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R E S E A R C H A R T I C L E

Formulation and Evaluation of Zafirlukast

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A B S T R A C T

Development of chewable tablets containing different pharmaceutical compositions with simple manufacturing procedures using different excipients. Zafirlukast is a selective, orally acting leukotriene receptor antagonist that is used for the treatment of asthma and seasonal allergic rhinitis. Zafirlukast chewable tablets were prepared by both wet granulation and direct compression methods using suitable excipients. The granules were evaluated for pre-compression parameter. The formulated tablets were evaluated for post – compression parameters. Ideally chewable formulations should have smooth texture upon disintegration, pleasant taste and no bitter or unpleasant after taste. Chewable tablets facilitate more rapid release and hence more rapid absorption of active ingredients and provide quick onset of action. The in-vitro release study of formulation F7 showed 98.8%drug release at the end of 30 min.

Keywords: Zafirlukast, chewable tablets, granules, Mannitol, Crospovidone, Magnesium Stearate.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Chewable tablets are the tablets which are required to be broken and chewed in between the teeth before ingestion. A pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant taste. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing. Administration of drugs through oral route is the most common and the easiest way to administer a drug. However, pediatric, geriatric patient shows inconvenience swallowing conventional tablets or capsules due to difficulties in swallowing with lesser amounts of water with the medication, unable to tolerate the taste of many drugs when formulated as liquid dosage forms, resulting in poor patients compliance. Choosing the appropriate excipients to

perform a specific function in a tablet formulation such as disintegration or lubrication can be critical to achieve acceptable manufacturing performance. Sweeteners both naturally occurring and synthetic are one type of functional excipients commonly used in chewable tablet formulation to mask unpleasant taste and it facilitate pediatric dosing. Ideally chewable formulations should have smooth texture upon disintegration, pleasant taste and no bitter or unpleasant after taste. Zafirlukast is an oral leukotriene receptor antagonist that is used for treatment of asthma and seasonal allergic rhinitis. Zafirlukast are a group of naturally occurring chemicals in the body that promote inflammation in asthma and seasonal allergic rhinitis. It is used for the treatment of asthma, seasonal allergic rhinitis, and prevention of exercices induced brancospasm and being working after 3 to 14 days of therapy. It should not be used for the treatment of an acute asthmatic attack. The recommended dose of Zafirlukast in adults is 10 mg daily for treatment asthama and allergic rhinitis and 10 mg two hours before excercising for prevention of exercise indused brancospam. Zafirlukast should be taken in the evening with or without food when used for asthama or allergic rhinitis. The 4 and 5 mg tablets are used in the children .children find it difficult to swallow the normal tablet of Zafirlukas .so in order to avoid this problem, chewable tablets are most preferable. Chewable tablets facilitate more rapid release and hence more rapid absorption of active ingredients and provide quick onset of action.

2. Materials and Methods

Zafirlukast was obtained from aurabindo pharama .Ltd. Hyderabad, L-HPC 11, Aspatame and crospovidone were produced from Hetero drugs, mannitol, Aerosil, magnesium stearate were of Analytical grade.

Identification and Flow Property Zafirlukast

Zafirlukast was identified by organoleptic evaluation U.V spectroscopy. Flow property of zafirlukast were determined by Carr's index, Hausner's ration and angle of repose.

Preparation of Zafirlukast Chewable Tablets:

Chewable tablets containing 10 mg of zafirlukast were prepared with a total tablet weight of 15 mg wet granulation method. Exactly weighed quantities of mannitol (intragranular0, zafirlukast, L-HPC 11 and aspartame were weighed and were passed through #30 mesh Add little water to the dry mix and knead to form granules. Pass the wet mass through #30 mesh and dry the granules in hot oven. diluents were weighed according to ratio and sifted through #30 mesh and added to the above and mixed for 5 min. Sift the dried granules through the #30 mesh along with the remaining quantity of mannitol (extra granular) Superdisintegrant crosprovidone weighed was also added, Sweetener and flavor were weighed and passed through #30 mesh and added to the mixture .The lubricant magnesium stearate was weighed and sifted through #30 and added to the above mixture and blended with the mixture for 1 mi the final blend was mixed thoroughly for 2-3 min in poly bag tables were compressed in 7 nm round flat punches.

