Research Article

FORMULATION AND EVALUATION OF ORO-DISPERSIBLE TABLETS OF MONTELUKAST SODIUM BY DIRECT COMPRESSION METHOD

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ABSTRACT

The aim of this study was to formulate oro-dispersible tablets of montelukast sodium using combination of the super disintegrants and ludiflash by direct compression method and comparing the disintegration efficiency of the tablets. Three formulations having combination of superdisintegrants and three formulations having ludiflash at different concentration levels were prepared. The efficiency of disintegrants in tablets was compared by various tests like disintegration time, dissolution test and wetting time. The rapid disintegration observed for the formulation F6 containing 66.7% ludiflash. The formulation containing of croscarmellose sodium and sodium starch glycolate required less wetting time and disintegration time compared to other combinations.

Keywords: Montelukast sodium, ludiflash, oro-dispersible tablets, superdisintegrants.

INTRODUCTION

Novel oral drug delivery systems that dissolve or disperse quickly in few seconds after placement in the mouth without water can alleviate the problem of swallowing tablets. They enhance the potential for improved compliance in patients. These dosage forms rapidly disintegrate and/or dissolve and release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for pediatric and geriatric patients. Difficulty in swallowing conventional tablets and capsules is common among all age groups, especially elderly and dysphagic patients.[1, 2]

ODTs are not only indicated for people who have difficulties in swallowing, but also ideal for active people. Drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than that observed from conventional tablet dosage form.[3]

The disintegrating property of the tablet is attributed to quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation.[4]

Their characteristic advantages are administration without water, anywhere, anytime leading to their suitability to geriatric and pediatric patients and is useful for travellers. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of 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.[5]

Several Technologies are available to manufacture oro-dispersible tablets.[6, 7] The most common preparation methods are moulding, lyophilisation or freeze drying, direct compression, spray drying and sublimation. Direct compression, is one of the techniques that requires the incorporation of a superdisintegrant into the formulation.

Radke RS *et al.,* prepared orodispersible tablets of baclofen using various concentrations of superdisintegrant agents like Ac-Di-Sol, crospovidone, sodium starch glycolate by direct compression method. It was concluded that superdisintegrants addition technique is a useful method for preparing orodispersible tablets by direct compression method.[8]

In the present investigation, montelukast sodium Oro-dispersible tablets were prepared using different combinations of superdisintegrants and ludiflash by direct compression method and tried to judge the disintegration efficiency of disintegrants by comparing various parameters such as preformulation parameters and post-formulation parameters like disintegration time, wetting time and dissolution study of tablet.

Montelukast selectively antagonizes leukotriene D_4 (LTD_4) at the cysteinyl leukotriene receptor, $CysLT_1$, in the human airway. Montelukast inhibits the actions of LTD_4 at the $CysLT_1$ receptor, preventing airway edema, smooth muscle contraction, and enhanced secretion of thick, viscous mucus. So Montelukast sodium is used in the treatment of asthma.[9]

MATERIALS AND METHODS

Materials

Montelukast Sodium is gift sample from UNIMARK REMEDIES LTD., Vapi. Superdisintegrants like crospovidone (K. P. Pharmaceuticals), croscarmellose sodium (K. P. Pharmaceuticals.), L-HPC (Vara Pharma chem. Ltd), Pregelatinized starch (Rosswell industries), sodium starch glycolate (Vara Pharma chem. Ltd), mannitol (Hebei Huaxi Pharmaceutical. China), Ludiflash (signet chemical corporation LTD) were purchased. For compression of materials, into tablets using tablet machine Rimek mini press-1, Karnavati Engineering Ltd, Mehsana, Gujarat (punches flat-faced, 6.34mm diameter) was employed.

Methods

Preformulation studies

Fourier Transform Infrared Spectroscopy: FTIR spectra were obtained on a 8400s spectrophotometer (shimadzu, japan). Samples were prepared as KBr disks (1 mg sample in 100 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}. FTIR studies confirmed that there are no interactions between the drug and the excipients.[10]

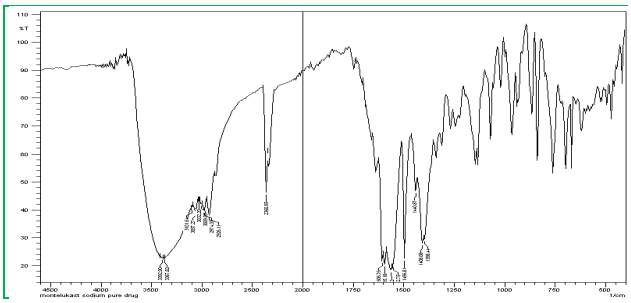

Figure 1: FTIR Spectrum of montelukast sodium (Pure Drug).

