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FORMULATION DEVELOPMENT AND EVALUATION OF FIXED DOSE COMBINATION TABLETS CONTAINING MONTELUKAST AND LEVOCETIRIZINE

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ABSTRACT

The primary goal of this investigation was to formulate and evaluate the fixed dose combination of tablets containing the montelukast 10 mg and levocetirizine 5 mg in tablet dosage form. Under the preformulation studies solubility, loss on drying, water content by KF, tapped density, and hygroscopic nature were carried out. This combination formulation was formulated by using various excipients hence that cause rate of drug release gradually enhanced. These studies showed satisfactory results for further formulation. This combination tablets were showing the effective results in various quality control parameters and dissolution profile and assay of the developed product also complies with the Indian Pharmacopoeial (IP) specification and inhouse specifications of Bal Pharma Limited. The result of the prototype formulation showed that the batch 5 and batch 6 produce effective drug release results and it is found to be more cost effective when compared to the existing formulation.

Keywords: Montelukast, Levocetirizine, Drug Release, Asthma

INTRODUCTION:

Different classes of tablets are available, of which are classified according to their route of administration. Coating is used to mask up and protect items that are vulnerable to oxidation and moisture, as well as drugs that have an unpleasant taste or odour **[1-4]**. Granulation attempts to improve the flow of powdered materials by forming spheres like aggregates called granules. Direct compression is a process where the ingredients are compressed directly without going for granulation process. In asthma there are various cells involved, such as mast cells and

eosinophils as well as T-lymphoma and neutrophil cells and epithelial cells and cellular components that are involved in the chronic inflammatory condition of the airways **[5]**. Respiratory symptoms such as wheezing, shortness of breath, chest tightness, and coughing are common in vulnerable individuals **[6]**. An airflow restriction is often the cause of these signs and symptoms. During inflammation, the bronchial hyperresponsiveness (BHR) of the airways is increased. Histamine, eosinophils, and neutrophils are released into the bloodstream as a consequence of mast cell disintegration in the presence of allergens **[7]**. the chemo tactic is an important consideration This causes mucosal oedema and mucus secretion as a consequence of leukotriene C4, D4, and E4. In the treatment of seasonal allergic rhinitis and to prevent exercise-induced bronchoconstriction, the leukotriene receptor antagonist montelukast is employed **[8]**. Chronic allergic rhinitis and simple chronic idiopathic urticaria may be treated with levocetirizine, an H1-receptor antagonist **[9-11]**. Using appropriate excipients, the formulation of fixed dosage combination tablets comprising 10 mg of Montelukast and 5 mg of levocetirizine was tested in this study **[12-13]**.

MATERIALS AND METHODS:

Drugs and Chemicals:

Montelukast sodium and Levocetirizine was provided as a free sample from MSN Pharmaceuticals and Symed labs limited, India respectively. A sample of Microcrystalline cellulose, mannitol DC, povidone, primellose was given by FMC Germany. The Magnesium stearate, talc, aerosil were purchased from Kemphason, India respectively. Analytical-grade chemicals and reagents were employed in this experiment.

Instruments:

Electronic weighing balance, Bulk density apparatus, Tray drier, Electronic LOD measurement apparatus, Sifter, Dissolution apparatus, Friability test apparatus, Coater, Coating pan, Compression machine-10 station, HPLC.

PREFORMULATION STUDIES:

Solubility:

In order to make a saturated solution at the same temperature and pressure, a drug molecule's solubility is the quantity of the drug that dissolves in the solution **[14]**.

Loss On Drying:

1 to 2 grams of the drug should be well mixed and weighed. By crushing fast, you can get the particle size down to roughly 2 mm if the material has huge crystals. After 30 minutes of drying under the same circumstances as those used in the determination of the weight, use a glass-

stopper, shallow weighing bottle to tare. Replace the cap on the bottle, then weigh the container and its contents precisely. As evenly as possible, distribute the test specimen to a depth of approximately 5mm, but not more than 10mm for bulky materials. Remove the stopper and place it in the drying chamber (LOD oven) with the loaded bottle. Specify the temperature and duration for drying your test specimens.