Physical Characteristics of Zafirlukast Chewable Tables

General Appearance, Diameter and Thickness:

The general appearance of all tablets, its visual identity and overall elegance is essential for consumer acceptance. The formulated chewable tablets were evaluated for size, shape, organoleptic characters such as, colour, order. And taste. The formulated chewable tablets were evaluated for size, shape, organoleptic characters such as colour, odor, and taste. The diameter and thickness of the tablets were measured by using vernier caliper.

Harness:

Hardness is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The hardness was measured using Monsanto Hardness tester, the values were expressed in Kg/cm^2.

Weight Variation:

Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablets was noted .Average weight was calculated and the individual weights were compared with average weight. The weight of not more two tablets must not deviate from the average weight by more than 5%.

Wetting Time:

A glass petri dish was partially filled with water and tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from lower surface of the tablet. Time required for water to reach the center of upper surface of tablet was noted as wetting time.

Friability:

The friability of tablets was determined by using roche friabilator. Ten tablets were weighed and placed in friabilator and rotated at 25 rpm for 4 min. Then the tablets were taken out, dusted and reweighed. The percentage friability of the tablets was calculated by the formula

Percentage friability = [(Initial Weight - Final Weight) / Initial Weight] X 100

Disintegration Time:

Disintegration time was carried out by using disintegration test apparatus .one tablet is placed in each tube and basket rack was positioned in a1- liter beaker of water, at $37^o \pm 2^o$ c. A standard motor –driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per min. the time taken for the tablet to disintegrate completely was noted.

Drug Content Estimation:

Drug content in all formulations was estimated by U.V Spectrophotometric method. Two tablets each batch were taken into 0.5% SLS containing in 100 ml paper no :40. First 10 ml was discarded. The clear filtrate was collected and diluted suitably with .5% SLS measured at 350 nm.

In-vitro Dissolution Studies:

Dissolution test has been performed by using dissolution apparatus USP Type II with a paddle. The dissolution fluid was 900 ml of distilled water with 0.5% SLS and a speed of 50 rpm and a temperature of $37^o \pm 0.5^o$ The sample of dissolution medium (5 ml) were withdrawn through a filter of 0.45 µm at different time intervals ,suitably diluted and assayed for Zafirlukast by measuring absorbent at 30 nm. Samples withdrawn were analyzed for the percent of drug released.

Stability Analysis:

The formulation F8 was subjected to stability studies, by storing at 40º±2ºC/75º±5%RH for a period of 30 days. At the optimized period, samples were analyzed for drug content disintegration time and in vitro dissolution studies.

3. Results and Discussions

Zafirlukast found to be white to off-white crystalline powder , tasteless, odorless, in organoleptic evaluation .U.V Spectroscopy study showed that the maximum absorbance at 350 nm after a baseline correction in the U.V Spectrophotometer, when a 6 mcg/ml solution of Zafirlukast in 0.5% SLS was scanned between 200 to 400 nm . IR spectrum of pure drug Zafirlukast, Zafirlukast with L-HPC 11and zafirlukast with crospovidone has exhibited IR spectra indicating presence of hydroxylic of carboxyl and tertiary carbon. Hence it exhibited broad band around 3451 cm $^{-1}$ indicating overlapping of these peaks. Peak due to C-H peaks has appearance as shoulder between 2900cm^{-1} and 3100 cm^{-1}.The C=O peak has appeared at 1636cm^{-1} along with a merged peak 1636.66 cm $^{-1}$ This is due to the complex structure of drug molecule. These are the characteristic absorption peak of zafirlukast which shows compatible with excipients. Depending on the above favorable compatibility test the formulation is designed and the formulation aspects initiated. The various post compression parameters that lie within the limits as per individual evaluation parameters. The flow properties of the granules are essential as per the handling and filling is concerned.

