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Research Article

In-Vitro Comparative Study of Levocetirizine Dihydrochloride and Montelukast Sodium Release Profiles in Xyzal M Suspension and Other Marketed Syrup Formulations

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Abstract

Objectives: *In-vitro* comparative analysis of the release profile of levocetirizine dihydrochloride and montelukast sodium in Xyzal M Suspension and three commercially available syrup formulations.

Method: The active components and their impurities were initially assayed in all formulations using a validated HPLC method. The enantiomeric impurities of montelukast sodium in different pH media were determined using the HPLC method specified in the United State Pharmacopoeia (USP) monograph. Additionally, dissolution studies and the soluble fractions of the components were evaluated in pH media that mimic the conditions of the gastrointestinal tract. The particle size was also analyzed using microscopic analysis. All parameters were examined in fresh, stressed, and aged samples of each formulation.

Results: The assay results indicate the claimed potency of formulations. The total and enantiomeric impurities meet the limits set by the Indian Pharmacopoeia (<2%) and USP monograph (<0.2%), respectively. The particle size analysis demonstrated that montelukast remained suspended throughout the Xyzal M suspension. Levocetirizine in all formulations exhibited a soluble fraction of >70% after 1 and 24 hours in various pH media. For montelukast, the soluble fraction exceeded 50% in all syrup formulations. However, in Xyzal M suspension, montelukast was found to be 100% insoluble in all pH media after 1 and 24 hours, except in simulated intestinal fluid (~40-45%) after 24 hours. The absence of S-enantiomer, even in simulated intestinal fluid, indicates its presence in the pharmacologically active form.

Conclusion: Xyzal M suspension is a promising dosage formulation for achieving desired pharmacological action, outperforming the syrup formulations.

Keywords: Levocetirizine dihydrochloride, Montelukast sodium, Release profile, Suspension, Syrup, S-enantiomer

INTRODUCTION

Montelukast sodium and levocetirizine dihydrochloride are two potential molecules that have shown promising results in the treatment of respiratory disorders and are widely used to manage allergic rhinitis, asthma, and cough, among other conditions[1]. The combination of montelukast sodium and levocetirizine dihydrochloride offers several benefits, including reduced risk of drug accumulation, no known pharmacokinetic interactions, convenient dosing, with prolonged duration of effect[2,3].

The biopharmaceutical properties of drugs such as BCS classification provide important information, which can help in the rational selection of appropriate formulation approaches. A considerable number of compounds under development may fail to reach the market because of their poor water solubility. Most marketed formulations of montelukast sodium and levocetirizine dihydrochloride combinations are offered in the form of syrups; however, montelukast, being a BCS class II molecule, exhibits low solubility and high permeability[4]. In contrast, levocetirizine dihydrochloride is a class I molecule in the BCS, exhibiting high solubility and high permeability with a Log P value of about 0.87[5]. Montelukast has insufficient aqueous solubility of 0.2 µg/ml at 25 °C and high membrane permeability with a log P of 8.98[6,7,8]. Its overall aqueous solubility increases to 100–1000 µg/ml through the formation of a sodium salt, which is the commercialized form of montelukast[9]. However, various studies have shown that the available market dosage formulations of montelukast sodium have stability challenges[4]. Therefore, it remains a challenge to ensure the stability of montelukast-loaded formulations over time.

Suspension is a suitable dosage formulation for insoluble or poorly soluble drugs as it improves chemical stability, exhibits a higher rate of bioavailability, provides a controlled release profile, and masks the unpleasant bitter taste of drugs. The suspension dosage forms provide relatively higher concentrations of drugs[10]. A poorly soluble drug cannot dissolve completely in a syrup and may not be uniformly distributed throughout the liquid, leading to uneven dosing and reduced efficacy. In addition, suspension dosage forms provide a controlled release pattern which leads to sustained absorption of drugs from the gastrointestinal tract to systemic

circulation, showing more efficacy and prevents sudden increases in blood concentration.

The different commercially available oral liquid formulations, including Xyzal M suspension and syrup N, syrup L, and syrup A, have been studied to differentiate and discriminate with respect to potency by assay, soluble-insoluble fraction analysis, particle size distribution, impurity profiling, estimation of enantiomeric form of montelukast, and *in-vitro* dissolution testing of the drugs in media with different pH levels (pH 1, pH 4.5, pH 6.8, and pH 7.4). The chosen pH levels were selected to mimic the different regions of the gastrointestinal tract. The present *in-vitro* study compares the release profiles of levocetirizine dihydrochloride and montelukast sodium in Xyzal M suspension and the marketed syrup formulations.

MATERIAL AND METHOD

Materials

AR grade of sodium acetate (Rankem), glacial acetic acid (Rankem), monobasic potassium phosphate (Merck), sodium hydroxide (Merck), and hydrochloric acid (Merck), Montelukast sodium WS (Synzeal), levocetirizine dihydrochloride WS (Allmpus), pancreatin (Loba Chemie), and pepsin (Loba Chemie). HPLC grade of methanol (Finar), acetonitrile (Finar), trifluoroacetic acid (TFA) (Merck), and water. Sodium acetate buffer (pH 4.5), 0.1N hydrochloric acid (pH 1.0), phosphate buffer (pH 6.8 and 7.4), 0.05% sodium lauryl sulfate as solublizer, marketed syrup formulations (syrup N, syrup L, and syrup A), Xyzal M suspension, Automated Sotax Dissolution apparatus SDT SFC (Sotax), 0.45µ Nylon syringe filter Apparatus.

Assay of the Active components

Using a validated and in-house developed High Performance Liquid Chromatography (HPLC) method, the quantity of levocetirizine dihydrochloride and montelukast sodium was determined in three different samples of Xyzal M suspension (Dr. Reddy's Laboratory Ltd, India), including fresh (commercially available), aged (near expiry), and stressed samples (exposed to 60°C for 7 days). The potency of three other marketed syrups, named syrup N, syrup L, and syrup A, was also claimed using the same method.

