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FORMULATION DEVELOPMENT AND STABILITY STUDY OF FIXED DOSE COMBINATION (FDC) TABLET OF MONTELUKAST AND LORATADINE

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Abstract

Fixed-dose combinations (FDC) are drug products that contain more than one active component in a single dosage form. The pharmaceutical industry has shown increased interest in developing FDC drug products to improve patient compliance and extend product life cycles. FDCs offer potential synergistic efficacy and reduced pill burden, with successful applications in areas like diabetes, HIV/AIDS and cardiovascular diseases. Montelukast and loratadine, two well-known drugs used to treat allergy disorders, are combined as a fixed dosage combination (FDC). To provide potential benefits in terms of effectiveness, patient adherence, and convenience, the FDC utilizes complementary modes of action. The main objective of the research study was to formulate a stable fixed dose combination tablet of Loratadine 10mg/ Montelukast 10mg. different formulations of montelukast and loratidine were prepared using wet granulation technique. The samples were tested for different quality control parameters at pre and post compression level. For confirmation of incompatibility, all the samples were evaluated for their FTIR and XRD spectra. The spectra of both FTIR and XRD revealed no extra peaks. Similarly all the pre compression parameters of all formulations like bulk density, tapped density, angle of repose, hausner ratio, carr's index were within normal limits. The formulated tablets underwent comprehensive post-compression quality control evaluations, with resultant parameters conforming to the specified standards and limits outlined in the United States Pharmacopeia (USP) and British Pharmacopoeia (BP).

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INTRODUCTION

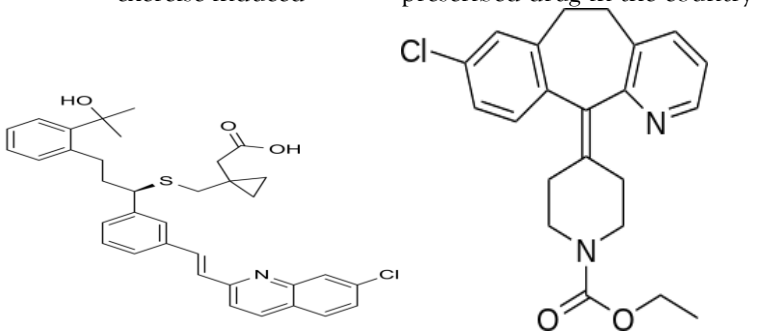
Tablet is considered as the most commonly used dosage form of drugs among all the dosage forms available because of many reasons i.e it is easy administer, lower price, high compliance and aesthetic appearance (Nyol and Gupta, 2013).

Tablet consists mainly of one or two active pharmaceutical ingredients along with other ingredients called excipients which is important for tablet manufacturing (Pifferi et al., 1999). Tablet preparation involves production of granules which is ultimately compressed into tablet dosage form. Therefore it is very important to have good compressibility behavior of all the ingredients. The granules produced should have good flow properties and should be tested for different quality control tests of flow behavior for the production of ideal tablets. These tests include determination of tapped density, bulk density, hausner ratio, Carr's index, angle of repose etc. After compression of granules compressed into tablets and these tablets should have the quality control tests limits within pharmacopeia limits (Prakash et al., 2020).

For the last 3 to 4 decades the scientists working hard to improve the medicinal products by minimizing its effects and also to improve patients compliance by using different strategies (Shortell et al., 1998). Among all these, one is to produce fixed dose combination drugs which contain two more active ingredients compressed into a single tablet (Desai et al., 2013). Such formulation aims to reduce cost of formulations as well as patient's compliance along with reduced side effects and enhance beneficial effect of the drug (Wen et al., 2015).

Montelukast is a leukotriene receptor antagonist called montelukast is used to treat seasonal allergic rhinitis, reduce exercise-induced bronchoconstriction, and treat asthma (Kemp, 2009). The US FDA in 1998 first approved Montelukast for clinical uses as Mercks brand name Singulair. The drug belonged to the class of medications recognized as leukotriene receptor antagonists (LTRA) (Hon et al., 2014). Although they have the potential to be beneficial, such LTRAs as montelukast are often used in step treatment for asthma in addition to or as a complement to inhaled corticosteroids or other medications (Bjermer and Diamant, 2002). Nevertheless, FDA-led examinations concerning the potential for montelukast to cause neuropsychiatric side effects in patients who took the drug, such as agitation, hallucinations, suicidal behavior, and others, took place in 2008 and 2009. Although millions of prescriptions for montelukast are written each year and these kinds of side effects are presently listed in the official prescribing instructions, the medication is nevertheless widely used throughout the world (Matada et al., 2021). It is also now offered as both a generic and a brand-name pharmaceutical.

Loratadine was approved in 1993 by FDA an American agency, and was limited in access in the United States with prescription until 2002. In 2002 its patent expired and the drug was approved to sales as over the counter drug (Harrington, 2002). Loratadine is indicated for different types of allergies. Hives and allergic rhinitis (hay fever) are examples of this. As loratadine/pseudoephedrine, it is also offered in conjunction with the decongestant pseudoephedrine (Spector, 1997). It is consumed orally. Many generic versions of loratadine are available as over the counter drug in the United State (Oishi et al., 2017). In 2020 more than 9 billion prescriptions were written, it was the 73rd most widely prescribed drug in the country (Schiess et al., 2022).



A. Montelukast **B. Loratadine**

Figure 1: Structure of (A) Montelukast & (B) Loratadine

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METHODOLOGY

Chemical

Montelukast sodium (zhejiang tiayu pharmaceutical.co.ltd china), Loratadine U.S.P (Morepen laboratories ltd india), Aerosil 200 (evonik resources difficincy gmbd germany), Sodium stearyl fumarate ((Linghu xinwang chemical Co, ltd huzhou city, china.) , Starch (Rapfhan maize product fiasalabad pakistan), Lactose (Kerry ingredients india private ltd india), Microcrystalline cellulose (Ningtai taoyuan city, Taiwan), Klucel. All the chemical were kindly provided by Ferozsons laboratories, Nowshehra, Pakistan.

