WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 8, 1559-1577. Research Article ISSN 2277– 7105

IMPROVEMENT IN PURIFICATION METHODS OF MONTELUKAST INTERMEDIATE

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Article Received on
26 May 2020,

Revised on 17 June 2020,
Accepted on 08 July 2020,

DOI: 10.20959/wjpr20208-18126

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ABSTRACT

Deplorably asthma is the most common chronic disease worldwide among children's. Asthma is ranked 16th among the leading causes of years lived with disability and 28th among the leading cause of deaths with approximately 250,000 reported deaths annually. It affects around 23.5 million people (5-10%) including 7% of children. Montelukast is a potent antagonist of cysteinyl leukotrienes and it represents as the first category of drug which is effective in numerous biological and pathophysiological mechanisms involved in asthma. It improves theasthmatic symptoms, rescue pulmonary function and liberates medication use, and abridged the rate of exacerbation and the level of blood eosinophils, in mild-to-moderate asthmatics patients that were not treated with inhaled corticosteroids (ICS). The aim of present work is to improve the purification method of montelukast intermediate at 7th stage (MT07) of its manufacturing process. The quality improvement is achieved by using methanol in water as solvent in different ratios for purification to get better yield of more potent, stable and compatible drug in fewer expenses of time and money.

KEYWORDS: Montelukast; Pathophysiology; Leukotrienes; Asthmatic; Potent and Compatible.

INTRODUCTION

Asthma is a debilitating, chronic, progressive lung disease described by inflammation that causes the bronchi to swell and airways narrowing results in breathing problems from mild to fatal range. Unfortunately it is the most common chronic disease worldwide among children's. Asthma is ranked 16th among the leading causes of years lived with disability and

28th among the leading cause of deaths with approximately 250,000 reported deaths annually. It affects around 23.5 million people (5-10%) including 7% of children.[1] It results from complex interactions between an individual inherited genetic makeup and the environment.[2] The characteristics symptoms include cough, wheezing, shortness of breath and chest tightness.[3] Various risk factors are responsible for asthma such as family history; Viral Respiratory illness; Obesity; Exposure to cigarette smoke and Allergic rhinitis.

Leukotriene receptor antagonists (LTRAs) (except anti-immunogloblin (Ig) E monoclonal antibodies), are merely the new category of anti-asthmatic drugs to enter the market in the last 10 years. By the end of the 1990s, beta2-agonists and corticosteroids were widely used for asthma treatment. The LTRAs novelty was that they target a specific mechanism, the binding of leukotrienes to their receptors, which is part of the complex pathway involved in asthma. Some competitive antagonists of the cysteinyl-leukotrienes (Cys-LTs); zafirlukast, pranlukast and montelukast were developed and launched in the market along with the inhibitors of 5-lipoxygenase or other enzymes involved in the generation of leukotrienes. Among them, montelukast shows the best efficacy, potency, stability and thus widely used as anti-leukotriene.

Role of leukotriene in asthma pathophysiology

Leukotrienes are naturally occurring molecules that function as intercellular Molecules in mammals. The leukotrienes are a family of lipid mediators formed by the action of the 5-lipoxygenase enzyme and 5-lipoxygenase-activating protein on the cell membrane phospholipids, arachidonic acid. Leukotrienes are produced by many cells of the body and mediate many aspects of the inflammatory response. In the lung, the leukotriene cascade, due to the activation of intracellular 5-lipoxygenase with subsequent release of sulphidopeptide leukotrienes (LTC4, LTD4 and LTE4: Cys-LTs), is activated by different stimuli acting on many inflammatory cells, either resident (such as mast cells) or recruited in the airways (eosinophils, macrophages, etc.), but also on epithelial cells]. Cys-LTs mediate several different effects on airway cells and structures. In particular, LTD4 is the most potent broncho-constricting agent on a molar basis, but Cys-LTs also have chemo-attractive properties for many inflammatory cells (mainly eosinophils), effects on vascular permeability, mucous secretions and sensory nerve activation, and are responsible for part of the pathophysiology of asthma **(Fig. 1 and 2).**[4]

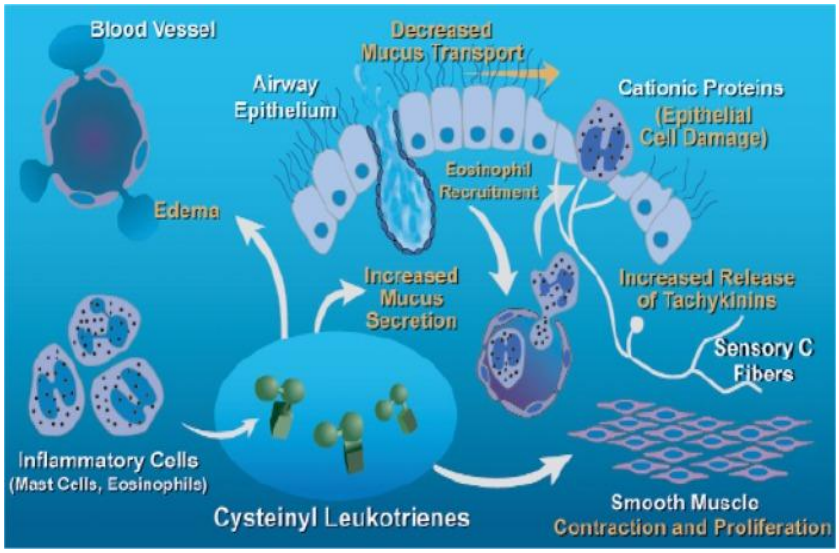


Figure 1: Different targets of cysteinyl leukotrienes on the resident and recruited cells in the airways in asthma.