The analysis was conducted as per United States Pharmacopeia (USP) monograph using the Waters e2695 HPLC instrument with the Agilent Eclipse Plus C18 column (100 mm x 4.6 mm x 3.5µ). The mobile phase A (1.5:1000 v/v TFA: water) and mobile phase B (1.5:1000 v/v TFA: acetonitrile) were used with a 10µl sample injected and a run time of 25 minutes. The detection was carried out at 238 nm and 310 nm using UV detector dual wavelength mode with a flow rate of 1.2 ml/min. The ratio of mobile phase A and B was 60:40 for the first six minutes, 50:50 from 7 to 19 minutes, and 60:40 from 20 to 25 minutes[11,12].

Impurity of the Active components

The total impurities of levocetirizine dihydrochloride and montelukast sodium along with an individual impurity of montelukast sodium were evaluated using two different HPLC methods in fresh, stressed, and aged samples of all formulations[11,12].

Method 1

Using the HPLC instrument, the Agilent Zorbax column (50 mm x 4.6 mm x 1.8µ) was utilized to conduct the analysis. The column was heated at a temperature of 30°C, while the sample cooler temperature was maintained at 25°C. A mobile phase consisting of A (1000: 1.5 v/v water:TFA) and B (1.5:1000 v/v TFA: acetonitrile) was used, with a 10µl sample injected and a run time of 20 minutes. The detection was carried out at 238 nm using a UV detector, with a flow rate of 1.2 ml/min. The ratio of mobile phase A and B was 60:40 for the first fifteen minutes, 49:51 for 16 minutes, and 60:40 from 17 to 20 minutes. A gradient pump mode was utilized, and the diluent used was methanol: water (90:10 v/v).

Method 2

Using the HPLC instrument, the Agilent Zorbax SB-C8 column (250mm x 4.6 mm x 5µ) was utilized to conduct the analysis. The column was heated at a temperature of 25°C, while the sample cooler temperature was maintained at 25°C. A mobile phase consisting of A (1000: 0.4 v/v Water: H_2SO_4) and B (acetonitrile) was used, with a 10µl sample injected and a run time of 30 minutes. The detection was carried out at 230 nm using a UV detector, with a flow rate of 0.5 ml/min. The ratio of mobile phase A and B was 60:40. An isocratic pump mode was utilized, and the diluent used was methanol: water (9:1 v/v).

Enantiomeric impurity of montelukast sodium

Montelukast molecule exists in S and R-enantiomeric forms. The montelukast sodium is more potent than the S-form. The USP monograph limit for the S-form is not more than 0.2% for formulations containing montelukast. The enantiomeric impurity was evaluated by the HPLC method for all the products of fresh, aged, and stressed samples.

The analysis was conducted as per the USP monograph using the HPLC instrument with the Chiral pak C18 column (150 mm x 4.00 mm x 5µ). The column was maintained at a temperature of 30°C, while the sample cooler temperature was set at 25°C. A mobile phase containing A (ammonium acetate buffer with a pH of 5.7) and B (methanol: acetonitrile; 60:40 v/v) was utilized, and a 10µl sample was injected with a run time of 30 minutes. The detection was performed at 280 nm using a UV detector with a flow rate of 0.9 ml/min. The ratio of mobile phase A and B was maintained at 70:30, and a gradient pump mode was utilized. The diluent used was a mixture of acetonitrile and water in the ratio of 50:50.

Soluble-insoluble fraction of active components

To study the dissolution and absorption pattern of the drugs from all the products was done by taking the exact dose of the products and treating them at different pH media with specific volume. Evaluation of the soluble fraction of each active component from all the products was done by preparing different pH media, like 0.1N Hydrochloric acid (pH 1.2), Acetate buffer (pH 4.5), Phosphate buffer (pH 6.4), Phosphate buffer (pH 7.4). Simulated saliva, gastric, and intestinal fluid were prepared using buffers and enzymes like alfa amylase, pepsin and pancreatin. These pH media resemble the environment of the gastro-intestinal tract of the buccal cavity, stomach, intestine, and simulated fluids of saliva, gastric and intestine.

Simulated saliva fluid preparation

Take about 3.775g of Potassium Chloride, 0.925g of Potassium Dihydrogen Phosphate, 1.7g of Sodium hydrogen carbonate, 0.125g of Magnesium dichloride hexahydrate and 0.015g of Ammonium carbonate into 250 mL volumetric flask containing about 150 mL of Purified water sonicate to dissolve. Cool to room temperature and make up to the mark with purified water.

Simulated intestinal fluid preparation

Dissolved 6.8 gm of Monobasic Potassium Phosphate into 250 mL of water, mix and add 77 mL of 0.2N Sodium Hydroxide

and 500 mL of water. Add 10g of Pancreatin mix and adjust the resulting solution with either 0.2N Sodium Hydroxide or 0.2N Hydrochloric Acid to a pH of 6.8 ± 0.1. Dilute with water to 1000 mL.

Simulated gastric fluid preparation

Dissolve about 2.0g of Sodium Chloride and 3.2 g of purified pepsin that is derived from porcine stomach mucosa with an activity of 800 to 2500 units per mg of protein, in 7.0mL of Hydrochloric acid and sufficient water to make 1000 mL. This test solution has a pH of about 1.2.

Particle Size Distribution

The particle size distribution of all formulations was evaluated using a microscopy method. It was also used to study particle size distribution in all formulations at different pH. A sample was prepared by mixing 0.5ml of samples in 15ml of water and analyzed using magnification value 4X and voltage value 3.5v using an Olympus microscope with IPS class software (Image ProVision).

Impurity Profiling Study at different pH

The soluble fraction study of both active components of fresh, stressed, and aged samples of all products was analyzed for the total and individual impurities of all samples by the HPLC method. Impurities in different pH media correlate with the level of impurity at the different locations of the GI tract.

The soluble fraction study was performed for both active components, levocetirizine dihydrochloride and montelukast sodium, for all products. For this, 5 ml of each sample was taken and diluted to 100 ml with the respective pH media (0.1N Hydrochloric Acid, Sodium acetate buffer, Phosphate Buffer at pH 6.8 and pH 7.4) containing 0.05% Sodium Lauryl Sulfate as solublizer. The samples were then stirred for 30 minutes at 37°C. After that, the samples were centrifuged at 10,000 rpm for 10 minutes, and the supernatant was collected for analysis using the HPLC method used for the determination of total impurity.

Estimation of Enantiomeric form of Montelukast at different pH

The soluble fraction study of all the samples was analyzed for the enantiomeric purity of montelukast by the HPLC method mentioned in USP monograph of montelukast. The S-enantiomeric form in different media was detected to correlate at different locations of the gastrointestinal tract[11,12].