In an oven within a specified temperature range: The drying is done in an oven at a temperature stated in the monograph. Immediately after opening the chamber, place the bottle in a desiccator and let it warm up to room temperature before weighing. When the phrase "drying to constant weight" is used, it signifies that the weights of the dried product must be within 0.5 mg of one another, with the second weight taken after the required amount of time has passed (1 hour is usually suitable).

Tapped Density:

In a graduated cylinder, a predetermined weight of powder was measured out up to the 70 ml marking and was tapped using a tapped density tester for 500taps/750taps/1250taps, till the level of powder in a measuring cylinder is less than 1ml after tapping. The final volume mark as then observed and bulk density, tapped density was calculated.

Water Content (By KF):

Test preparation: Use a portion of the specimen that contains 10 to 250 mg of water, carefully weighed or measured. At temperatures and relative humidity that are known to have no effect on the outcome, use powder made from no less than four pills, ground to a fine powder.

Standardization of the reagent: Titrate with the reagent until the electrodes are covered by enough methanol or other appropriate solvent. Titrate to the end point by adding 150 to 300 mg of sodium tartrate correctly weighed by difference and fast.

Procedure: Unless otherwise specified, transfer 35 to 40 ml of methanol or other suitable solvent to the titrate with the reagent to the electronic or visual endpoint to consume any moisture that may be present. Quickly add the preparation, mix and again titrate with the reagent to the electronic or visual end point **[15]**.

Hygroscopic Nature:

Procedure: Accurately weigh 20 gm of the test specimen in Petri dish and note down the weight. Expose to 50, 75 and 95% RH at 25°c for 7 days and note down the difference in weight. The above mentioned preformulation results were reported in **Table 5**.

PROTOTYPE FORMULATION:

Batch 1 – 1000 Tablets (Target weight of a core tablet - 160 mg; Target weight of a coated tablet - 165 mg).

Table 1: Ingredients used in the formulation for Batch 1

S. No.	Ingredients	Master Formula	Working Formula
1	Montelukast sodium	10.80	10.80
2	Levocetirizine dihydrochloride	5.10	5.10
3	Microcrystalline cellulose	121.10	121.10
4	Aerosil	3.00	3.00
5	Povidone	1.50	1.50
6	Isopropyl alcohol	qs	qs
7	Methylene chloride	qs	qs
8	Magnesium stearate	1.00	1.00
9	Talc	1.50	1.50
10	Aerosil	5.00	5.00
11	Microcrystalline cellulose (RANQ)	10.00	10.00

Procedure:

All the ingredients were weighed **(Table 1)** for the required amount. A sieve number 40 was used to remove all materials except magnesium stearate and talc from the mixture. Only magnesium stearate and talc made it past filter no. 60 without contamination. Mix the montelukast, microcrystalline cellulose and aerosol for 10 mins in a double poly bag. Disperse povidone in isopropyl alcohol and methylene chloride mixture and granulate the above blend using this binder solution. The above granules were dried at 30°c. Mix levocetirizine and aerosol in a poly bag for few min. add microcrystalline cellulose (RANQ) and mix well. The above prepared granules were mixed with the already dried granules. Pass primellose through sieve no. 40 and add to the mixed granules. The granules were lubricated with magnesium stearate and talc. The lubricated granules were compressed using 8 mm NC plain punches.

Coating for Batch 1:

Table 2: Ingredients used in the formulation for coating (batch size 1000)

S. No.	Ingredients	Master Formula	Working Formula
1	Talc	0.60	0.60
2	Titanium dioxide	1.00	1.00
3	HPMC 15 CPS	3.00	3.00
4	Isopropyl alcohol	qs	qs
5	Methylene chloride	qs	qs
6	Propylene glycol	0.40	0.40

Procedure:

All the ingredients were weighed to the quantity given **Table 2**. A mortar and pestle were used to grind talc and titanium dioxide into a fine powder. Isopropyl alcohol and methylene chloride were milled in a colloidal mill; to this talc and titanium dioxide were added until a uniform solution is obtained. Finally, to this solution propylene glycol was added and mixed well. The coating of the compressed tablets was done in a conventional Coating pan **[16]**.