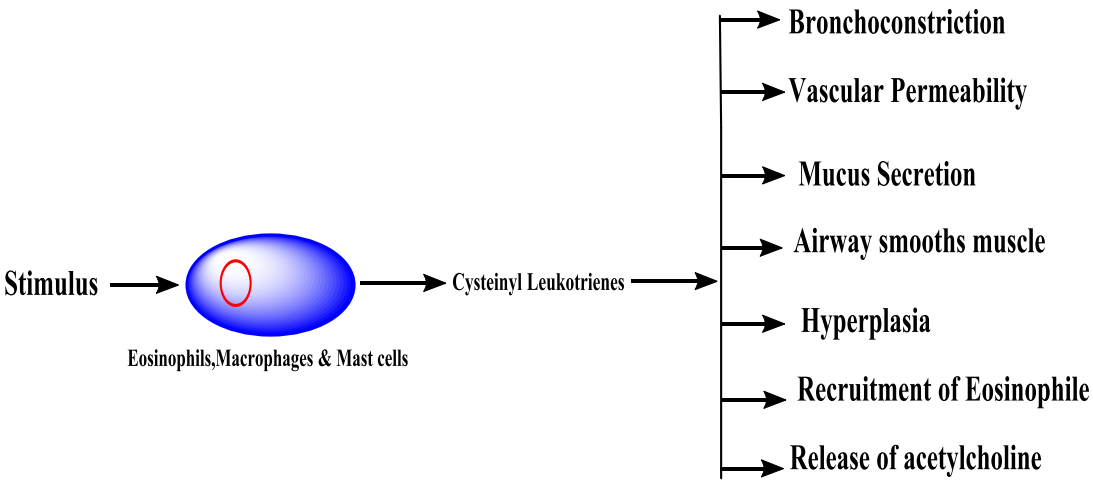
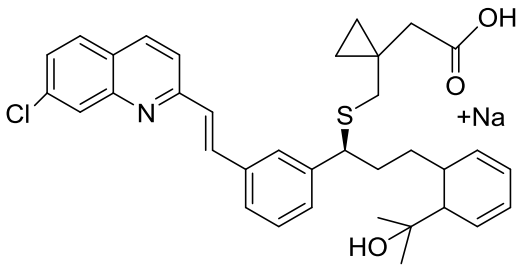


Figure 2: Physiological effects of cysteinyl leukotriene.

Montelukast**(Table 1: Properties of montelukast)** is an oral leukotriene receptor antagonist for the treatment of asthma and to relieve symptoms of seasonal allergies. It is not fully used for treatment of acute asthma attacks, so patients should also be supplied with rescue medication such as albuterol inhaler. Montelukast block the action of LTD4 on cysteinyl leukotriene receptor thus inhibiting bronchoconstriction. The medication is categorized in the FDA pregnancy category B. It is marketed by Merck and Co. with the brand name Singulair. It is available as oral tablets, chewable tablets and oral granules. It inhibits bronchoconstriction due to antigen challenge. It is a selective leucotriene receptor antagonist of cysteinyl leukotriene receptors. Cysteinyl leukotrienes are the products of arachidonic acid metabolism that are released from various cells including mast cells and eosinophills. They

bind to cysteinyl leukotrienes receptors found in human airway. Binding of cysteinyl leukotrienes to leukotriene receptors has been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction and attired cellular activity associated with the inflammatory process. It's binding to Cys LT1 receptor is high affinity and selective preferring the Cys LT1 receptor to other pharmacologically important airway receptors such as prostanoid, cholinergic or beta adrenergic receptors. Montelukast inhibits the physiologic actions of LTD4 at Cys LT1 receptors without any agonist activity.[5]

Table 1: Properties of Montelukast.[6]

Properties of Montelukast	
Structure of Montelukast Sodium	
IUPAC name	[(R)-(E)-1-[[[-1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropane acetic acid ; sodium salt.
Chemical Formula	$C_{35}H_{35}ClNNaO_3S$
Molecular Weight	608.18
Melting Point	145 to 148 °C
Appearance	White to pale yellow color powder
Nature	Hygroscopic
Solubility	Freely soluble in ethanol, methanol and water Insoluble in acetonitrile
Drug Class	Leukotriene receptor antagonist
Adverse Effects	Most Frequent: headache. Less Frequent: Abdominal; fatigue; cough; dizziness; dyspepsia; fever; gastroenteritis; skin rashes. Incidence not determined: drowsiness; edema; anthralgia; insomnia; irratibility myalgia; mydriatis; increased sensitivity of eyes to light; thirst; hyperkinesia.
Indications	For prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.
Storage Conditions	Tightly closed container at room temperature. Out of reach of children
Dosage	(- 10mg/day) adults and adolescents aged 6 to 14 years. (- 5mg/day) children aged 6 to 14 years.