The formulation is optimized based on over all evaluation. The composition of chewable tablets is presented in table-1. Different concentrations of super disintegrates were investigated. The final blend of drug and excipients of all the formulations were evaluated for flow properties and was found to be good. Micrometric properties of all formulations showed an excellent angle of repose i.e < 25 except the formulation F1. Percentage compressibility was found to be less than 21, ensuring good flow properties and results are presented in table-2. Hauners' ratio values were well below 1.15.All the formulations were subjected to physical –chemical evaluation like weight variation, thickness, hardness, friability, drug content , disintegration test, modified disintegration test, and wetting time were carried out in order to assess the suitability of the formulation with respect to the dosage form and intended therapeutic purpose.

All the tablet formulations passed all test. The disintegration time evaluation parameters as it forms the bases for developing orally disintegrating tablets. It shows the wetting time of most of the formulation and lied within the range i.e. 13-31 second. The lowest (13 second) was obtained with obtained with formulation F7. The comparison of all the wetting time of formulation is given above. The disintegration time for each tablets was found to be less than a minute and the results shown. The tablet contain crospovidone 10 mg showed lowest disintegrate time of 10 seconds when compared to other formulations. Zafirlukast chewable tablets from all formulations and marketed sample were subjected to in vitro release studies. In drug release studies of F_1,F_2,F_3,F_4,F_5,&F_6 formulations, prepared by wet granulation technique and crospovidone was not added intra granularly hence % drug release is slow.

In F2 and F3 more amount of mannitol was added in intra granular thus showing slow dissolution. In F3 more amount of crospovidone is added in extra granular thus initially showed fast release but later slow drug release due to more amount of mannitol. Mannitol is a slow dissolving diluents. In the formulation F4 mannitol was not added in extra granular so that it is gets dissolved faster but the drug release was slow as even the amount of crospovidone on extra granular was reduced. In F5 amount of mannitol was reduced and the amount of crospovidone was increased thus shoeing a good drug release In f6 formulation there was no significant release. Both these formulations were prepared by the crospovidone intra granularly and aerosol was added in F8 formulations.F7 formulation showed excellent % drug release compared to all other formulation. Both the formulations were prepared by wet granulation containing 10 mg of pure drug in the formulation. The optimized formulation F7 containing the drug , mannitol, LHPC 11, crosspovidone , aspartame, magnesium stearate showed bio equivalent % drug release with the marketed product which was formulated by the addition of mannitol, MCC, HPC, red ferric oxide, crosscaramellose sodium, cherry flavor, Aspartame and Magnesium stearate.