***In Vitro* Dissolution Study**

The Automated Sotax Dissolution Apparatus was set up according to the manufacturer's instructions. 5 ml of each syrup formulation (syrup N, syrup L, and syrup A) and Xyzal M suspension were dispensed into separate dissolution vessels containing pH media of volume 500 ml (pH 1.0, 4.5, 6.8, and 7.4) with 0.05% Sodium Lauryl Sulfate as solublizer. The dissolution vessels were degassed and equilibrated at 37°C temperature. The dissolution was performed using USP II (Paddle) with an agitation rate of 75 rpm. At different time points (15 min, 30 min, 45 min, 1 Hr, 2 Hrs, and 3Hrs), 10 ml of samples were collected along with the same volume of media replacement. The collected samples were filtered through a 0.45µ Nylon syringe filter.

The percentage release of levocetirizine dihydrochloride and montelukast sodium in the samples was analyzed by a robust HPLC method. The percentage release of levocetirizine dihydrochloride and montelukast sodium at different time points was calculated using the calibration curve of standard solutions of levocetirizine and montelukast, respectively. The release profile of each formulation was plotted against time for each pH media.

All the parameters were analyzed in Topiox research Center, Mumbai, Maharashtra, India.

RESULTS

The assay results indicate that the claimed potency of all formulations has been proven and meets the requirements to achieve efficacy. This study provides important information regarding the quality and efficacy of the formulations containing levocetirizine dihydrochloride and montelukast. The percentage of levocetirizine dihydrochloride and montelukast present in the formulations ranged from 97.8%-111.4% and 119.8-127.5%, respectively (Table1). The results were within the acceptable limits specified by the USP for the potency of levocetirizine dihydrochloride and montelukast sodium.

Table 1: Assay of the active components in fresh, aged and stressed samples of all formulations

Name of the products	Fresh sample		Aged sample (near expiry)		Stressed sample	
	% Assay of LD	% Assay of Montelukast	% Assay of LD	% Assay of Montelukast	% Assay of LD	% Assay of Montelukast
Xyzal M	97.8	127.5	-	-	102.6	140.3
Syrup N	98.0	120.9	91.2	118.5	99.5	128.9
Syrup L	111.4	124.5	-	-	114.6	169.8
Syrup A	99.3	119.8	92.7	128.0	102.2	137.3

LD –Levocetirizine Dihydrochloride; "-", Not performed

The total and individual impurities impurities of levocetirizine dihydrochloride and montelukast in all samples of the products were found within the acceptable limits specified by the Indian Pharmacopeia (2%)[13](Table 2a & b). The total impurities for all the products were found at <2.0% for fresh samples and <5.0% in aged and stressed samples (Table 2a). The two different HPLC methods used in this study showed comparable results. These findings indicate the quality and stability of the products.

Table 2a: Detection of total impurities in fresh, aged, and stressed samples of all formulations

Name of the products	Fresh sample		Aged sample (near expiry)		Stressed sample	
	% Assay of LD	% Assay of Montelukast	% Assay of LD	% Assay of Montelukast	% Assay of LD	% Assay of Montelukast
Xyzal M	ND	2.34	-	-	ND	4.53
Syrup N	ND	1.33	ND	4.64	ND	2.21
Syrup L	ND	2.19	-	-	ND	4.19
Syrup A	ND	2.94	ND	3.29	ND	2.94

ND, Not detected; LD, Levocetirizine Dihydrochloride; "-", Not performed

Table 2b: Detection of individual impurities of montelukast in fresh, aged, and stressed samples of all the formulations

samples of all formulations	Sulphoxide	Cis-Isomer	Michael Adducts	Methylketone	Methylstyrene
Fresh samples					
Xyzal M	1.78	0.06	ND	ND	0.50
Syrup N	0.82	0.06	0.03	0.11	0.32
Syrup L	1.96	0.01	0.06	0.03	0.15
Syrup A	2.78	0.01	0.06	0.06	0.03
Aged samples (near expiry)					
Xyzal M	-	-	-	-	-
Syrup N	3.53	0.27	0.05	0.12	0.66
Syrup L	-	-	-	-	-
Syrup A	2.79	0.01	0.02	0.02	0.45
Stress samples					
Xyzal M	1.99	0.17	1.94	0.07	0.36
Syrup N	1.96	0.01	0.06	0.03	0.15
Syrup L	3.66	0.00	0.05	0.06	0.42
Syrup A	2.78	0.01	0.06	0.06	0.03

ND, Not detected; "-", Not performed

All samples of formulations which contain montelukast, had only the R enantiomer, with no detectable levels of the S-enantiomer. The percentage of enantiomeric impurity was found to be less than 0.2% in all samples, which is within the United States Pharmacopeia (USP) monograph limit for the S-form. These results indicate that the molecule is in a desirable form for pharmacological action.

In case of the soluble fraction study, the soluble fraction of Levocetirizine dihydrochloride was found to be more than 70% for the fresh samples of all formulations in all the media corresponding to the buccal cavity except simulated intestinal fluid, where it was more than 50% for all syrups. However, in Xyzal M suspension, levocetirizine dihydrochloride soluble fraction was 19.3% in simulated saliva fluid. On the other hand, in all the samples of formulations, the montelukast sodium was found in almost 100% insoluble state at pH 6.4, 7.4, and simulated saliva fluid (Table 3).

The soluble fraction of levocetirizine dihydrochloride in fresh samples of all formulations in the stomach, intestinal, and large intestinal pH was >75% and >80% after one and 24 hours, respectively. In case of montelukast sodium, after one hour, the soluble fraction in syrup N, syrup L, and syrup A formulations ranged from 10.5-96.4%, 104.9-118.9%, and 46.3-103.8, respectively in all pH media. After 24 hours, the soluble fraction in all pH for syrup N, syrup L and syrup A ranged from 28.1-77.9%, 85-122.7%, and 21.3-109.1%, respectively. However, the montelukast sodium of Xyzal M suspension was found to be 100% insoluble form in all pH of stomach, small and large intestine media, after one hour. Also, after 24 hours, in Xyzal M suspension, montelukast sodium was 100% insoluble in fresh, aged, and stressed samples except in simulated intestinal fluid where it was found ~40-45% in soluble form in fresh and stressed samples. It indicates that montelukast sodium in suspension form is not rapidly absorbed in all parts of the gastro-intestinal tract (Table 3). This study also revealed that the Montelukast is released slowly from the suspension formulation in simulated intestinal fluid (Table 4&5). These results indicate that the absorption profile of montelukast sodium is slower than Levocetirizine dihydrochloride, and it is released slowly from the suspension formulation in the intestinal media.