Mechanism of Action of Montelukast

It inhibits broncho-contriction due to antigen challenge. It is a selective leucotriene receptor antagonist of cysteinyl leukotriene receptors. Cysteinyl leukotrienes are the products of arachidonic acid metabolism that are released from various cells including mast cella and eosinophils. They bind to cysteinyl leukotrienes recepyors found in human airway. Binding of cysteinyl leukotrienes to leukotriene receptors has been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction and attired cellular activity associated with the inflammatory process. It's binding to Cys LT1 receptor is high affinity and selective preferring the Cys LT_1 receptor to other pharmacologically important airway receptors such as prostanoid, cholinergic or beta adrenergic receptors. Montelukast inhibits the physiologic actions of LTD_4 at Cys LT_1 receptors without any agonist activity.[7,8]

Clinical Pharmacology

1. The cystenyl leukotrienes, the product of arachidonic acid metabolism are released from various cells including mast cells and eosinophiles. These eicosanoids bind to cysteinyl leukotriene receptors. The CysLT1 receptors are found in the human airway and on other pro-inflammatory cells. Cysteinyl leukotrienes have been correlated with the pathophysiology of asthma and allergic rhinitis.
2. In asthma, leukotriense mediated effects include airways edema, smooth muscle contraction and altered cellular activity associated with the inflammatory process.
3. In allergic rhinitis, cysteinyl leukotrienes are released from the nasal mucosa after allergen exposure during both early late phase reaction and are associated with symptoms of allergic rhinitis.
4. Intranasal challenge with cysteinyl leukotriene has been shown to increase nasal airway resistance and symptoms of nasal obstruction.
5. Montelukast is an orally active compound that binds with high affinity and selectively to the CystLT1 receptor. Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any against activity.[9,10]

Like any other synthetic compound, montelukast can contain extraneous compounds or impurities that can come from many sources. They can be unreacted starting materials, by-products of the reaction, products of side reactions, or degradation products. Impurities in montelukast or any other pharmaceutical ingredient(API) are undesirable and, in extreme

cases, might even be harmful to the patient being treated with the dosage form containing API. It is also known that the impurities in an API may arise from degradation of the API itself, which is related to the stability of the pure API during storage, and the manufacturing process, including the chemical synthesis. Process impurities include unreacted starting materials, chemical derivatives of impurities contained in starting materials, synthetic by-products, and degradation products.

In addition to stability, which is a factor in the shelf life of API, the purity of the API produced in the commercial manufacturing process is clearly a necessary condition for commercialization. Impurities introduced during commercial manufacturing processes must be limited to very small amounts, and are preferably substantially absent. For example, ICH Q7A guidance for API manufacturers requires that process impurities be maintained below set limits by specifying the quality of raw materials, controlling process parameters, such as temperature, pressure, time and stoichiometric ratios, and including purification steps, such as crystallization, distillation, liquid-liquid extraction, in the manufacturing process. The product mixture of a chemical reaction is rarely a single compound with sufficient purity to comply with pharmaceutical standards. Side products and by-products of the reaction and adjunct reagents used in the reaction will, in most cases, also be present in the product mixture. At certain stages during processing of an API, such as (R)-montelukast, it must be analysed for purity, typically, by HPLC or TLC analysis, to determine if it is suitable for continued processing and, ultimately, for use in a pharmaceutical product. The API need not be absolutely pure, as absolute purity is a theoretical ideal that is typically unattainable. Rather, purity standards are set with the intention of ensuring that an API is as free of impurities as possible, and thus safe as possible for clinical use. As discussed above in, United States, the Food and Drug Administration guidelines recommend that the amounts of some impurities be limited to less than 0.1 percent.

In the preparation of montelukast 14 stages were involved out of which stage 7 is the purification stage. Various solvents were tried at the 7^{th} stage (MT07) stage for its purification; like hexane, ethanol, methanol, water, propan-2-ol and tetrahydrofuran. But, methanol is considered as the most suitable solvent due to its easy availability, cheap rates and good solubility of MT07and hence, methanol is previously used as purification solvent. Moreover, there is loss of yield while purification with pure methanol because MT07 is readily soluble in it.

Therefore this study is performed with the objective of modifying the purification method of Montelukast at the7th stage (MT07). And it was observed that when MT07 is purified by the mixture of methanol and water, methanol acts as solvent for dissolution and water as anti-solvent, MT07 was very soluble in it, recovery of methanol was easy. Therefore, MeOH : Water was selected as the solvent for purification.