Equipments & instumentation

Different equipment and instruments including digital balance (Sartorius digital, Germany), moisture analyzer (Shimadzu, Japan), sieve shaker fitted with standard sieve size (Yenchen Taoyuan, Taiwan), high share granulator (Yenchen, Taiwan), bin mixer (Yenchen, Taiwan), fluidized bed drier, try drier (Nano, china.), rotary granulator (yenchen, Taiwan), rotary compression machine (ZP 29, China), DSC, XRD, pH meter (wtw, Germany), dissolution apparatus (Pharma test, Germany), tablet friabilator (Pharma test Germany), HPLC System (Shimadzu, Japan), FTIR (Shimadzu, Japan), UV visible spectrophotometer (Shimadzu, Japan), disintegration apparatus (Pharma test hamburg Germany), stability chamber (Memmert, Germany), hardness and thickness testers (Pharma test hamburg Germany), bath sonicator (Elmasonic, Germany), was used for formulation development, tablet preparation and evaluation of developed formulations.

Table 1: Active ingredients and excipients along with their roles in tablet formulation

S. No	Product Description	Role of Ingredient
01	Montelukast Sodium	API
02	Loratadine U.S.P.	API
03	Aerosil 200	suspending, dispersing and thickening agent
04	magnesium stearate	Lubricant
05	Lactose	Binder
06	Klucel Exp	Sweeting agent
07	Starch 1500	Disintegrant
08	Avicel PH 101	Filler

Table 2: different combinations of APIs and excipients for stability studies

Samples	Compositions
S-1	API-A (Loratadine)
S-2	API-B (Montelukast sodium)
S-3	API-A + API-B
S-4	API-A + API-B (with moisture)
S-5	All the excipients (without any drug)
S-6	All the APIs +Excipient
S-7	All the APIs +Excipient (with moisture)

API; Active Pharmaceutical Ingredients

Preformulation studies

Preformulation studies were carried out to determine any incompatibility.

Drug Excipient Compatibility Study

Active drugs and excipient compatibility study was carried out to determine any possible incompatibility after analyzing all the formulation ingredients on FTIR. The samples were prepared using binary mixture with and without the use of moisture. The

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spectra obtained were carefully evaluated for any extra peaks or disappearance of any peak from the spectra. The samples were then stored under stress conditions for a period of one month and again checked for any incompatibility and stability using FTIR and XRD (Dave et al., 2015).

The prepared samples stored under stress conditions (45 ± 2ºC and relative humidity 75 ± 5%) were regularly checked for physical changes like color, consistency etc and for the determination of moisture using Gravimetric method. Moisture analyzer was used to determine moisture in which a specific amount of sample was placed in the moisture analyzer and percent loss was calculated (Tanner, 2020).

FTIR Analysis

This technique was used for the identification of compatibility of the product. FTIR spectra of the compounds were generated by dispersing sample with Potassium Bromide (KBr) and compress it into disc by apply pressure through a dedicated Hydraulic press. The IR radiations in the range of 4000 to 400/200 cm-1 were used to scan the disc/Press and the spectra obtained were thoroughly evaluated (Derrick et al., 2000).

X ray diffraction

X-Ray diffraction (XRD), an analytical technique used for the structure determination of powdered materials. It was used for the identification of crystal structure, physical characteristics of materials and chemical composition etc. So before compression and granulation, the excipients and the APIs are exposed to XRD analysis to determine it compatibility. After compatibility study the compatible excipients were selected for formulation (Holder and Schaak, 2019).

Tablet Preparation by Wet Granulation Technique

FDC tablets of montelukast and loratidine were prepared by wet granulation technique. Weight of the exact quantity of API and excipients (Loratadine, Montelukast sodium, magnesium stearate, AvecilPH101, Aersol200, Lactose, Klucel, Exp-Pregelalinized Starch 1500) were taken through a calibrated balance for wet massing and mixed it well. In a beaker 1.5 % (0.61g) of HPMC (hydroxy propyl methyl cellulose E-6) was taken and its binding solution was prepared with 10ml of distilled water. The wet massing was carried out by slowly and continuously adding binding solution to the above mixed materials. The wet mass material was dried in a tray drier for about 20 minutes and tested for LOD. Finally, dried materials were passed via mesh number 20 for sizing.

Table 3: Different Compositions of FDC tablets

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Loratadine	10	10	10	10	10	10	10
Montelukast	10.4	10.4	10.4	10.4	10.4	10.4	10.4
Pregelatinized Starch 1500	9	8	11	12	12	7	10
Mg Stearate	4	5	3	4	4	4	4
Avicel PH101	57.67	56.67	58.67	54.67	50.37	57.67	57.67
Lactose	153.73	154.3	152.3	153.3	160.73	155.3	152.3
Aerosil 200	1	1	1	1	1	1.2	2.2
Klucel Exp	4.2	4.2	4.2	4.2	4.2	4	3.5

Evaluation of tablet granules

In pre compression evaluation, the granules were tested for their ability to flow using the following parameters (Shah et al., 2008):

Bulk density (g/ml)

To determine the bulk density, 10mg of granules was accurately taken in the graduated cylinder after passing through sieve. The following equation was used to calculate bulk density; (Momin et al., 2017).