Table 3: % Soluble fraction in the *in-vitro* environment of buccal cavity in fresh, aged, and stress samples

Samples of all formulations	pH 6.4, 5ml		pH 7.4, 5ml		Simulated Saliva Fluid, 5ml	
	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast
Fresh samples						
Xyzal M	75.8	0.0	71.7	0.0	19.3	0.3
Syrup N	90.5	70.4	93.8	89.2	51.9	56.5
Syrup L	92.7	100.7	86.4	95.3	74.7	82.4
Syrup A	96.6	80.4	81.6	60.0	51.8	61.4
Aged samples						
Syrup N	49.8	51.6	49.8	52.4	48.9	51.4
Syrup A	50.8	59.8	51.1	60.9	51.9	61.0
Stress samples						
Xyzal M	25.4	0.5	23.2	0.0	25.9	0.5
Syrup N	49.6	52.1	49.2	52.1	55.2	50.7
Syrup L	90.9	98.9	41.9	43.3	74.5	82.2
Syrup A	60.3	60.3	51.0	60.1	52.1	61.0

Table 4: % soluble fraction in the *in-vitro* environment of stomach, small intestine and large intestine after 1 Hour and 24 Hour of fresh samples

Products name	pH 1.2, 100mL		pH 4.5, 100 ml		pH 6.4, 100 ml		pH 7.4, 100 ml		Simulated gastric fluid, 100 ml		Simulated intestinal fluid, 100 ml	
	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast
Fresh samples after 1 hour												
Xyzal M	89.7	0.0	76.4	0.0	78.56	0.0	80.32	0.0	96.7	6.8	90.9	0.0
Syrup N	98.7	35.3	97.7	96.4	98.20	86.2	97.60	95.1	96.8	10.5	93.3	70.6
Syrup L	105.1	104.9	106.8	116.6	110.90	117.9	107.40	118.9	112.8	112.7	109.8	109.4
Syrup A	96.6	61.6	97.8	103.8	96.70	93.6	97.40	101.8	96.5	46.3	93.7	101.0
Fresh samples after 24 hours												
Xyzal M	95.3	0.0	89.4	0.0	90.5	0.0	94	0.0	96	0.0	90.2	**40.5**
Syrup N	104.1	28.1	84.6	56.3	93.7	60.9	97.2	77.9	95.9	76.6	80.8	52.9
Syrup L	109.4	85.8	109.2	119.0	109.4	118.3	109	122.7	110.6	93.9	108.2	108.0
Syrup A	104.5	21.3	95.4	101.9	97.2	103.2	99.9	109.1	94.4	89.0	93.6	97.4

LD, Levocetirizine dihydrochloride.

Table 5: % soluble fraction in the *in- vitro* environment of stomach, small intestine, and large Intestine after 1 Hour and 24 Hour for aged and stress samples

Products name	pH 1.2, 100mL		pH 4.5, 100 ml		pH 6.4, 100 ml		pH 7.4, 100 ml		Simulated gastric fluid, 100 ml		Simulated intestinal fluid, 100 ml	
	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast
Aged and stress samples after 1 hour												
Xyzal M (s)	96.0	0.0	95.5	0.0	95.2	0.0	96.0	0.0	97.3	0.0	93.2	0.0
Syrup N (s)	93.8	30.5	90.4	94.5	93.2	101.5	93.8	117.7	93.6	29.0	90.4	70.1
Syrup L (s)	106.5	102.9	108.6	118.3	109.7	117.0	110.5	121.5	109.2	111.0	109.7	110.7
Syrup A (s)	98.0	70.1	96.2	116.3	94.7	113.2	97.1	148.6	96.8	82.7	94.6	82.5
Syrup N (A)	92.4	9.8	92.6	90.1	92.8	75.1	93.0	80.9	93.9	39.1	90.5	46.2
Syrup A (A)	94.6	38.1	93.9	106.2	94.0	93.9	93.9	88.0	96.8	51.4	95.0	81.5
Aged and stress samples after 24 hours												
Xyzal M (s)	97.3	0.0	97.1	0.0	89.4	0.0	97.7	0.0	96.7	0.0	94.3	**45.5**
Syrup N (s)	93.5	79.7	93.5	98.5	92.9	92.5	92.5	94.2	91.8	84.0	90.1	81.6
Syrup L (s)	108.9	84.3	110.0	84.9	110.6	121.4	106.1	120.0	110.1	92.2	105.8	104.8
Syrup A (s)	95.7	79.0	95.1	108.7	95.6	104.1	96.0	107.4	95.2	95.9	95.4	103.3
Syrup N (A)	93.4	79.2	93.0	94.1	92.2	94.3	93.2	96.5	90.8	74.5	90.9	86.3
Syrup A (A)	95.1	99.7	95.7	110.3	96.5	109.7	95.5	109.7	94.4	90.3	94.4	100.4

(A), Aged; LD, Levocetirizine dihydrochloride; (s), stress.

The microscopic evaluation of all products was performed. It revealed the presence of particulate matter in the Xyzal M suspension, which was visible, and its distribution varied at different pH. Montelukast sodium was in an insoluble form, and the D_{90} value was 77µ, indicating that the drug particles were suspended in the Xyzal M suspension and remained in a suspended form throughout, which correlates with the % insoluble fraction of montelukast in the different pH media. Although all the ingredients were soluble in the syrup formulations, particles were visible in two syrups, where there were either no visible particles or D_{90} values of about 35µ (Table 6).