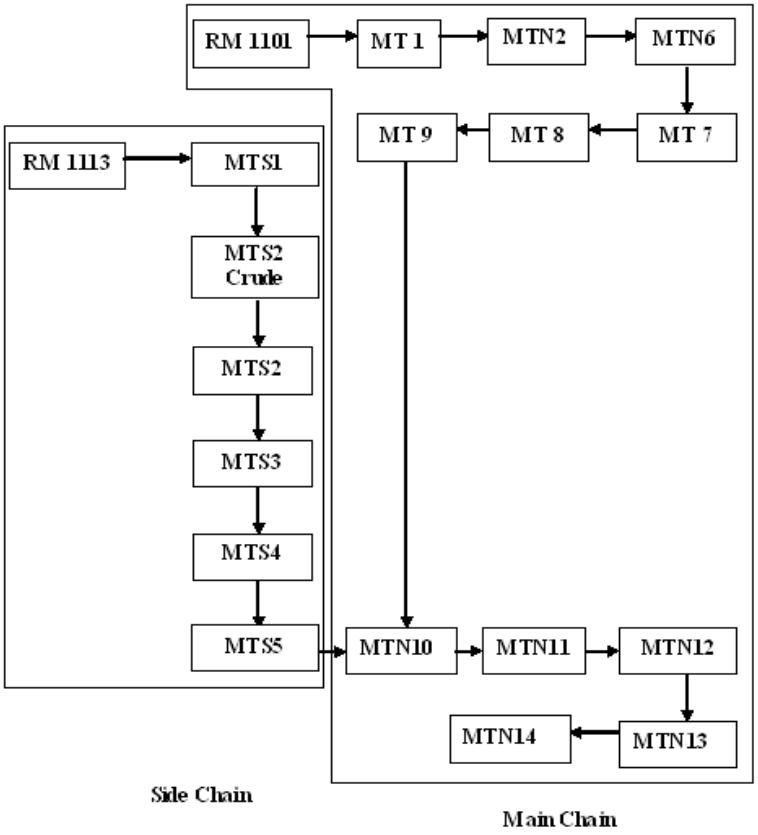


Figure 3: In-process list of stages of Manufacturing of Montelukast Sodium.

Table 2: Purification Profile of Montelukast.[11,12]

S.No.	Name of impurity	Solvent used for purification	Chemical Name Of Impurities	Year	Inventor
1	Montelukast keto	Tetra hydro furan	[(R)-(E)]-1-[[[-1-[3-[2-(7-CHLORO-2-QUINOLINYL(ETHENYL]PHENYL]-3-[2-ACETYLPHENYL]THIO]METHYL] CYCLOPROPANE ACETIC ACID	2006	Gasanz Guillen, Yolanda
2	Montelukast vinyl	Tert-butyl methyl ether	1-[[[(1R)-1-[3-[2(1E)-(7-CHLORO-2-QUINOLINYL)ETHENYL]PHENYL]-3-[2-(1-METHYL-1-ETHENE)PHENYL]PROPYL]THIO]METHYL]CYCLOPROPANE ACETIC ACID	2007	EsteveQuimica, S.A.
3	Montelukast sulphone	Toluene	[(1R)-(E)]-1-[[[-1-[3-[2-(7-CHLORO-2-QUINOLINYL)ETHENYL]PHENYL]-3-[2-(1-HYDROXY-1-METHYL	2007	Monsalvatz, Ilagostera,

			ETHYL)PHENYL]PROPYL]SULPHONYL]METHYL] CYCLOPROPANE ACETIC ACID		Pedro
4	Montelukast vinyl	Methanol	1-[[[(1R)-1-[3-[2(1E)-(7-CHLORO-2-QUINOLINYL)ETHENYL]PHENYL]-3-[2-(1-METHYL-1-ETHENE)PHENYL]PROPYL]THIO]METHYL]CYCLOPROPANE ACETIC ACID	2007	Mahendru Manu, India

MATERIAL AND METHODS

Materials

Chemicals and reagents

All the chemicals and reagents used were of RANKEM^{TM}. Methanol, Tri-ethylamine (TEA), Propan-2-ol, Hexane and Tetrahydrofuran (THF) are of HPLC Grade and Ethanol is of AR Grade.

Operating parameters and instruments

1. Thin Layer Chromatography: For Reaction Monitoring

The TLC is the fastest and highly efficient method to monitor the course of an organic reaction. The silica plates were employed for determining the presence of starting material (MT06) in the reaction mixture and also for qualitative analysis of the rate of formation of product (MT07).

Mobile Phase

n-hexane	:	Ethyl acetate
7	:	3

Work Up

To 5ml of sample, 5 ml water and 1 drop di-ethanolamine were added. Them the mixture was extracted with 5 ml ethyl acetate. Spot ethyl acetate (upper layer).

Spotting

Spot 5 ul each of

- 0.2% solution of MT06 in MDC.
- Spot extracted sample.
- Co spot

OBSERVATION

Observe the plate under UV light.