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$$Density = \frac{Mass\ of\ Granules}{Bulk\ Volume\ of\ Granules}$$

Tapped density

To determine tapped density, 10 mg of granules was precisely taken in a graduated cylinder, taped it constantly till the full capacity. Tapped density was determined by dividing mass of powder by its tapped volume, using following equation; (Altino et al., 2021).

$$Density = \frac{Mass\ of\ Granules}{Tape\ Volume\ of\ Granules}$$

Carr's index (CI)

It can be calculated by subtracting bulk density from tapped density and dividing by bulk density

$$C.I = \frac{Dc - Da}{Dc} X100$$

Carr`s Index (%)
DC: granules tapped density (g/ml)
DA: granules bulk density (g/ml)

Inter Particle Porosity

To measure inter particle porosity tapped density and bulk density was used, by given equation
(Abdullah and Geldart, 1999)

$$Ie = DC - DA/DCXDA$$

Ie: Inter Particle porosity
DC: tapped density of the granules (g/ml)
DA: bulk density of the granules (g/ml)

Hausner ratio

Hausner ratio can be calculated by using bulk density and tapped density of granules. The Equation is shown as (Santomaso et al., 2003).

$$Hr = Dc/Da$$

Where Hr: Hausner ratio of Granules

Angles of Repose

Funnel Method was used to determine angle of repose. The granules were allowed to flow from the height of the table of surface. Based on the height and radius of the powders heap, Angle Repose is measured, using the following equation; (Al-Hashemi and Al-Amoudi, 2018).

$$\propto = \tan^{-1}\left(\frac{H}{r}\right)$$

Angle of repose of powder (o) = α
H = Height of the Cone Formed by powder (cm)
r = Radius of the base of cone formed by powder (cm)

Powder flow:

Accordingly, to the European Pharmacopeia (EU) powder flow can be calculated by measure the time necessary for powder (100 g) to flow via the oral cavity of a Glass funnel fixed at specific height (4 cm) (Oyebola, 2004).

Loss on drying:

According to the USP LOD is calculated by a Halogenated Moisture Analyzers. One gram of last blended powders is taken into the pan of wetness analyzer and heat it for five min at 100 °C and the percent loss is noted (Holberg and Huynh-Ba, 2022).

Hygroscopicity:

The hygroscopicity of a powder sample is assessed by placing it in a climate chamber for 24 hours at Ambient temperature and a relative humidity of 75% 5%. By reweighing the material, the amount of weight growth was assessed after 24 hours. Its hygroscopic properties were revealed by a documented increase in sample weight (Li et al., 2016).

Particle size distribution:

To determine the distribution of particle sizes, a sieve shaker equipped with conventional Endecott, England, sieves with pore sizes of 850, 600, 425, 300, and 250 m was employed. 100 g of powder was added to the top sieve, and the sieve shaker was running for 20 minutes. Calculated was the percentage of powder retained across each mesh (Khan, 2019) .

Post compression Tablet Evaluation

The tablet granules were subsequently compressed into tablets. The compressed tablets were evaluated for physical parameters, mechanical strength, disintegration behavior, drug substance and drug discharge (Turkoglu and Sakr, 2009).

Physical Evaluation

Physical appearance of Tablet

The compressed tablets were examined visually for any physical changes, such as changes in color, spots on tablets etc.

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Weight Variation

Twenty tablets were chosen at random, correctly weighed, and their mean was calculated to account for weight variation. The following formula was used to determine the deviations in weight of the tablets from the mean weight (Hill et al., 2009).

$$Weight\ Variation = \frac{Wi - Wa}{Wa}\ X\ 100$$

Wi = Individual Weight of tablets

Wa = Average weight of tablets

Thickness and weight Variation

Digital tablet tester (Pharma Test, Germany) was used to measure the thickness of 10 randomly chosen tablets, and the mean and standard deviation was determined (Podczeck, 2012).

Hardness test

To determine hardness test, 10 tablets were selected at ranzdom and using the digital tablet tester (Pharma Test, Germany) the crushing strength of the tablets was calculated (Podczeck, 2012).

Friability:

A friability test for tablets was conducted according to official compendia (Bushra, Shoaib, Aslam, Hashmat, & Rehman, 2008). Tablets were randomly chosen, de-dusted, and weighed. The tablets were put in friabilator's drum, and operated for four minutes at a speed of 25 rpm. The tablets were then dusted and reweighed. Weight loss was calculated as a % loss by using the equation (Shareef and Bushra, 2013)

$$Friability = \frac{W1 - W2}{W1}\ X\ 100$$

W1 = Initial weight of tablets

W2 = Weight of tablets after subjecting to friability test

Disintegration test

According to USP, the disintegration time of the tablets was measured using distilled water kept at 37ºC as the disintegration medium (Bushra et al., 2008). The average disintegration time of 6 tablets was used to calculate the disintegration time of each individual tablet (Shareef and Bushra, 2013).

Assay of the Tablet.

Montelukast

For the assay of montelukast the following procedure was used.

First the diluent was prepared by mixing methanol with water in a ratio of 3:1. The standard solution of montelukast 0.5mg/ml was prepared in the diluents. For preparation of the sample solution the number of tablets equivalent to 100 mg was transferred to a flask and 70% of the diluents was added to it. The flask was sonicated for about 30 minutes followed by another 30 minutes shaking. Finally the volume was made up with diluents followed by stirring again for 30 minutes. This solution was filtered and the filtrate was used for analysis by HPLC (Tablets, 2022).