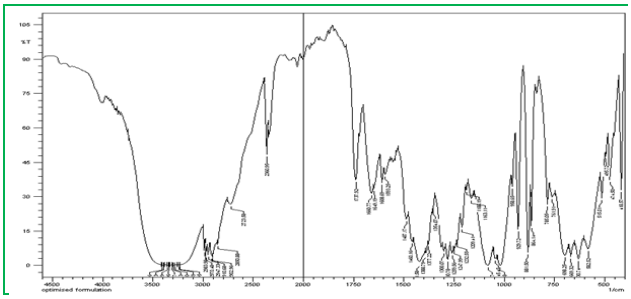

Figure 2: FTIR Spectrum of Optimized F6 formulation.

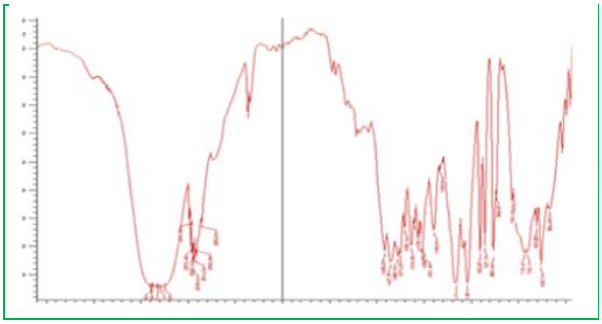

Figure 3: FTIR Spectrum of Optimized F1 formulation.

Evaluation of Powder Blends

The powder blend was evaluated for flow properties as follows and reported in table 2:

Angle of repose: Angle of repose was determined by funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated. It is the angle produced between the heap of the pile and base of the pile.[11]

Angle of repose, $\tan(\theta) = h / r$

Where, θ = Angle of repose, h = Height of heap, r = Radius of pile.

Carr's index: Carr's ''percent compressibility" was calculated using the equation $([\rho_{tap} - \rho_{bul}]/\rho_{tap}) * 100$. The bulk and tap densities were determined as follows: A known quantity of each sample (25 g) was poured through a funnel into a 100-mL graduated cylinder. The cylinder was then lightly tapped twice to collect all the powder sticking on the wall of the cylinder. The volume was then read directly from the cylinder and was used to calculate the bulk density. For tap density, the cylinder was tapped from a height of 2.5 cm 50 times on a wooden bench top to attain a constant volume reading from the cylinder.[12, 13]

Where,

ρ_{bul}= Bulk density=weight of powder / bulk volume of powder

ρ_{tap}= Tapped density = weight of powder / tapped volume of powder

Hausner's ratio:[11] Hausner's ratio is an indirect index of ease of powder flow.

Hausner ratio = ρ_{tap} / ρ_{bul}

Where, ρ_{tap} = Tapped density, ρ_{bul} = Bulk density

Evaluation of tablets

Uniformity of weight:[14] Twenty tablets were selected randomly from each batch and weighed individually on electronic balance. The weight of each tablet is then compared with average weight for the weight variations. Results are presented as mean value± standard deviation (SD).

Hardness:[15] Five tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester. The mean values and standard deviation for each batch were calculated.

Tablet Friability:[16] The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight or a sample of 5 tablets are placed in a friabilator and rotated for a fixed time (100 revolutions) and dedusted and weighed again. Percentage friability was calculated from the loss in weight as given in equation as

below. The weight loss should not be more than 1%. Determinations were made in triplicate.

Friability = [(Initial weight- Final weight) / (Initial weight)] x 100%

Wetting time:[17] A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting of the tablet was measured.

Drug content uniformity:[18] 10 tablets were powdered and the blend equivalent to 10 mg of montelukast was weighed and dissolved in 100ml of 0.5%SLS solution. Solution was filtered, and 15ml of first stock solution was diluted up to 100ml with 0.5%SLS solution. Drug content was analyzed using shimadzu UV-Visible double beam spectrophotometer at 345 nm. Each sample was analyzed in triplicate.

***In vitro* disintegration time:**[17] *In vitro* disintegration time was measured using 200ml distilled water in 250ml beaker at 37± 0.5°C temperature. Time required for disintegration of the tablets was noted.

***In vitro* dissolution studies:**[18] *In vitro* release of montelukast sodium from tablets was determined by using USP XXIV paddle dissolution apparatus at 50 rpm using 900 ml of 0.5% SLS solution and temperature was maintained at 37±1°C throughout the study. 5 ml samples were collected at regular intervals of 30 secs and the same volume of fresh medium was replaced. The drug content in each sample was analysed by Shimadzu 1800 UV-Visible spectrophotometer at 345 nm.