2. Laboratory Tests For MT07

a) Determination of Water Content: By Karl Fischer Titration Method

Karl Fischer titration is commonly used for quantitative analysis of water content in the reaction.

The fundamental principle behind it is based on the Bunsen Reaction between iodine and sulfur dioxide in an aqueous medium. In other words it is based on iodine/iodide reaction. The titration reaches its end-point when all the water is consumed. The process uses an organic base (pyridine), primary alcohol (methanol) as the solvent, iodine and sulfur dioxide.

For determination of water content, about 40ml of dry methanol was added to the Karl Fischer titration vessel**(Fig. 4)** and titrated with Karl Fisher reagent for neutralization. Then 0.5g of sample was added quickly, stir for 1 min and again titrated with Karl Fisher reagent, till the amphoteric end point reached.

$$\% \text{ Water Content (w/w)} = \frac{V.F.100}{W.1000}$$

Where,

V = Vol. of KarlFischer reagent consumed

F = Karl Fisher factor in mg/ml

W = weight of sample in gram

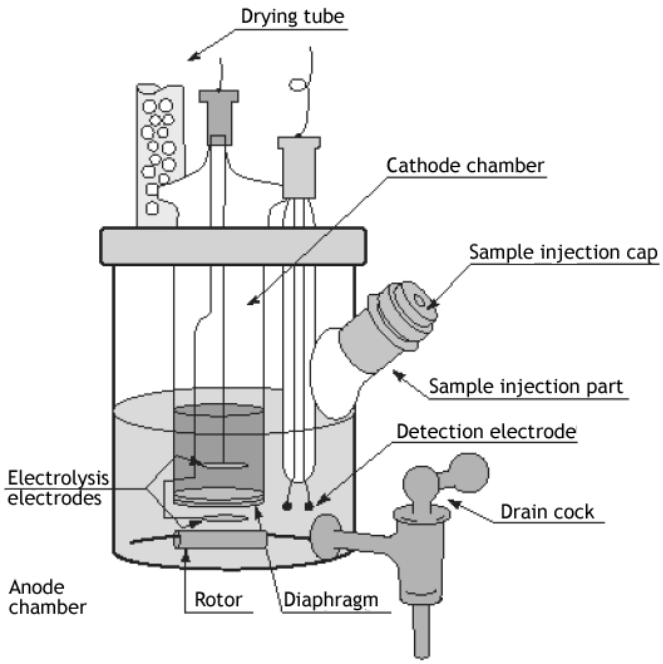


Figure 4: Karl Fischer titration vessel.

b) Specific optical rotation(S.O.R.): By Polarimetry

The specific rotation [α], is defined as a fundamental and intrinsic property of chiral compound that is expressed as the angle of optical rotation when plane-polarized light is passed through a sample with a path length of 1 decimeter and a sample concentration of 1 gram per 1 millitre at a particular temperature, wavelength, and concentration. It is measured by polarimetry (**Fig 5: Principle and components of Polarimeter)**. A negative value means levorotatory rotation and a positive value means dextrorotatory rotation.

$$[\alpha]^{T}\lambda = \frac{\alpha^{T}\lambda}{I.c} \qquad \text{or} \qquad S.O.R. = \frac{\alpha.c.100}{w.ld}$$