Drug content of the sample was calculated using,

$$Percent\ Drug\ Content = \frac{Peak\ Area\ of\ Sample\ Solution}{Peak\ Area\ of\ Standard\ SOlution}\ X\ 100$$

Loratadine

Loratidine was analyzed on HPLC according to USP official monograph. First of all different solutions of buffers and mobile phase was prepared. Buffer A (0.01M dibasic potassium phosphate) was prepared by by dissolving 1.74 g/L of anhydrous dibasic potassium phosphate in water while buffer B (0.6 M dibasic potassium phosphate) was prepared by dissolving 105 g/L anhydrous dibasic potassium phosphate in water . For the preparation of 0.05 N HCl 500 ml water was taken in 1000 ml volumetric flask, 83 ml of HCl was added to it and the volume was made upto the mark with water. Again 50 ml from this solution is diluted to 1000 ml with water to prepare 0.05 N HCl. Mobile phase was prepared by mixing buffer, acetonitrile and methanol in a ratio of 70:60:60. The pH of the mobile was adjusted to 7.2 with phosphoric acid. For the preparation of diluent 400 ml of 0.05 N HCl and buffer B 80 ml was taken in1000 ml volumetric flask and diluted with mixture of methanol and ACN in 1:1 upto the required mark. Standard solution of loratidine was prepared in strength of 0.4 mg/ml in diluents. Sample solution was prepared by taking 10 tablets in 250 ml flask followed by addition of 100 ml of 0.05 N HCl and put the flask in shaker for 40 minutes for complete disintegration of tablets. Then a mixture of ACN and methanol (75 ml) was added to it. Finally 20 ml of buffer B was added and mixed for 5 minutes. The volume was made upto the mark with

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methanol and ACN mixture. The standard and sample solutions were then analyzed by HPLC by the following formula (Mohamed, 2015).

$$Percent\ drug\ released = \frac{ru}{\text{rs}}\ X\ 100$$

Dissolution Rate

Loratadine

The dissolution test of loratidine was carried out according to USP. Dissolution apparatus 2 was used to determine the dissolution rate of loratidine. The media used was 0.1N hydrochloric acid. The apparatus was operated at 50 rpm for a period of 60 minutes after putting one tablet each in six chambers. The samples were collected at different time interval and were analyzed by UV visible spectrophotometer at a wavelength of 280 nm (Naveed et al., 2018).

$$Percent\ drug\ released = \frac{A\ sample}{\text{A standard}}\ X\ 100$$

Where

Absorbance of sample solution =A sample

Absorbance of standard solution= A standard

MONTELUKAST

The dissolution test of Montelukast was carried out according to USP. Dissolution apparatus 2 was used to determine the dissolution rate of Montelukast. The medium used was 0.5 % w/v sodium dodecyl sulfate in water 900 ml for each of six tablets. The apparatus was operated for a specific period of time and the sample was taken at different time interval and was analyzed at HPLC. The column used was 4.6mm*10 cm with a flow rate of 1.5ml/min and injection volume of 25 µl. The detector was set at 389 nm. After analysis the percentage of drug release at each specific time was determined (Chen et al., 2017).

$$Percent\ drug\ released = \frac{ru}{\text{rs}}\ X\ 100$$

Stability testing of Samples

The stability of all formulations were determined accroding to ICH guidelines in which the formulations were kept 40°C +/- 2°C and 75% Relative humidity +/- 5%. The formulations were kept in stability chamber for a specific period of time. After the required times the sames wrere tested any physical change and and were also analyzed by IR spectrophotometer to observes any chemical change in the formulations (Sengupta et al., 2018).

RESULTS AND DISCUSSION

Pre formulation study

Pre formulation studies were carried to find out any compatibility between the excipients and with active drugs, to prevent any defects in the final product and to produce a stable product. The excipients and active drugs were mixed by binary approach and were subjected to different types of evaluations for the confirmation of any incompatibilities including FTIR evaluation, XRD determination and evaluation for physical appearance and chemical contents (Chadha and Bhandari, 2014).

The mixtures produced for different formulation were evaluated for physical appearance after storing under stress conditions of 40ºC±2 ºC. There were no any significant changes observed in the physical appearance and moisture contents of different formulation. The formulations were also subjected to FTIR and XRD evaluation to determine any significant incompatibilities between excipients and active drugs montelukast and loratidine. Active drugs and excipients were tested by FTIR alone and then in different combinations. FTIR works on the basis of absorption of infrared radiations at specific wavelength by different functional groups. If there is any incompatibilites occur it will observe in the spectra. The FTIR spectra of excipients and active drugs before mixing and after mixing were shown **figure 2** . These graphs indicated there was no extra peaks observed in the spectra of FTIR which was confirmation of the fact that there was no incompatibility observed between the excipients and active drugs.

The incompatibility was also determined by XRD analysis, in which heat is used to determine the increase in temperature of different formulation before and after mixing. The presence of any extra peaks in the spectra confirms any type of incompatibility. Thus the mixtures of different formulations produced were subjected to XRD analysis. The results obtained were shown in below in **figure 3 & 4.**

The XRD graphs indicated that there was no extra peak observed in the spectra which is confirmation of