Batch 2 to 6 – 1000 Tablets (Target weight of a core tablet - 160 mg; Target weight of a coated tablet - 165 mg)

Table 3: Ingredients used in the formulation for various batches

S. No.	Ingredients	Working Formula in mg per tablet				
		B2	B3	B4	B5	B6
1	Montelukast sodium	10.80	10.80	10.80	10.80	10.80
2	Levocetirizine dihydrochloride	5.10	5.10	5.10	5.10	5.10
3	Mannitol DC	74.30	72.30	70.30	68.30	68.30
4	HPC LH 11	4.80	4.80	4.80	4.80	4.80
5	Avicel pH 112	60	60	60	60	60
6	Primellose	2	4	4	4	4
7	Talc	1.50	1.50	1.50	1.50	1.50
8	Magnesium stearate	1.50	1.50	1.50	1.50	1.00

Procedure:

All the ingredients were weighed **(Table 3)** for the required amount. Except for talc and magnesium stearate, all of the components were screened via sieve number 40. Filtered via filter number 60 were Magnesium stearate and Talc. Mix montelukast and mannitol DC for 10 min in a double poly bag. Add HPC LH 11 to the above blend and mix well for a few minutes. Add primellose to the blend and mix gently. Pass all the above mixed blend powder through sieve no: 40. The granules were lubricated with magnesium stearate and talc. The lubricated granules were compressed using 8mm NC plain punches.

EVALUATION PARAMETERS:

Thickness:

Vernier caliper was used to determine the thickness of each batch of randomly taken tablets, and the average thickness was recorded for each batch.

Hardness:

The Monsanto hardness tester was used to determine the tablet's hardness, and the findings were documented.

Weight Variation:

Randomly weigh 20 units of formulated tablets separately, and determine its average weight of the tablets for each batch. As per IP limit, no more than twice the average weight may be deviated from by any one tablet, and even then, only two tablets may stray from the average.

Friability:

Full tablet samples equivalent to 6.5 g should be taken, when a tablet's average weight is less than 0.65 grams, or when a tablet's average weight is more than 0.6 grams, ten tablet samples should be obtained. Formulated tablets were below 0.65 g in weight, thus use 6.5 g of sample tablets to do the test. Set the RPM to 25 and allow to revolve the drum for 4 minutes after thoroughly dusting and properly

weighing the tablets. Ensure that the tablets are dust-free before weighing them and determining the percentage loss at the conclusion of the procedure.

Disintegration time:

In order for the wire mesh to stay at least 2.5 cm below liquid surface on the upward stroke and to descend not less than 2.5cm from vessel bottom on the downward stroke, the beaker must be filled with the necessary liquid. In each of the six tubes, place one pill or capsule and a disc. Water at 37°C+2°C should be used as the immersion fluid to operate the instrument. Lift the basket out of the fluid at the conclusion of the time limit given in the monograph and inspect the pills. To be considered unusable, tablets must have completely dissolved. The test should be repeated with an extra 12 numbers if one or two pills fail to dissolve fully. At least 16 out of the entire number of numbers examined fully disintegrate.

Dissolution Test:

Dissolution apparatus operating procedure: For dissolution test, USP type 2 (Paddle) apparatus was used. 4% SLS medium was taken as a dissolution medium and operated the dissolution apparatus for 100 rpm speed at 45 minutes. Dissolution test was determined by HPLC method and that chromatographic conditions were listed in **Table 4**.

Preparation of 4% SLS: Weighed a required amount (240gm in 6 liter of water) and dissolved in water to produce the required amount.

Preparation of standard solution: Weighed and transferred accurately about 0.0446g of montelukast sodium and 0.0221g of levocetirizine and dissolved in 100 ml of methanol. From this took 5ml of the solution and dilute it to 200ml with dissolution medium. Filter the solution through 0.45um filter.

Preparation of sample solution: As previously discussed, configure the dissolving apparatus settings. Start the dissolution test by placing a pill in each of the six dissolving containers (type 2). Each dissolving jar should be emptied of 10 ml of the dissolution at the conclusion of the time period. Proceed to 0.45um filter the solution.