Table 6: Particle size distribution in control sample and at different PH

Product		Control sample (size-µ)	PH 1.2 (size-µ)	PH 4.5 (size-µ)	PH 6.4 (size-µ)	PH 7.4 (size-µ)
Xyzal M	D_{10}	20.487	14.585	15.165	14.585	14.585
	D_{50}	38.365	26.809	30.045	22.107	25.034
	D_{90}	77.067	66.321	69.039	59.222	55.617
Syrup L	D_{10}	12.227	12.227	No particles observed	12.227	No particles observed
	D_{50}	15.165	15.165		14.585	
	D_{90}	34.913	34.913		26.809	
Syrup S	D_{10}	No particles observed	No particles observed	No particles observed	No particles observed	No particles observed
	D_{50}					
	D_{90}					
Syrup A	D_{10}	10.723	No particles observed	No particles observed	No particles observed	No particles observed
	D_{50}	14.585				
	D_{90}	29.171				

The impurity profiling study revealed that in all the samples of the soluble fraction study, the total impurities of montelukast sodium increased from about 15% to 27% in all the syrup formulations after 24 hours in gastric media (Table 7). However, in Xyzal M suspension, no impurities were formed as the drug was not released to the gastric media. This was also observed in the remaining media for the syrup formulations, where the total impurities were formed but not observed for Xyzal M suspension. These results suggest that the impurity profile of montelukast in Xyzal M suspension was found to be very low (Table 8 and 9).

Table 7: % impurity in the *in-vitro* environment of stomach, small intestine, and large intestine after 1hour and 24 hours of fresh, stress, and aged samples of all formulations

Products name	pH 1.2, 100 ml		pH 4.5, 100 ml		pH 6.4, 100 ml		pH 7.4, 100 ml		Simulated gastric fluid, 100 ml		Simulated intestinal fluid, 100 ml	
	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast
Fresh samples after 1 hour												
Xyzal M	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Syrup N	ND	19.42	ND	2.32	ND	2.52	ND	2.01	ND	3.44	ND	5.95
Syrup L	ND	8.53	ND	5.17	ND	5.86	ND	5.61	ND	7.26	ND	5.9
Syrup A	ND	14.87	ND	1.97	ND	3.02	ND	3.44	ND	11.72	ND	5.57
Fresh samples after 24 hours												
Xyzal M	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Syrup N	ND	16.64	ND	2.15	ND	2.81	ND	2.66	ND	21.75	ND	11.45
Syrup L	ND	23.14	ND	4.28	ND	6.07	ND	5.15	ND	17.56	ND	5.12
Syrup A	ND	15.70	ND	2.35	ND	2.34	ND	2.44	ND	12.34	ND	5.82
Stressed and aged samples after 1 hour												
Xyzal M (s)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Syrup N (s)	ND	1.51	ND	5.1	ND	5.3	ND	5.6	ND	15.4	ND	4.9
Syrup L (s)	ND	8.7	ND	5.3	ND	5.5	ND	5.0	ND	7.4	ND	6.0
Syrup A (s)	ND	9.0	ND	4.4	ND	4.2	ND	4.1	ND	11.2	ND	4.8
Syrup N (A)	ND	8.8	ND	4.1	ND	6.2	ND	7.3	ND	15.2	ND	0.9
Syrup A (A)	ND	6.9	ND	2.9	ND	1.4	ND	2.2	ND	10.9	ND	2.8
Stressed and aged samples after 24 hours												
Xyzal M (s)	ND	D	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Syrup N (s)	ND	1.67	ND	4.4	ND	4.8	ND	4.5	ND	14.0	ND	11.5
Syrup L (s)	ND	23.1	ND	4.3	ND	6.1	ND	5.2	ND	17.2	ND	5.4
Syrup A (s)	ND	24.7	ND	4.6	ND	4.4	ND	4.6	ND	20.3	ND	5.8
Syrup N (A)	ND	15.2	ND	6.7	ND	7.1	ND	6.9	ND	23.3	ND	7.6
Syrup A (A)	ND	11.3	ND	7.0	ND	4.2	ND	4.4	ND	12.3	ND	8.6

(A), Aged sample; LD, Levocetirizine dihydrochloride; ND, Not detected; (s), stressed sample.

Table 8: % Impurity in the *in-vitro* environment of buccal cavity in fresh, aged, and stressed samples of all formulation

Samples of all formulations	pH 6.4, 5ml		pH 7.4, 5ml		Simulated Saliva Fluid, 5ml	
	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast	% Soluble fraction of LD	% Soluble Fraction of Montelukast
Fresh samples						
Xyzal M	ND	ND	ND	ND	ND	ND
Syrup N	ND	4.65	ND	4.98	ND	2.69
Syrup L	ND	ND	ND	4.67	ND	4.78
Syrup A	ND	4.26	ND	3.57	ND	4.21
Stressed and aged samples						
Xyzal M (s)	ND	ND	ND	ND	ND	ND
Syrup N (s)	ND	4.6	ND	4.8	ND	4.7
Syrup L (s)	ND	ND	ND	4.7	ND	ND
Syrup A (s)	ND	4.3	ND	4.1	ND	3.6
Syrup N (A)	ND	7.0	ND	6.9	ND	4.1
Syrup A (A)	ND	3.9	ND	3.9	ND	1.3

(A), Aged sample; LD, Levocetirizine dihydrochloride; ND, Not detected; (s), stressed sample.

Table 9: % Individual impurity of montelukast sodium in different pH media after 24 Hours

Product	Sulphoxide	Cis-Isomer	Michael Adducts	Methylketone	Methylstyrene
In pH 1.2 media					
Xyzal M	ND	ND	ND	ND	ND
Syrup N	4.84	10.98	0.4	ND	0.42
Syrup L	1.83	17.01	0.04	0.12	4.14
Syrup A	1.93	12.06	0.55	0.21	0.95
In pH 4.5 media					
Xyzal M	ND	ND	ND	ND	ND
Syrup N	1.54	0.09	ND	0.02	0.50
Syrup L	2.72	1.52	0.04	ND	ND
ALM	1.31	0.39	0.10	ND	0.55
In pH 6.4 media					
Xyzal M	ND	ND	ND	ND	ND
Syrup N	1.8	0.36	0.08	ND	0.57
Syrup L	4.32	1.48	0.09	0.18	ND
Syrup A	1.78	0.06	ND	ND	0.5
In pH 7.4 media					
Xyzal M	ND	ND	ND	ND	ND
Syrup N	1.79	0.24	0.06	0.09	0.48
Syrup L	2.88	1.19	0.19	ND	0.89
Syrup A	2.19	0.02	0.01	ND	0.22
In simulated gastric fluid					
Xyzal M	ND	ND	ND	ND	ND
Syrup N	1.43	18.04	ND	0.20	2.08
Syrup L	1.95	12.29	0.29	ND	3.03
Syrup A	2.80	7.75	0.31	ND	1.48
In simulated intestinal fluid					
Xyzal M	ND	ND	ND	ND	ND
Syrup N	8.89	0.34	0.57	0.06	1.59
Syrup L	3.79	1.17	0	0.03	0.13
Syrup A	3.42	0.23	1.29	0.03	0.85