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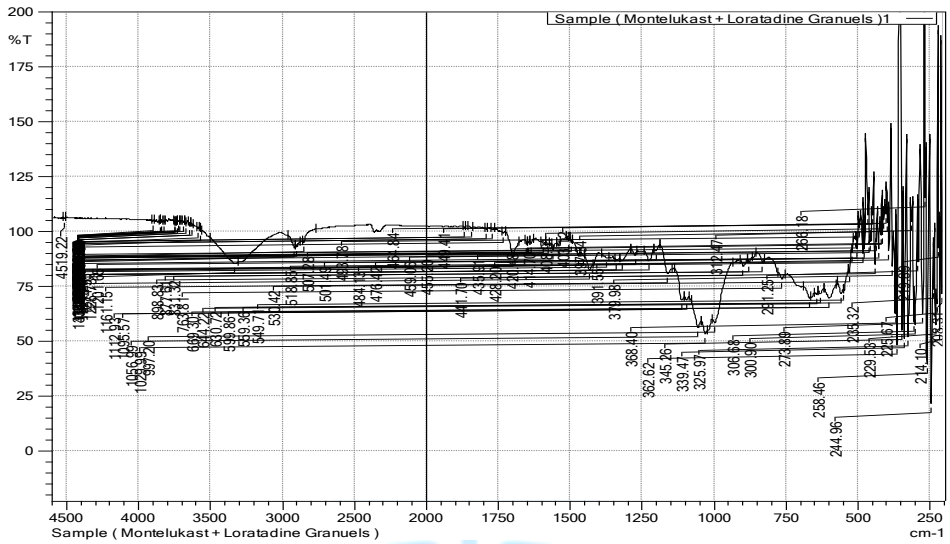
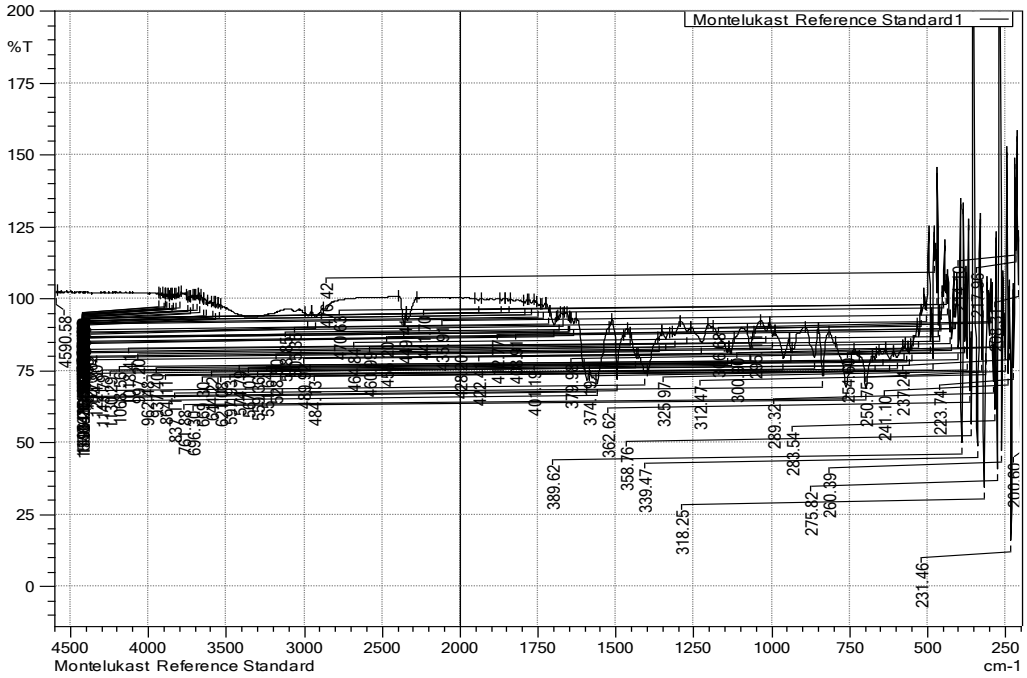
the fact that there was no incompatibility found between the excipients and active drugs

Similarly all the formulations were subjected to accelerated stability under which the formulations were observed under high temperature and humidity for specific period of time. The formulations were subsequently checked for any physical or chemical changes under stress conditions. There were no significant physical changes observed in any formulation nor any chemical changes were observed when analyzed by FTIR.



(A) . Montelukast + Loratadine granules



(B) . Montelukast references standard

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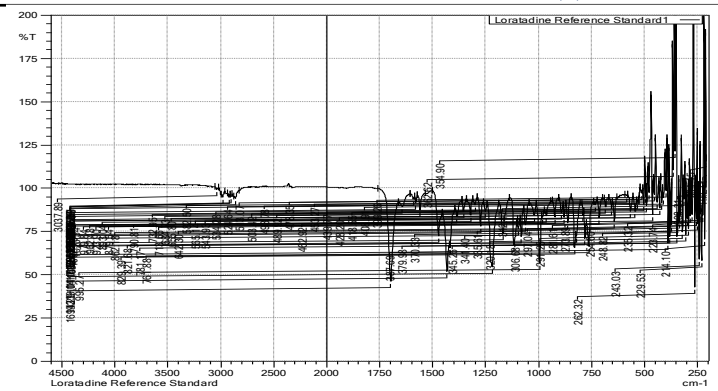
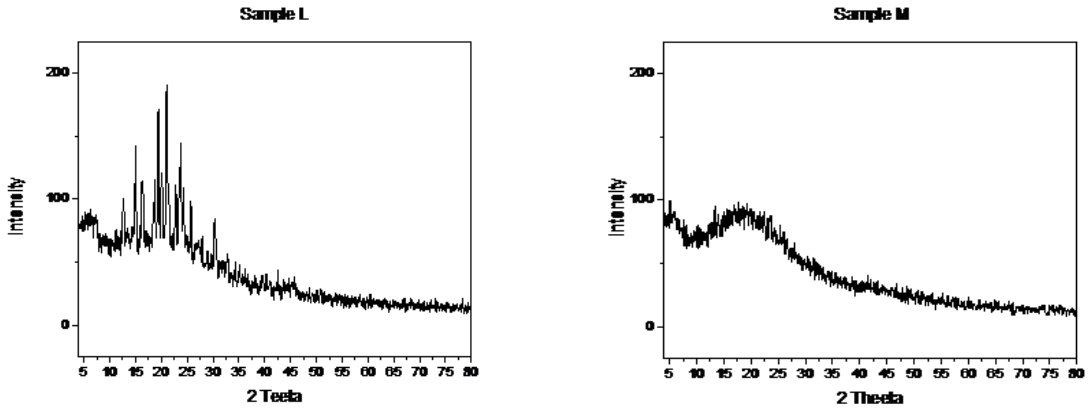


(C) . Loratadine references standard

Figure 2: FTIR spectra of a Mixture Of (A) Montelukast/loratadine with Excipients, (B) Montelukast and (C) Loratadine.