Evaluation of system suitability: Injected 10 µl of standard solution in five replicate injections and recorded the chromatograms. The tailing factor of for the peaks due to montelukast and levocetirizine were not more than 2.0 percent and RSD for the peak area of the five replicate injections of montelukast and levocetirizine peaks were not more than 2.0%.

Procedure: Injected 10 µl of sample solution and recorded the chromatograms and measured the peak

areas at 240 nm. From the retention time of montelukast was found to about 15.8min. and for levocetirizine is around 5.7 min.

Assay:

Table 4: Chromatographic Condition to evaluate the formation by HPLC

S. No.	Chromatographic Conditions
1	Column - C18 (250×4.6)
2	Flow rate - 1.5 ml/min
3	Detection - 240 nm
4	Injection volume - 10 µl
5	Column temperature - Ambient

Mobile phase: 350:650:2 Buffer : acetonitrile : triethyl amine and adjust ph to 6.0 with orthophosphoric acid. Mobile phase buffer prepared by dissolving about 2.2 gm of potassium dihydrogen phosphate in 1 liter of water.

Preparation of standard solution: Weighed accurately about 0.052 g of montelukast sodium and 0.0250 g of levocetirizine sample working standards and sonication to dissolved and diluted to 50 ml in a 100 ml volumetric flask with 5 ml of methanol. By serial dilution took 5 ml from this and made up to 50ml. Filter the solution through 0.45um filter.

Preparation of sample solution: Weighed accurately a quantity of tablet powdered equivalent to about 10 mg of montelukast and 5 mg of levocetirizine and dissolved it in methanol and made up the volume up to 50 ml with same solvent. From this solution took 5ml and made up to 50 ml methanol.

Evaluation of system suitability: Injected 10 µl of standard solution in five replicate injections and recorded the chromatograms. The tailing factor of for the peaks due to montelukast and levocetirizine were not more than 2.0 percent and RSD for the peak area of the five replicate injections of montelukast and levocetirizine peaks were not more than 2.0%.

Procedure: Injected 10 µl of sample solution and recorded the chromatograms and measured the peak areas at 240 nm. From the retention time of montelukast was found to about 15.8min. and for levocetirizine is around 5.7 min.

RESULT AND DISCUSSION:

Preformulation Studies:

Table 5: Preformulation studies for formulation

S. No.	Test	Montelukast Sodium	Levocetirizine
1	Description	Montelukast is a yellow to white powder.	Levocetirizine is a white to off white powder.
2	Solubility	Soluble in methanol and water insoluble in acetonitrile.	Freely Soluble in water and insoluble in acetonitrile.
3	Loss On Drying	1.2% w/w	0.8% w/w
4	Water Content by KF	1.64% w/w	0.23% w/w
5	Tapped Density	0.45 g/cc	0.40 g/cc
6	Hygroscopic Nature	Montelukast is of hygroscopic nature study period for 7 days.	Levocetirizine is of non-hygroscopic nature study period for 7 days

Evaluation Parameters:

Disintegration time was not found within the limit and the presence of relative substances was not within the limit. Even the release of drug was found to be very low for batch 1. Rate of drug release gradually increased in batch 6 when compared to subsequent batches (batch 2 to 6). The individual batches evaluation results were reported in **Table 6 and 7**. The formulated batches (B1 to B6) were within the specified limit **(Table 8)**. The physic-chemical properties of the finished product especially dissolution and assay comply with the in-house specifications of Bal Pharma Limited.