The study of the detection of the presence of chiral impurities in drugs in different media is important due to their potential differences in biological activities. The S-enantiomer of montelukast is often considered an undesired form. In the case of Xyzal M suspension, no S-enantiomer of montelukast sodium was formed in fresh, stressed, and aged samples in media of the buccal cavity, stomach, and simulated gastric fluids as montelukast was not released in acidic media which may form S-enantiomer (Table 10, 11 & 12). However, in simulated intestinal media, where some montelukast sodium is released, the S-enantiomer is not formed, indicating that the montelukast sodium is stable in its pharmacologically active form at this pH.

Table 10: % S Enantiomer in the *in-vitro* environment of buccal cavity in fresh, aged, and stressed samples of all formulations

Samples of all formulations	pH 6.4, 5ml	pH 7.4, 5ml	Simulated Saliva Fluid, 5ml
	% S Enantiomer of Montelukast		
Fresh samples			
Xyzal M	ND	ND	ND
Syrup N	0.41	0.59	0.4
Syrup L	0.59	0.42	2.4
Syrup A	0.44	0.27	ND
Aged samples			
Syrup N	17.9	2.3	4.1
Syrup A	4.6	0.6	1.3
Stressed samples			
Xyzal M	ND	ND	ND
Syrup N	35.3	1.2	4.7
Syrup L	ND	ND	ND
Syrup A	31.5	0.2	3.6

ND; Not detected.

Table 11: % S Enantiomer in the *in-vitro* environment of stomach, small intestine and large intestine after 1 hour and 24 hours of fresh samples of all formulation

Products name	pH 1.2, 100mL	pH 4.5, 100 ml	pH 6.4, 100 ml	pH 7.4, 100 ml	Simulated gastric fluid, 100 ml	Simulated intestinal fluid, 100 ml
	% S Enantiomer of Montelukast					
Fresh samples after 1 hour						
Xyzal M	ND	ND	ND	ND	ND	ND
Syrup N	30.7	7.8	10.70	2.00	ND	91.6
Syrup L	ND	ND	ND	ND	0.3	ND
Syrup A	23.8	18	8.70	1.00	ND	96.9
Fresh samples after 24 hours						
Xyzal M	ND	ND	ND	ND	ND	ND
Syrup N	8.97	ND	0.30	0.52	ND	ND
Syrup L	6.79	ND	ND	ND	2.87	ND
Syrup A	12.84	0.52	0.40	0.34	ND	ND

ND; Not detected.

Table 12: % S Enantiomer in the *in-vitro* environment of stomach, small intestine and large intestine after 1 hour and 24 hours of aged and stressed samples of all formulation

Products name	pH 1.2, 100 ml	pH 4.5, 100 ml	pH 6.4, 100 ml	pH 7.4, 100 ml	Simulated gastric fluid, 100 ml	Simulated intestinal fluid, 100 ml
	% S Enantiomer of Montelukast					
Aged and stressed samples after 1 hour						
Xyzal M (s)	ND	ND	ND	ND	ND	ND
Syrup N (s)	28.5	7.8	11.60	5.6	ND	3.7
Syrup L (s)	ND	ND	ND	5.0	ND	ND
Syrup A (s)	25.6	17.5	6.5	4.1	ND	5.1
Syrup N (A)	28.2	7.5	12.5	7.3	1.4	3.9
Syrup A (A)	22.9	18.2	6.7	2.2	ND	ND
Aged and stressed samples after 24 hours						
Xyzal M (s)	ND	ND	ND	ND	ND	ND
Syrup N (s)	2.9	ND	ND	ND	1.0	ND
Syrup L (s)	ND	3.4	ND	ND	ND	ND
Syrup A (s)	6.0	ND	ND	ND	1.2	ND
Syrup N (A)	ND	ND	ND	ND	4.3	6.6
Syrup A (A)	ND	ND	ND	ND	3.8	ND
(A); Aged sample; ND, Not detected; (s), stressed sample.						

The release patterns of levocetirizine dihydrochloride and montelukast sodium in different formulations were analyzed by dissolution study. The study found that levocetirizine dihydrochloride was released at a rate of 70-80% within 30 minutes in all the media tested (Figure 1). Similarly, all the syrup formulations showed a consistent release pattern of montelukast sodium, with a release percentage ranging from 70% to more than 100%. In contrast, Xyzal M suspension exhibited a slower release of montelukast sodium at pH 1.2 media, with a recovery rate of up to 12%, and at pH 4.5, the release percentage observed was up to 13%. The release rate increased at pH 6.4 media, with up to 62% release, and at pH 7.4, up to 36% release was observed, indicating a steady release of the drug in different regions of the gastric media (Figure 2). The release curves of all the formulations showed a clear pattern of controlled release, and a plateau stage was reached after 2 hours of testing.