(A) (B)

Figure 3: XRD spectra of (A) loratidine and (B) Montelukast

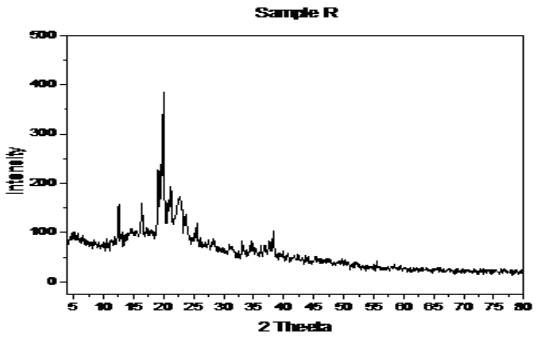


Figure 4: XRD spectra of loratidine/montelukast sodium along with excipients

PRE-COMPRESSION EVALUATION: All the pre-compression parameters for the formulated granules are given in the table 4 below

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Table 4: Precompression parameters of all seven formulations of loratidine and montelukast sodium fixed dose tablet granules

Parameters	S-1	S-2	S-3	S-4	S-5	S-6	S-7
Bulk density	0.51	0.49	0.47	0.45	0.47	0.50	0.48
Tapped Density	0.56	0.63	0.53	0.58	0.57	0.56	0.54
Carr'sIndex	12.07	17.30	15.22	15.07	13.90	14.55	12.06
Cohesion Index	127.3	84.16	81.02	88.18	126.7	114.6	86.12
Hausner Ratio	1.21	1.18	1.19	1.17	1.15	1.16	1.14
Angle of Repose	25.93	24.65	26.15	27.45	32.42	26.05	23.50
Inter Particle porosity	0.211	0.135	0.278	0.253	0.42	0.358	0.283
Hygroscopicity	0.063	0.0624	0.045	0.058	0.054	0.066	0.075
Homogeneity Index	0.007	0.006	0.009	0.008	0.015	0.012	0.017
Moisture content	3.5%	3.85%	3.65%	3.61%	2.45%	2.61%	2.33%

Different physical parameters were evaluated for all the formulation presented in table 1. Bulk density of all formulation was in the range of 0.45 to 0.51 g/ml, while tapped density was in the range of 0.53-0.63 suggesting a good value for both bulk and tapped density. Similarly, the values of Carr's index, Hausner ratio, Angle of repose and Inter particle porosity was in the range of 12.06-17.30, 1.14 to 1.21, 23.50 to 32.40 and 0.13 to 0.42 respectively. These precompression values lies within the normal ranges and indicates the good flow characteristic of trial batches**.** Precompression evaluated data was presented in table 1 above.

POST COMPRESSION EVALUATION

All the formulation selected were compressed and evaluated by different quality control tests. The results of different quality control tests wete presented in **table 5** below.

Table 5: Evaluation of different quality control tests of all formulations

S.NO	WEIGHT VARIATION (mg)	Hardness (kg/cm2)	THICKNESS (mm)	FRIABILITY (%)	DISINTEGRATION (per minute)
F-1	247	5.2	3.56	0.12%	2.1
F-2	249	4.8	3.57	0.14%	2.5
F-3	250	6.0	3.58	0.13%	2.3
F-4	248	5.5	3.60	0.15%	2.4
F-5	249	6.2	3.48	0.12%	2.3
F-6	248	5.5	3.60	0.15%	2.4
F-7	250	6.0	3.58	0.13%	2.3

WEIGHT VARIATION

The "Weight Variation" parameter evaluates the uniformity of tablet weights throughout a batch. To guarantee consistency in medication content, tablets were weighed against a target value. The data presented in the table 7 and figure 9 indicates there is no much variation among different formulations and all the results lies within the official limits of USP. The results also indicate the homogenous mixing of active ingredients with excipients.

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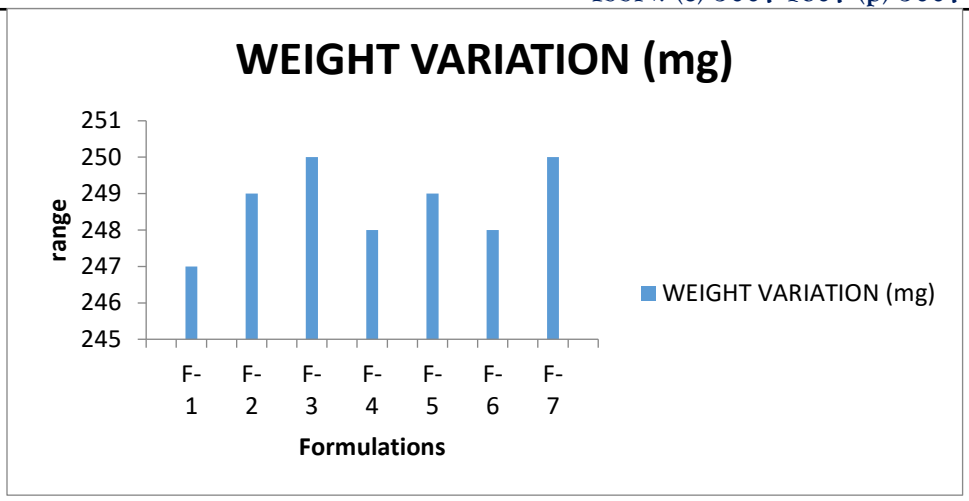

Figure 5: weight variation graph of all formulations

HARDNESS

This test describes how much tablet is resistant to breaking or disintegrating when subjected to pressure in hardness tester. The findings in the table above revealed the amount of pressure necessary to break the tablet. The hardness values for all formulations ranging from 4.8 to 6.2 kg/cm^2.