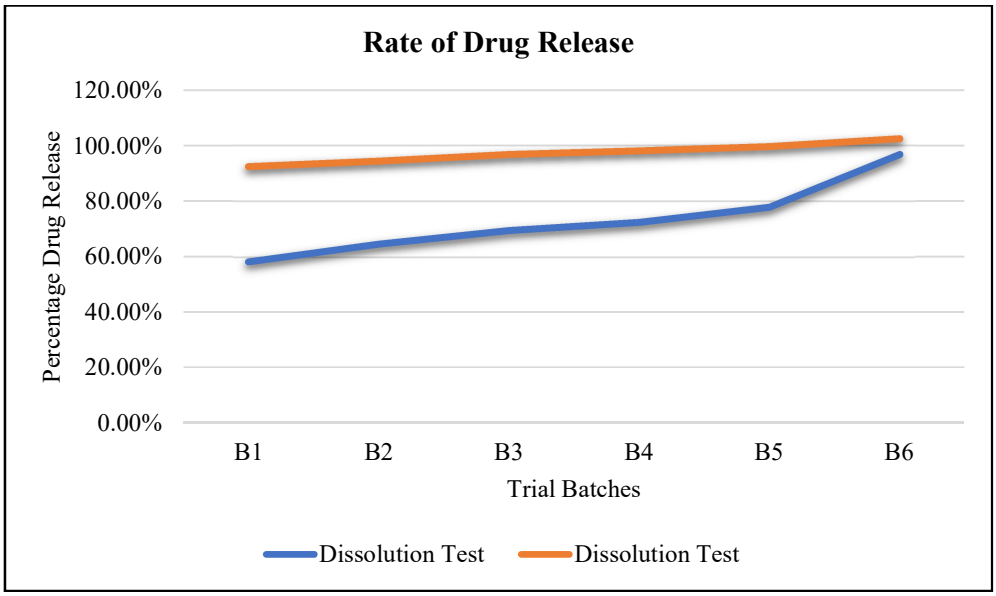

Figure 1: Rate of drug release for Montelukast and Levocetirizine

Table 6: Post compression test for formulated tablets

S. No	Formulation	Thickness (mm)	Hardness Kg/cm^2	Average Weight (mg)	Friability (%)	Average Disintegration Time
1	B1	3.5	5.5	164.5	0.277	10 min 25 sec
2	B2	3.5	5.0	165.2	0.74	6 min 20 sec
3	B3	3.6	4.8	166.2	0.44	5 min 40 sec
4	B4	3.5	5.0	165.7	0.416	5 min 30 sec
5	B5	3.6	4.6	164.8	0.879	4 min 10 sec
6	B6	3.5	4.7	166.5	0.37	3 min 5 sec

Table 7: Dissolution test and assay for formulated tablets

S. No	Formulation	Dissolution Test % Drug Release		Assay (mg)	
		Montelukast	Levocetirizine	Montelukast	Levocetirizine
1	B1	58.4%	92.5%	9.8	4.95
2	B2	64.7%	94.5%	10.0	5.02
3	B3	69.6%	96.8%	9.9	5.01
4	B4	72.5%	98.2%	9.5	5.02
5	B5	78.0%	99.7%	9.8	5.03
6	B6	96.8%	102.5%	10.05	5.01

Table 8: Summary of the finished product specification & results

S. No	Parameters	Results obtained	Acceptance criteria
1	Description	Complies	White to off white collared circular, biconvex. Film coated tablets.
2	Identifications	Complies	A comparison of the chromatograms of both the assay preparation and std preparations shows that their retention times are almost identical.
3	Average weight	166.5 mg	162 to 168 mg
4	Thickness	3.4 mm	3.3 mm to 3.7 mm
5	Hardness	4.7 kg/cm2	4.0 to 6.0 kg/cm2
6	Disintegration time	3 min 5 sec	NMT 10 min
7	Dissolution Montelukast sodium Levocetirizine dihydrochloride	96.8% 102.5%	90 % to 110 % of the average value
8	Assay Montelukast sodium Levocetirizine dihydrochloride	10.05 mg 5.01 mg	9.8 mg to 11.0 mg 4.9 mg to 5.5 mg

CONCLUSION:

The fixed dose combination tablet containing Montelukast 10 mg and Levocetirizine 5 mg has been successfully formulated and evaluated with 6 batches. In a study of six batches, B6 was found to have the satisfaction result of drug release behaviour can be greatly affected by Avicel pH 112. All the formulated tablets were found to be within the limit as per Indian Pharmacopoeial specifications and inhouse specifications of Bal Pharma Limited. The final suitable combination was achieved fruitfully by the direct compression method. This formulation was a successful approach for the treatment of allergic rhinitis and asthma, it is found to be more cost effective when compared to the existing formulation. Further, this development for long-term pharmacokinetic and pharmacodynamic investigations in humans are needed to evaluate the drug's effectiveness and safety.

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