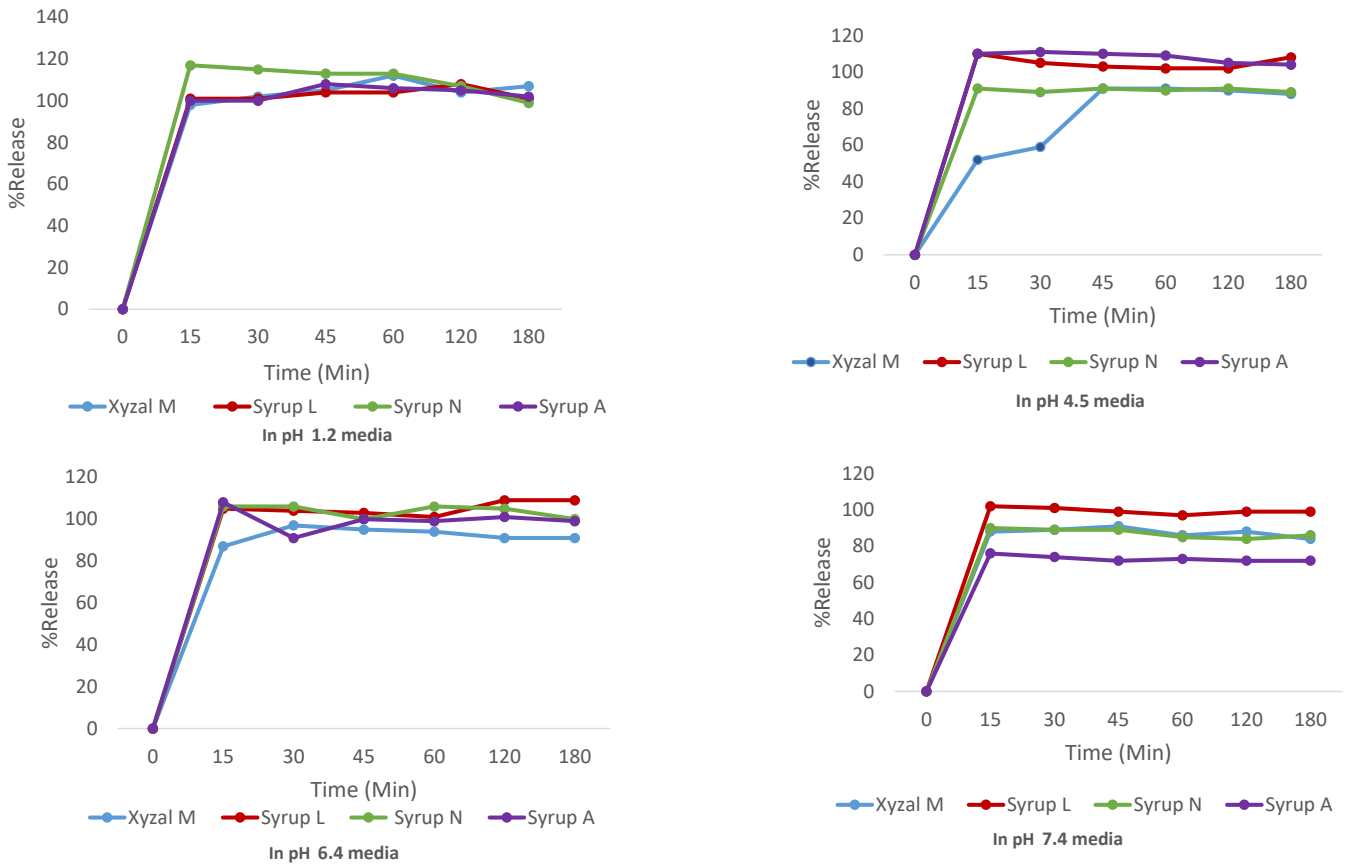

Figure 1: Dissolution profiling of %release vs time (minutes) of levocetirizine dihydrochloride of all formulations at different pH media

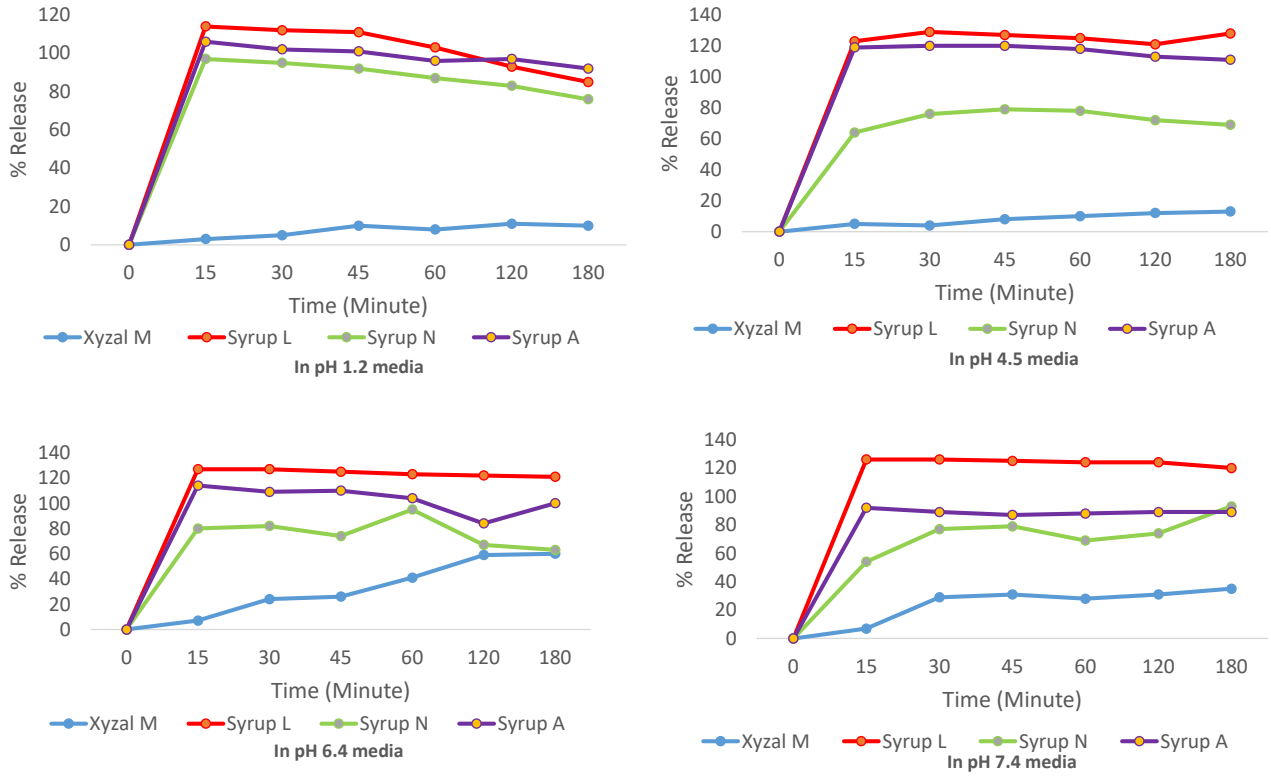

Figure 2: Dissolution profiling of release rate vs time (minutes) of montelukast sodium of all formulations at different pH media

DISCUSSION

Promising results have been demonstrated in the treatment of allergic rhinitis, asthma, and cough with the combination of montelukast sodium and levocetirizine dihydrochloride[1]. This therapy offers several benefits, including convenient dosing, prolonged duration of effect, and reduced risk of drug accumulation, with no known pharmacokinetic interactions[2,3]. However, manufacturers face challenges in converting this combination into a suitable dosage form due to the solubility and chemical stability issues of montelukast sodium. Several syrup formulations of montelukast sodium are available in the market for the treatment of respiratory disorders. However, as montelukast sodium is a BCS II drug with poor solubility and high permeability properties, it cannot completely dissolve in a syrup and may not be uniformly distributed throughout the liquid, leading to uneven dosing and reduced efficacy[14]. Therefore, our study aimed to compare the stability and release profile of montelukast sodium in Xyzal M suspension dosage form with three syrup formulations (syrup N, syrup L, and syrup A formulations).

