±0.22	90.12±0.24

Uniformity of weight:

All the prepared fast dissolving tablets of Montelukast were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ± 5%.

Hardness and friability:

The hardness of the tablet formulations was found to be in the range of 3.15±0.44 to 3.42±0.26 kg/cm^2. The friability values were found to be in the range of 0.46±0.50to 0.58±0.50 %.

Uniformity of drug content:

The low values of standard deviation indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 88.91±0.29to 93.59±0.20percent (which was within the acceptable limits of ±5%.).All Formulations tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of the formulation was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

In vitro Dissolution studies:

The dissolution conditions used for studying the drug release from oro dispersible tablet:

Apparatus : USP apparatus II (Paddle)
Agitation speed (rpm) : 50rpm
Medium : 6.8 pH Phosphate buffer
Volume : 900 ml
Temperature : 37.0 ± 0.5 ^{0}C
Time : 5, 10, 15, 30, 45 and 60min

In-vitro dissolution Profiles for tablets:

Table-4: In vitro drug release studies of all formulations

Time (min)	F1	F 2	F 3	F 4
0	0	0	0	0
5	26.39±0.28	28.95±0.22	25.86±0.26	25.58±0.25
10	48.25±0.32	46.55±0.24	38.88±0.28	35.17±0.28
15	50.18±0.42	52.21±0.32	52.45±0.32	50.26±0.26
30	70.56±0.46	76.38±0.35	68.49±0.30	69.12±0.20
45	80.93±0.32	89.96±0.28	78.93±0.34	80.21±0.30
60	90.25±0.30	98.50±0.30	93.63±0.36	95.12±0.32

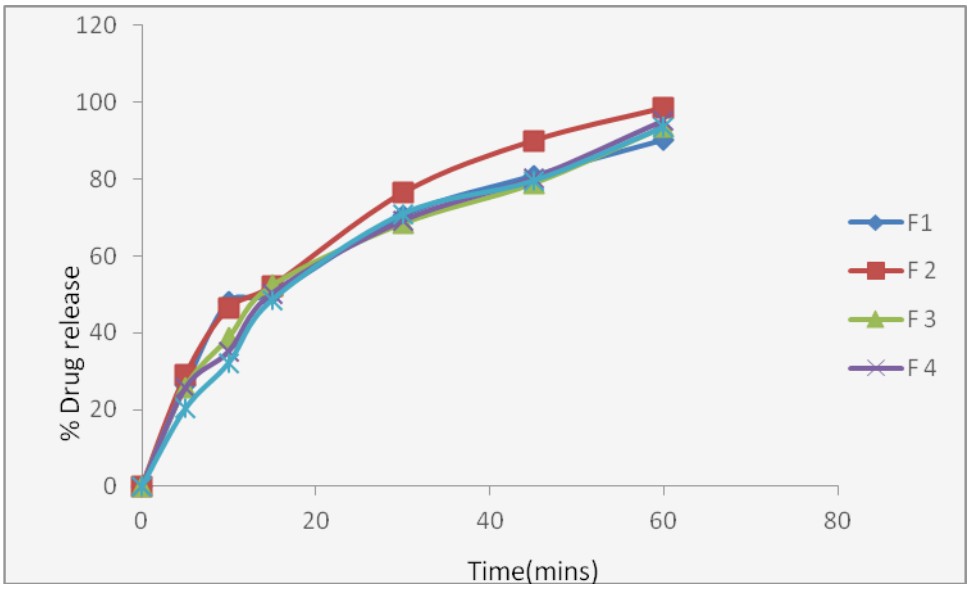

Fig-3: In-vitro dissolution Profiles for oro dispersible tablets

Among all formulations, F2 shows better drug release when compared with all other formulations. So formulation F2 selected as optimized formula.

Stability studies

Table-5: Stability Studies of Optimized Formulation

S.NO	Time in days	Physical changes	Mean % drug release		
			Oro dispersible tablet		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	92.50±0.30	92.50±0.36	92.50±0.31
2.	30	No Change	92.41±0.28	92.39±0.32	92.28±0.33
3.	60	No Change	92.16±0.24	92.15±0.28	92.11±0.28
4.	90	No Change	92.09±0.22	92.08±0.26	92.05±0.30

There was no significant change in physical and chemical properties of the tablets of formulation F2 after 90 days, parameters like % drug release at various conditions(at 40^0C/ 75% RH) as per ICH guidelines quantified at various time intervals were shown in Table and dissolution profile.

CONCLUSION

The aim of the present study was to formulate and evaluate for oro dispersible tablets containing Montelukast for the management of asthma. After pre-formulation studies it was decided to prepare oro dispersible tablets prepared by direct compression method. In the formulation of immediate release sodium starch glycolate, were used as super disintegrants.Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The compressed tablets were also evaluated for weight variation, hardness, friability, drug content, disintegration time and in vitro drug release.

In the above studies F2 formulation showed promising results. It was further supported by FTIR analysis which showed that F2 had no interaction with excipients. The stability studies were carried out for the optimized

formulation for 3 months and it showed acceptable results. The kinetic studies of the formulations revealed that dissolution is the predominant mechanism of drug release. So F2 formulation was considered as the optimized formulation.

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