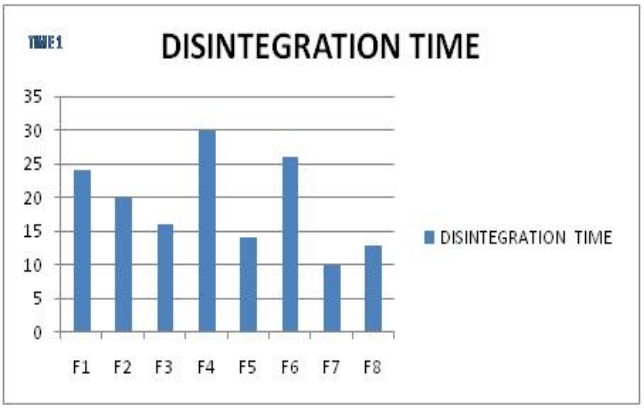

Figure 1: Disintegration Time of Formulations

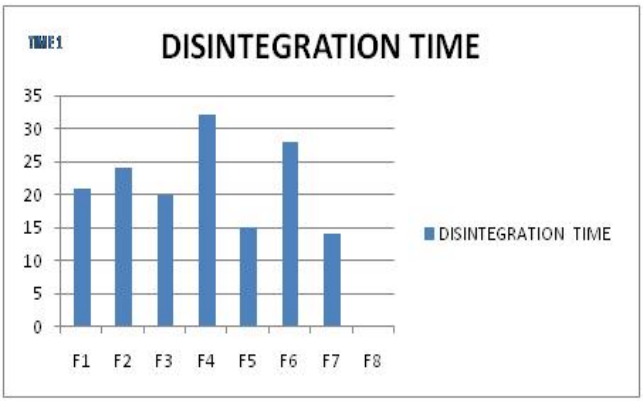

Figure 2: Wetting Time If Formulation

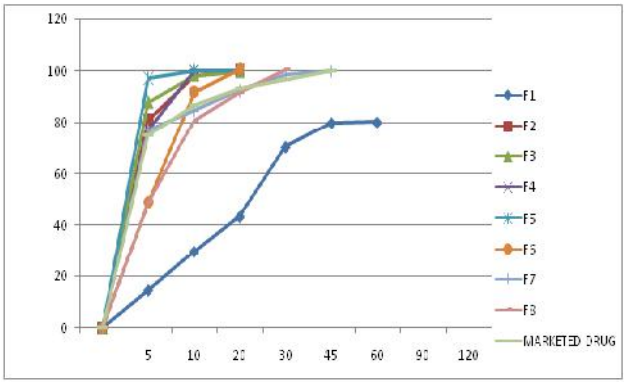

Figure 3: Dissolution Profile of Formulation

Stability Studies Results: The optimized formulation F7 was subjected to stability studies. The tablets were stored at 40ºC/75% rh and room temperature in a closed high density polyethylene bottles for three months. They were properly labeled and the kept for three months under these conditions and evaluated for appearance, disintegration time, % drug content and % drug release. The stabilize tablets were checked for their appearance and color and recorded. The optimized tablets were subjected to disintegration time check for any changes in their disintegration times. Percentage drug content at different conditions and dissolution profile were conducted and presented.

Table 1: Parameters

PARAMETERS	F1	F2	F3	F4	F5	F6	F7	F8
Thickness(mm)	0.70	0.71	1	0.64	0.63	0.63	0.72	0.72
Hardness(kg/cm$^{2)}$	3.5	3.4	3.5	3.6	3.5	3.6	3.6	3.5
Friability (%)	0.25	0.14	0.16	0.30	0.26	0.10	0.63	0.54
(%) drug content	98.02	97.23	99.21	99.01	99.89	100.2	100.03	99.24
Disintegration time(sec)	24	20	16	30	14	26	10	13
Wetting time(sec)	21	24	20	32	15	28	14	15

Table 1: General Appearance and Drug Content After Stability Studies

Time In Days	Appearance	40ºc/±75% RH	Room Temperature	Temperature-%Drug Content	
				Room Temperature	40ºc/±75% RH
	F7	F7	F7	F7	F7
0	White	10 (sec)	10 (sec)	100.6	100.4
30	white	11 (sec)	10 (sec)	100.4	100.1

Table-3: In-vitro Dissolution Profile for Formulation F7

Time In Minutes	% Drug Release	
	Initial	30 Days
5	76.84	76.31
10	84.43	84.87
15	92.21	90.91
20	98.40	97.04
30	99.85	98.93

4. Conclusion

In present study oral thin films of Tropisetron were developed to have a faster on set of action. The oral thin films were developed by using polymers HPMC E5, HPMC E 15 and PVP K90.Oral thin films were prepared by employing solvent casting method. Propylene glycol was selected as permeation enhancer and plasticizer. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F6, and all the formulations were evaluated for various physical parameters Physical appearance, Weight variation, Thickness, Folding endurance, Tensile strength, Drug content, Moisture uptake, Moisture content and all the results were found to be were found to be within the pharmacopeial limits, in-vitro drug release studies by using dialysis membrane. Among all the 6 formulations F1 formulation which contain HPMC E15 300mg and shown 98.2% cumulative drug release within 30 min. And compared to HPMC E15, HPMC E5 and PVP K90, HPMC E 15 showed better drug release profile.

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