Our study demonstrated that the claimed potency of fresh, aged, and stressed samples of all formulations was proven, and the total impurities were found within the limits specified by the Indian Pharmacopoeia. This ensures the desirable form, quality, and efficacy of the formulations for the treatment of respiratory disorders. Additionally, all samples of the formulations did not have detectable levels of the S-enantiomer (< 0.2% as per USP monograph), which is the undesired chiral form of impurity that does not have any pharmacological effect as an LTD4 receptor antagonist. This indicates that montelukast sodium in all formulations is present in its pharmacologically active enantiomeric form. The International Conference of Harmonization (ICH) Q7 guiding principal mandates strict control of the S-enantiomer content in montelukast sodium bulk drug[15]. Moreover, literature has shown that montelukast sodium, as an LTD4 receptor antagonist, is superior to its S-enantiomer in both *in-vitro* and *in-vivo* studies[16].

The HPLC methods utilized in this study for analyzing various parameters of all formulations have yielded accurate results, indicating their suitability for routine analysis of products containing levocetirizine dihydrochloride and montelukast sodium.

The soluble fraction of levocetirizine dihydrochloride in all formulations was >70% in all pH media, which indicates that it has faster action. This observation is consistent with the findings of Walsh (2006) that demonstrated the high bioavailability, rapid onset of action, limited distribution, and low degree of metabolism for levocetirizine dihydrochloride[17]. In contrast, montelukast sodium was found to be 100% insoluble in all buccal cavity pH media, as well as stomach, small and large intestinal pH media in Xyzal M suspension. The soluble fraction of montelukast sodium in simulated intestinal fluid after 24 hours was found to be only 40-45%, indicating a slow and controlled release pattern of Xyzal M suspension. The montelukast sodium in Xyzal M suspension was not rapidly released in acidic pH media (due to low solubility), but rather in the intestinal region, thereby preventing its degradation[14,18]. On the other hand, in all syrup formulations, the release of montelukast sodium was rapid in all regions of the gastrointestinal tract, leading to a higher degree of degradation of the drug. The acidic pH may cause the formation of montelukast sulphoxide, which is a degraded product of the drug and may also form the S-enantiomeric form, a chiral impurity. Therefore, higher S-enantiomeric impurity levels were observed in all syrup formulations evaluated in different pH media due to the release of montelukast sodium at acidic pH. Kim et al. (2016) also

reported that montelukast sodium showed degradation and a 2.4% increase in montelukast sulphoxide content when exposed to 0.1 M HCl solution for 6 hours[4]. A similar finding was also obtained in our study where the %impurity due to montelukast sodium degradation was found to be 15-23% in all syrup formulations because of its release in gastric pH media. However, in Xyzal M suspension, no %impurities were detected in fresh and stressed samples, as the release of the drug in gastric pH was arrested, thereby preventing its degradation. Table 10 also supported these findings and showed that sulphoxide and cis isomer were the main individual impurities, which were not found in the suspension but were found in higher amounts in all the syrup formulations, especially in gastric pH media. The release of montelukast sodium from the fresh and stressed samples of Xyzal M suspension in simulated intestinal media was found to be 40-45%, but no S-enantiomer was formed, indicating that the montelukast sodium is in desired enantiomeric form. The dissolution study carried out in this investigation revealed that levocetirizine dihydrochloride was released approximately 70-80% within 30 minutes from all the formulations in all pH media, indicating a faster onset of action. Similarly, montelukast sodium showed a release percentage ranging from 70% to >100% from all the syrup formulations. Conversely, Xyzal M suspension showed a slower release of montelukast sodium in different pH media, suggesting a consistent release of the drug in various regions of the gastrointestinal tract. The release profiles of all the formulations indicated a clear pattern of controlled release, and a plateau stage was reached after 2 hours of testing.

Xyzal M suspension is designed to provide sustained absorption, resulting in a prolonged pharmacological effect, and preventing fluctuations of plasma levels of montelukast sodium, which can lead to toxic levels of the drug in the blood or sudden elimination from the gastrointestinal tract. The pediatric gastrointestinal tract is highly sensitive to food and oral medications and can be affected by variable peristaltic movement and secretion of enzymes and gastric fluid. If drugs like montelukast sodium are administered in formulations that release too quickly, it may lead to fluctuations in drug plasma levels, causing adverse effects and toxicity. Thus, Xyzal M suspension's-controlled release pattern produces fewer untoward effects and prevents toxic systemic levels. Additionally, degradation of montelukast sodium in the stomach is arrested with Xyzal M suspension, making it stable and a better option for pediatric patients. The study also underscores the importance of dosage formulation in providing better safety and effective pharmacological action for medications.

CONCLUSION

In conclusion, the study compared the stability and release profile of montelukast sodium and levocetirizine dihydrochloride in Xyzal M suspension and three marketed syrup formulations. The results demonstrated that Xyzal M suspension has stable and desirable properties for producing effective pharmacological action. The combination of montelukast sodium and levocetirizine dihydrochloride in Xyzal M suspension has several pharmacokinetic benefits, such as prolonged duration of effect due to controlled release profile, better stability, and reduced risk of drug accumulation. In contrast, the syrup formulations showed a faster release of montelukast sodium in all the gastrointestinal pH media, leading to the degradation of the drug and the formation of undesirable impurities. Overall, Xyzal M suspension is a promising dosage form for the treatment of allergic rhinitis, asthma, and cough.

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