Where,

$[\alpha]^{T}\lambda$ = specific rotation at particular time and wavelength

α = Optical Rotation

T = Measurement Temperature

λ = Wavelength of light employed

I= Path Length

c = Concentration in grams per milliliter

w = weight of sample

ld = loss on drying

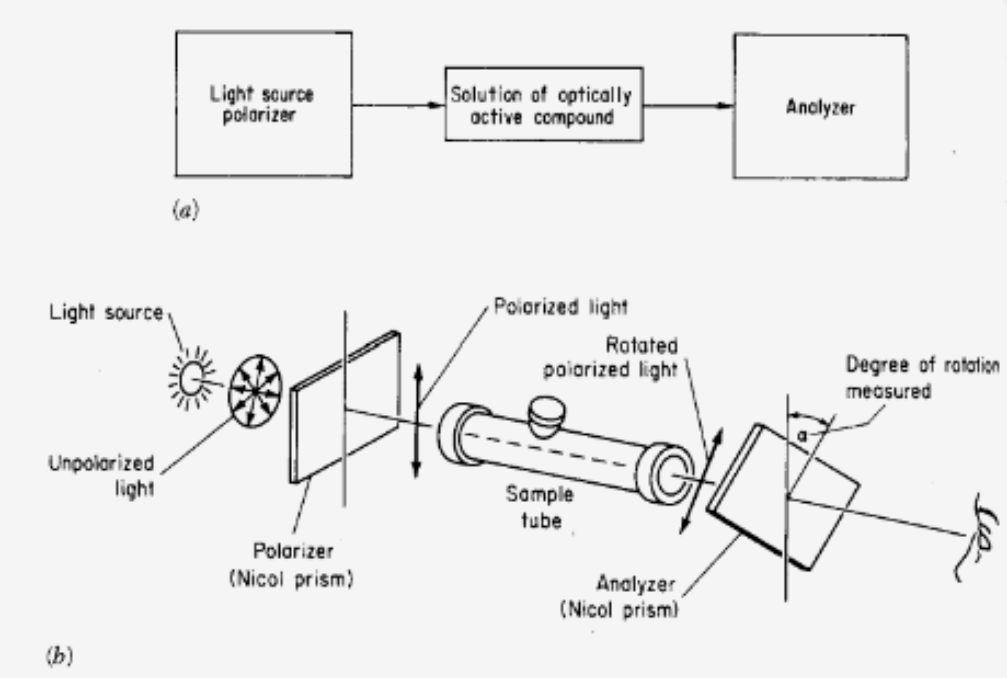


Fig 5: (a) Principle of a polarimeter set up, (b) Components of Polarimeter.

c) Relative Purity: By High Performance Liquid Chromatography (HPLC)

The percentage of the required compound in a given test sample is the relative purity. HPLC**(Fig 6: Components of High Performance Liquid Chromatography)** is the widely used chromatographic method used to determine the purity of a compound by peak area analysis. It is a method of separation based on the difference in the distribution of species between the two non-miscible phases in which the liquid mobile phase, percolates through the stationery phase (a column)at high pressure. This results in serial elution of separated compounds from the column. It works on different principals like adsorption, mass distribution, ion exchange, size exclusion or stereo-chemical interactions.

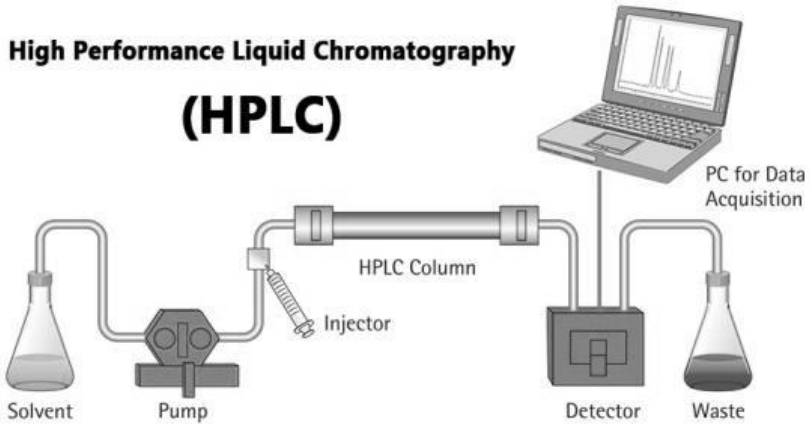


Fig 6: Components of High Performance Liquid Chromatography.

Column : Symmetry C18, 150*4.6 mm, ID 5 micro Particle size or equivalent

Flow rate : 1.2 ml/min

Injection volume : 20 microliter

Wavelength : 240nm

Run time : 40 min

Mobile Phase

(A) 1.5ml of o-phosphoric acid was accurately measured and dissolved in 750ml of Double Distilled Water; its pH is adjusted to 7.5 with tri-ethylamine and the mixture is filtered through 0.45 micro-membrane filter. 250 ml of tetrahydrofuran was added to it and then sonicated to degas.

(B) Methanol : Tetrahydrofuran (900 : 100)

(C) Composition of mobile phase and run time**(Table 3)**

(D) Delay time = 12 min

Sample Preparation

50mg of sample was accurately weighed and dissolved in sufficient quantity of Tetrahydrofuran (THF) in 50ml volumetric flask. Then the volume is made up to the mark with Methanol (MeOH). The sample was filtered prior injecting to determine the %area of principle peak.

Table 3: Composition of mobile phase and run time.

TIME	(A)	(B)	CURVE
0	70	30	-
30	20	80	6
45	20	80	6
46	70	30	1

METHODOLOGY

Preparation of MT07 from MT06

THF was taken in a beaker; MT06 was added to it at 17°C and stirred for 15 minutes. Then N-N-Di-isopropyl amine was added slowly and heated at 45°C for dissolution to get a clear solution. In another flask dip chloride was taken and was cooled to 8.7 for 2 hours. The above mixture was added to it at the same temperature for 3-4 hours with further rises in temperature to 25 °Cfor 1 hour. Stirring was done at 24°C for 8-12 hours. The progress of reaction was monitored by TLC. Then the above mixture was quenched with water for 20 min at room temperature. TEA was added at 22°0 C for 10 minutes and stirred for 30 minutes and for next 60 minutes after addition of Hexane to it. After quenching the reaction mixture was filtered in a centrifuge to remove excess of liquid. The product (MTN07) was washed with hexane and then dried at 30 °C for 12-16 hours. Moisture content and the percentage yield were calculated. (See **Table 4** for raw material and their standard quantity required in preparation of MTN07)

Yield of MT07 crude (theoretical) = 980g i.e. 98%

Table 4: Preparation of MTN07 from MTN06.