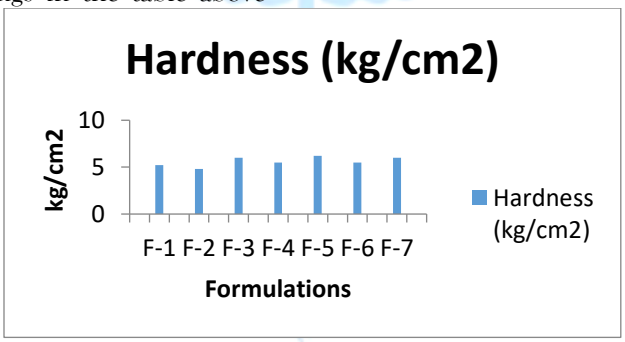

Figure 6: Hardness test graph of all formulations

THICKNESS

For dosage homogeneity and appropriate absorption in the body and also for packing and blistering, tablet thickness consistency is crucial. The thickness measurements are between 3.48 and 3.60 mm which is well within the normal limits.

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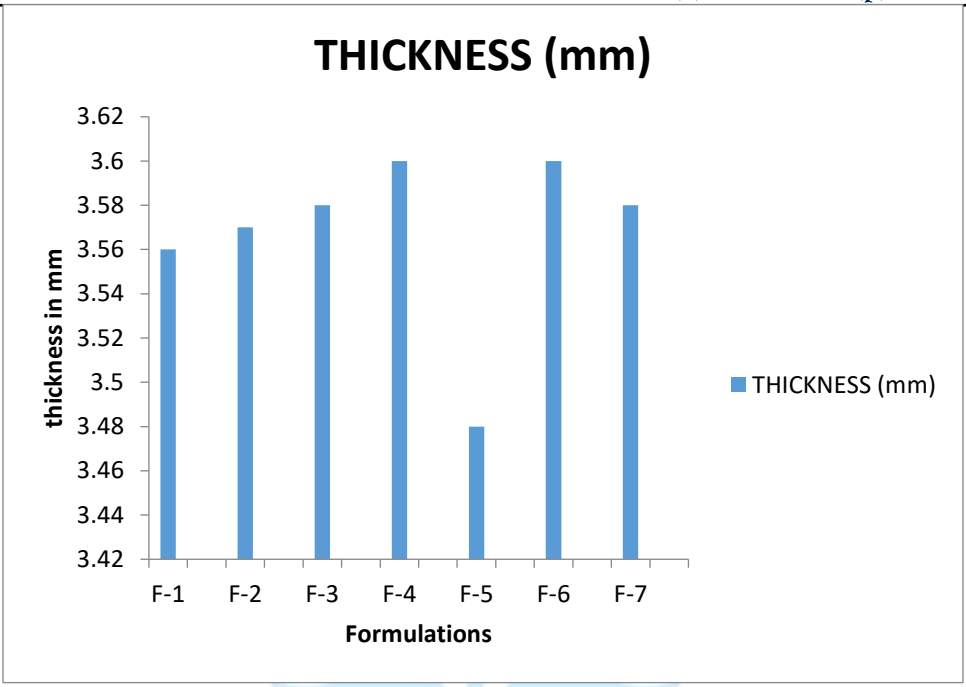

Figure 7: Thickness test graph of all formulations

FRIABILITY

Friability quantifies a tablet's propensity to disintegrate or crumble during handling. Following the application of mechanical force to the tablets, it is expressed as a percentage of weight loss. The table indicates above the friability results of all formulations ranges from 0.12% to 0.15% which is below the target value of 1% according to USP. The values suggested the tablets are hard enough and withstand the external forces during handling and transportation.

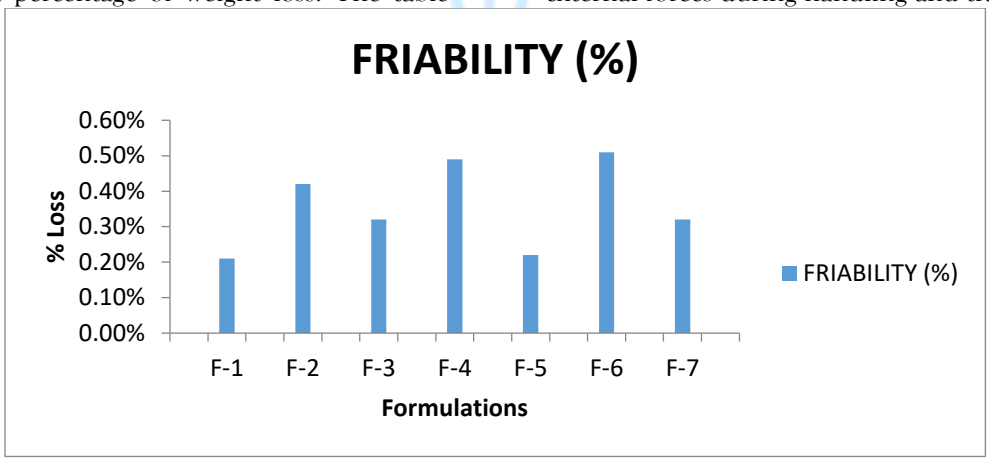

Figure 8: Graph of all formulations representing % loss after friability test

DISINTEGRATION

When a tablet is subjected to a simulated physiological environment, the disintegration time measures how long it takes for the tablet to totally disintegrate into smaller particles. All the formulations disintegrate efficiently in between 2.1 and 2.5 minutes which is in the range, according to USP.