Table 1: Formulation of Montelukast sodium oral dispersible tablets

Ingredients	F1	F2	F3	F4	F5	F6
	Formula (mg/tablet)					
Montelukast	10	10	10	10	10	10
Sodium starch glycolate	4.5	---	---	---	---	---
Croscarmellose sodium	4.5	4.5	---	---	---	---
L-HPC	---	4.5	---	---	---	---
Crospovidone	---	---	4.5	---	---	---
Pregelatinised starch	---	---	4.5	---	---	---
Microcrystalline cellulose	22.5	22.5	22.5	103.5	73.5	33.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5
Sodium stearyl fumarate	3	3	3	3	3	3
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol	102	102	102	---	---	---
Ludiflash	---	---	---	30	60	100
Total weight	150	150	150	150	150	150

Table 2: Physical Characteristics of Powder Blends.

Formula no	Bulk density	Tapped density	Carr's index	Hausner ratio	Angle of repose
F1	0.541±.030	0.619±0.02	12.50±0.098	1.143±0.425	13.49±0.856
F2	0.493±0.001	0.634±0.01	22.22±.020	1.286±0.027	13.49±1.052
F3	0.492±0.010	0.591±0.018	16.66±0.10	1.200±0.016	9.64±1.202
F4	0.500±0.002	0.563±0.02	11.11±3.93	1.12±0.053	11.3±1.5
F5	0.524±0.017	0.593±0.02	11.76±0.46	1.13±0.006	10.2±1.05
F6	0.500±0.001	0.563±0.03	11.11±3.93	1.12±0.053	11.3±0.525

Table 3: Evaluation of Oral dispersible Tablets

Formulation No	Weight variation (mg) ± s.d	Hardness* (Kg/cm^2)±s.d	Friability (%)	% Assay	Wetting time* (sec)± s.d	*In-vitro* disintegration time* (sec)± s.d
F1	150.75±5.84	3.0±0.51	0.802±0.56	105.60±0.53	54±3.45	26±1.50
F2	151.75±4.56	3.2±0.22	0.668±0.66	103.40±0.45	76±2.55	38±1.49
F3	151.05±5.66	3.3±0.27	0.667±0.81	97.90±0.10	90±1.48	35±2.07
F4	151.5±4.58	3.2±0.25	0.401±0.37	103.50±0.50	95±2.51	34±2.0
F5	151.45±5.84	3.1±0.27	0.403±0.36	98.50±0.31	66±3.44	30±1.5
F6	152.2±5.20	3.3±0.22	0.268±0.37	105.00±1.00	62±2.21	25±2.5

RESULTS AND DISCUSSION

All the formulations were prepared by direct compression. The data obtained for pre-compressional parameters such as bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose is given in table 2 and is found to be within acceptable pharmacopoeial limits. Post-compressional parameters like hardness, friability, weight variation, drug content, wetting time, *in vitro* disintegration time are mentioned in table 3. The tablets measured hardness was found to be in the range of 3.0±0.51 to 3.3±0.27 kg/cm^2. The percentage friability was less than 1% for all formulations ensuring mechanical stability of the formulated tablets. All formulations are then evaluated for variation in weight and results indicated that all formulations exhibit very low weight variation and lies within the pharmacopoeial limits i.e. ± 10%. The percentage drug content in all formulations was found to be in the range of 97.90% to

105.60% indicating the compliance with the pharmacopoeial limits. According to the pharmacopoeial standards the dispersible tablet must disintegrate within 3 min. All formulated batches have shown very low disintegration time of 25±2.5 to 38±1.49 seconds indicating suitability of formulation for fast dissolving tablet. Wetting time is found to be less for the formulation F1 containing combination of sodium starch glycolate and croscarmellose sodium as compared to other formulations and formulation containing ludiflash (F6 formulation) has less wetting time. The *in vitro* dissolution profile (Fig. 4) indicated that among all the formulations, faster and maximum drug release was obtained from formulation F6 containing ludiflash.

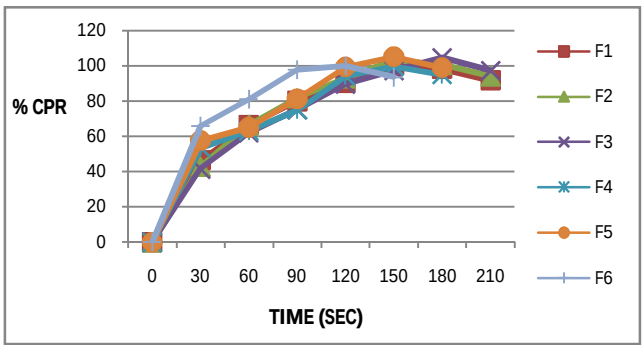

Figure 4: *In vitro* drug release profile of various Montelukast sodium formulations.

CONCLUSION

Oral dispersible tablets (ODT) of Montelukast Sodium were successfully prepared by using direct compression method.

Undoubtedly the availability of various technologies and the manifold advantages of ODT Will surely enhance their popularity in the near future due to patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effects and good stability. From the study, it can be concluded that combination of superdisintegrants and ludiflash showed better disintegration and drug release. The prepared tablets disintegrate within few seconds without need of water; thereby enhancing the absorption leading to its increased bioavailability.

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