Raw Materials Needed	Standard Quantity
MTN 06	1.00 Kg
TETRA HYDRO FURAN	4.50 L
N-N-DI ISOPROPYL AMINE	0.20 – 0.50 Kg
DIP CHLORIDE	2.0 – 2.5 L
HEXANE	1L IN FILTERATION 5L IN QUENCHING
TRI ETHYL AMINE	0.80 Kg
DT WATER	25L IN QUENCHING

Existing method of purification of MT07 crude

In a round bottom flask (RBF), mixture of crude MT07 in methanol (dissolved at 28)was taken. The RBF was fitted with Teflon blade, glass rod, stopper and a stirring motor and allowed to stir for 15 min at the same temperature. TEA was added slowly for 15-20 min and then stirring was done for 3.5hrs.at 31°C.The above mass was then filtered through Hyflo (filter aid) prepared in methanol. The filtrate was transferred into a flask, heated for 20 minutes at 35C, and then cooled for 1hr. at -8.5°C with further stirring of 10hrs. Methanol was recovered with condenser at 40°C for 90 min. After stirring, the material was washed with methanol through a Buckner funnel at -9°C. The filtrate was stirred for 3 hrs. Crystals of pure MT07 were obtained and then dried in oven at 35 °C for 10hrs. Moisture content was checked by the help of Karl Fischer Method. (See **table 5** for raw material and their standard quantity required in purification process of crude MTN07)

Table 5: Existing method of purification of MT07 crude.

Raw Materials	Standard Quantity
MTN7 crude	1.00 Kg
MeOH	10.00 L (In purification) 0.2 L (Preparing Hyflo) 0.5 L (Centrifuge for washing)
TEA	0.30 Kg
Hyflo	As required

Modifications done in the above Purification Method

Montelukast is prepared in 14 stages. The 7th stage is MT07 in which methanol is previously used as purification solvent. Various other solvents were also tried at this stage for purification; some of them are hexane, ethanol, methanol, water, propan-2-ol and tetrahydrofuran. Out of these, methanol is considered as the most suitable solvent due to its easy availability, cheap rates and good solubility of MT07. Moreover, there is loss of yield while purification with pure methanol because MT07 is readily soluble in it. Whereas it is insoluble in water, and it was also found that the yield and relative purity also increased when methanol in water [MeOH: Water (1:1)] is used for purification. The reason behind this was that the salts formed during the reaction were readily soluble. These salts contain water of hydration that were washed away along with the salts washed away during purification and thus results in monohydrate MT07 with reduced moisture content (3-4%). Because of introduction of water in the purification process results in better yield and low costing for purification as well as drying due to decrease moisture content. When MT07 is purified by

the mixture of methanol and water, methanol acts as solvent for dissolution and water as anti-solvent, MT07 was very soluble in it, recovery of methanol was easy. Therefore, MeOH : Water was selected as the solvent for purification.

Why only water is not used as solvent

Only water cannot be employed as purification solvent because MT07 is insoluble in water. So until the MT07 molecule does not get dissolved completely the impurities cannot be removed and therefore, results in entrapment of impurities inside the molecule. Hence, it is necessary for us to take mixture of methanol and water to remove both water soluble and methanol soluble impurities to get obtain better purity. Moreover, by considering methanol in water as solvent, the need of methanol recovery step was also eliminated as less amount of methanol is now employed in purification process. Due to decrease in polarity while using MeoH : H2O (1:1) results in partial solubility of MT07 in the solvent mixture results in better yield. Lesser will be the methanol, more will be the yield of MT07.

The mixture of methanol and water were used in various ratios 1:1; 2:1,3:1 and 1:2 for purification of crude Mt07.

RESULTS AND DISCUSSION

Table 6: Previously used solvents for purification of crude MT07 and the % yield obtained.

Requirements for purification	Solvent used for purification (1L)	% yield of pure MT07
Crude MTO7 = 100g TEA = 30g Hyflo = 20g	Ethanol	45.6
	Propan-2-ol	43.9
	Hexane	34.1
	Tetrahydrofuran	No purification

Product: MONTELUKAST

Stage: MT7 (P) purified with Methanol: water (1:0, 1:1, 2:1, 3:1,1:2)

Quantity: 100.00 g of MT07 impure taken initially. After purification, the following results came: **Table 7**

Table 7: Results Obtained After Purification.