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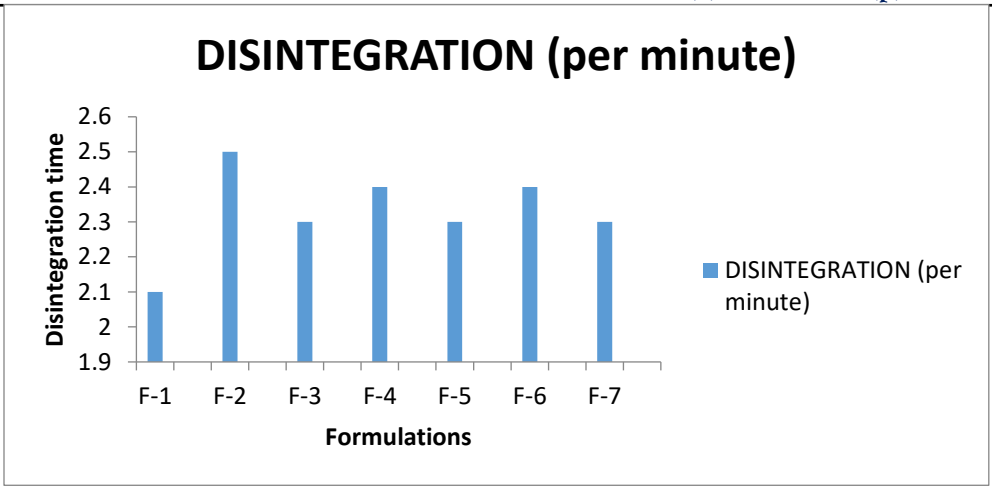

Figure 9: Disintegration test graph representing mean disintegration time of all formulations

PHYSICAL APPEARANCE

This section discusses the tablets' physical appearance. All tablets in the above table are reported as being "Off white," indicating a regular colour for every tablet that was tested.

Dissolution Rate of FDC Montelukast/Loratadine:

The pace at which a solid substance dissolves in a liquid to form a solution is referred to as the dissolution rate. It is an important consideration in several industries, including chemistry, material science, and medicines. The surface area of the solid, temperature, solute concentration, and solvent type are some of the variables that affect how quickly a substance dissolves, since there is more surface area available for the interaction between the solid and liquid molecules, substances having a higher surface area often dissolve more quickly. Another important factor is temperature; generally speaking, higher temperatures promote faster dissolution since they give the particles more energy to interact and fragment.

Dissolution rate is crucial in the pharmaceutical sector since it influences the bioavailability and efficacy of medications. To be absorbed by the body and enter the bloodstream, drugs must swiftly disintegrate. Dissolution rates are studied by scientists and researchers to improve drug formulations, ensuring that the medication is delivered in the body at a predictable and steady rate.

Dissolution test was carried out according to USP guidelines and the same procedure was used already mentioned in USP for montelukast and loratidine. Dissolution rate of montelukast and loratidine from FDC was determined separately at different timed interval was shown above in **table 6** and **table 7**. The dissolution rate after each interval was well within the official limits of USP which indicates that both montelukast and loratidine did not affect the release rate of each other when compressed into a single tablet.

Table 6: Drug release profile of loratidine from fixed dose tablet at different time interval.

Time	15 min	30 min	45 min	60 min
Tab.1 Drug release (%)	30%	59%	81%	105%
Tab.2 Drug release (%)	36%	63%	86%	103%
Tab.3 Drug release (%)	32%	57%	76%	99%
Tab.4	30%	54%	71%	94%

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Drug release (%)				
Tab.5 Drug release (%)	31%	56%	73%	97%

Table 7: Drug release profile of Montelukst from fixed dose tablet at different time interval

Time	15 min	30 min	45 min	60 min
T.1 Drug release (%)	35%	61%	79%	98%
T.2 Drug release (%)	31%	55%	73%	95%
T.3 Drug release (%)	38%	63%	87%	108%
T.4 Drug release (%)	34%	61%	84%	105%
T.5 Drug release (%)	30%	60%	77%	100%

Stability testing of Samples

Stability study is the time in which new formulation retain its chemical and physical stability. Stability study is the most important parameter used for the development of new formulations. It has a crucial rule in the determination of shelf life, efficacy, safety and quality of the formulation. Stability data fixes the expiration date of the formulation which may be affected by various factors like humidity, temperature, light and closure system etc. Shelf life is the time after which the product losses its 90% concentration. All the formulation subjected to stability was observed thoroughly for any physical change. No formulation showed any significant changes in their physical property. FTIR spectra revealed that there was no extra peaks observed which is indication of the fact that no chemical changesoccured during the stability testing.

Conclusion:

This study was carried out to develop a new FDC formulation of Montelukast10mg/Loratadine 10mg through wet granulation techniques. In the current study excipients were selected on the basis of their compatibility with drugs (Montelukast, Loratadine). During drug excipients compatibility it was identified that given drugs are compatible with its excipients used in the formulation. So given drugs were selected for formulation

For the treatment of allergic disorders, the fixed-dose combination tablet of loratadine and montelukast offers a promising strategy. The combination of loratadine's antihistamine effects with montelukast's anti-inflammatory capabilities results in a formulation that provides a thorough treatment for people who have both allergy symptoms and inflammation-related problems. Single-tablet convenience streamlines prescription regimes and improves patient adherence. Before advising this combination, medical experts should carefully evaluate the needs of each individual patient and any potential interactions, as is the case with all medical treatments. This combination tablet's position in the therapeutic landscape will be influenced by ongoing research and clinical evaluation, which will continue to provide information on its safety and effectiveness.

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