Test	Specifications	MeOH		$MeOH:H_2O = 1:1$		$MeOH:H_2O = 2:1$		$MeOH:H_2O = 3:1$		$MeOH:H_2O = 1:2$	
Physical appearance	Light yellow colored powder	Complies		Complies		Complies		Complies		Complies	
Melting range	95 -102 °C	97.9 – 101.8 °C		96.2-101.9 °C		95.3-100.2 °C		97.2-100.8 °C		94.6-99.1 °C	
Water	NMT 10 % w/w	$\frac{3.30x5.98x100}{0.5098 \times 1000}$	3.87	$\frac{3.29x5.77x100}{0.5044x1000}$	3.77	$\frac{3.37x5.84x100}{0.5039x1000}$	3.91	$\frac{3.39x5.86x100}{0.5046x1000}$	3.93	$\frac{5.35x5.93x100}{0.5051x1000}$	6.28
Specific optical rotation	NLT 97 %	$\frac{-0.071}{x25x100}$ 0.2504×96.13	99.01	$\frac{-}{0.069x25x100}$ $0.2511x96.23$	99.77	$\frac{-0.075x25}{x100}$ $0.2525x96.09$	98.75	$\frac{-}{0.074x25x100}$ $0.2541x96.07$	98.76	Not calculated because obtained yield is very less.	
Relative purity	- 6.5 ° to -8°	-7.37°		-7.20 °		-7.8 °		-7.58°			

NOTE:

S.O.R. is specific optical rotation. It tells us about the optical rotation of the molecule when subjected to the plane polarized light.

Factor for Karl Fischer reagent is taken out daily.

The signal shown in the graph at the end corresponds to the purity of the compound when purified with a solvent. This is known as validation.

PRACTICAL WORK DONE ON YIELD BASIS

Table 8: Solvent ratio for improved purification of crude MT07 and the % yield obtained.

Requirements for purification	Solvent used for purification (1L)	% yield of pure MT07
Crude MTO7 = 100g TEA = 30g Hyflo = 20g	Methanol (MeOH)	70.6
	MeOH : water(H_2O) [1:1]	76.4
	MeOH : H_2O [2:1]	74.7
	MeOH : H_2O [3:1]	72.1
	MeOH : H_2O [1:2]	53.1

Table 9: Experiment and detail on yield and purity basis.

Composition	Methanol (%)	Water (%)	%Yield	% Purity
1:0	100	00	70.60	99.01
3:1	75.00	25.00	72.10	98.76
2:1	66.66	33.33	74.70	98.759
1:1	50.00	50.00	76.40	99.77
1:2	33.33	66.66	53.10	-

SUMMARY

Process Analysis

Preparation of MT07 from MT06

Amount of MT06 taken = 1 Kg

Yield of MT07 (P) = 850 g

Conversion = 0.85 g

Reasons

- There is some manufacturing loss.
- Some MTN 07 gets dissolved in methanol, which cannot be recovered.
  After centrifuging, the liquid is again recovered to get some MTN 07. It increases yield but decreases purity.

Different compositions of MeOH:H_2O

1. MeOH:H_2O = 1:0

Yield decreased because MTN 07 is soluble in methanol. There was less effect on purity.

2. MeOH:H_2O = 1:1

Purity increased because both water soluble and methanol soluble impurities were thrown out. Polarity of methanol and water came down on mixing. Solubility of MTN 07 became low. Hence yield increased.

3. MeOH:H_2O = 1:2

Clarity of material decreased. Choking happened due to more water. Centrifuging got difficult. Purity affected. Moisture content increased. Drying took more time.

4. MeOH:H_2O = 2:1

Yield decreased as MTN 07 is soluble in methanol. More methanol, more solubility.

5. MeOH:H_2O = 3:1

Yield decreased a lot.

CONCLUSION

1. Yield

MT07 can be purified with methanol to get good relative purity of purified montelukast 07. But the relative purity got increased on using methanol and water in equal proportions i.e. 1:1.

Yield of MT07 increased on purifying it with MeOH:H_2O = 1:1. On using methanol and water, their polarity came down. Proper mixing resulted in less solubility of MT07 in methanol and water. Hence yield increased. Lesser will be the methanol, more will be yield of MT07.

But the quantity of methanol should be such that MT07 should be easily soluble in it.

2. Other Results

Melting point, specific optical rotation and moisture content also got in proper limit.

3. Methanol is costlier than water. On using water, cost of purification came low. There is no effect on solubility when water and MeOH mixture is used because Mt07 is soluble in the mixture. Water is taken to increase the relative purity of MT07 as water soluble impurities which were entrapped inside the Mt07 molecule are also removed. Quantity of solvent remained the same. Hence, MT07 was completely soluble in the mixture despite taking less MeOH. This resulted in saving MeOH and cost of production of MT07.

4. Relative purity increased on using the solvent MEOH and H_2O in the ratio 1:1.

5. Drying the purified MT07 with MeOH and H_2O took less time. It saved power and time.

- Best results were obtained on using MeOH:H_2O = 1:1.
- MT07 can be purified with methanol to get good relative purity of purified montelukast 07. But the relative purity got increased on using methanol and water in equal proportions.
- Melting point, specific optical rotation and moisture content also got in proper limit.
- Yield of MTO7 increased on purifying it with MeOH: H_2O = 1:1. On using methanol and water, their polarity came down. Proper mixing resulting in less solubility of MT07 in methanol and water. Hence yield increased.
- Methanol is costlier than water. On using water, cost of purification came low.
- Drying the purified MT07 with MeOH and H_2O took less time. It saved power and time.

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