Research Article

Preparation and Characteristic Evaluation of Polymorphism of Montelukast Sodium

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ABSTRACT

The purpose of this research was to develop polymorphs of montelukast sodium that led to higher dissolution rate and improved bioavailability. Montelukast sodium, which is well known and recommended, is used to treat symptoms of asthma, such as trouble breathing, wheezing, coughing, and a runny nose. Montelukast sodium is form a group of medicines called leukotriene receptor antagonists (LTRAs). Montelukast sodium is a BCS-II drug. Montelukast sodium is pharmacologically effective, but it has a lower solubility, which affects dissolution rate and bioavailability. The present study describes preparation of Polymorphic crystal, characteristic evaluation and dissolution enhancement of montelukast sodium by Polymorphism technique. The crystals prepared by using solvent evaporation method with various aqueous and non-aqueous solvents (Acetone, Cyclohexane, Ethanol and Distilled water). The prepared polymorphic Montelukast sodium crystals were evaluated in various parameters of Compound microscopic, Percentage yield, Melting point, FT-IR, and dissolution study. The prepared Montelukast sodium polymorphic crystal using Acetone solvent produce best dissolution rate.

Keywords: Montelukast sodium, Polymorphism, Acetone, Cyclohexane, Ethanol, Distilled water, Polymorphism, FT-IR.

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INTRODUCTION

Polymorphism is the combination of two Greek word one is poly means "**many**" and another is morphism means "**form**". When a substance exits in more than one crystalline form, the different form is designated as polymorphs and the phenomenon as polymorphism. Thus, it is defined as the ability of substance to exist as two or more crystalline phase that have different arrangement or conformations of the molecule in the crystal lattice. [1] Depending upon relative stability there two forms of polymorphs are, stable form and metastable form. A Polymorph is a solid crystalline phase of a compound, resulting from at least two different arrangements of the molecules of that compound in the solid state.[2] Polymorph can be classified in various class such as crystalline, amorphous, hydrate and solvate. Polymorphs are categorized into two types, enantiotropes and monotropes, depending upon their stability with respect to the range of temperatures and pressure. [3] The Study of polymorphism is necessarily predominant acquire comprehensive knowledge on rapid absorption of low solubility drugs in systemic circulation. [4] Such situation includes those in which faster dissolution rates or higher concentrations are desired in order to achieve rapid absorption and the efficiency or to achieve acceptable systemic exposure for low solubility drugs. [5] More importantly, polymorphisms of API directly affect drug product stability, dissolution and bioavailability. [6]

MATERIALS

The following chemicals were used Montelukast sodium (Gift samples from Yarrow chem products, Mumbai, India.), Acetone (Molychem, Mumbai), Cyclohexane (Avantor Performance Materials India Limited, Maharashtra), Ethanol (Kesari Scientific Chemicals, Chennai) Distilled water (Rajco Aqua Products, Virudhunagar) are used.

METHODS

Solubility study

Solubility of Montelukast sodium was checked in different solvents. It is listed in table 1.

Preparation of Standard Curve

For the preparation of dilution medium firstly 7.4 pH Phosphate buffer was prepared. The prepared buffer was sonicated for few minutes for obtaining uniform solution. Further 0.5% Sodium Lauryl Sulphate was mixed uniformly. About 10mg of Montelukast Sodium pure drug was weighed accurately and transferred into 10ml volumetric flask. The volume was made up to 10ml using ethanol to obtain a solution that has a concentration equal to 1 mg/ml standard solution. To a series of 10ml volumetric flasks,

carefully transferred aliquots of standard drug solution (0.2 to 1.0 ml, 10µg/ml) and the volume was made with the diluents. The instrument was for photometric mode and the absorbances of each solution were recorded at 287.3nm against the blank diluents. The absorbance measured and plotted against the concentrations. Mean absorbance values are shown in Table-2. [7]

Table 1: Solubility of Montelukast sodium in different solvents

S. No	Solvent Name	Solubility Inference
1.	Distilled water	Sparingly soluble
2.	Acetone	Freely soluble
3.	Cyclohexane	Freely soluble
4.	Ethanol	Very soluble
5.	Ethyl acetate	Very soluble
6.	Carbon tetra chloride	Freely soluble
7.	Acetonitrile	Insoluble

Table 2: Mean absorbance values and the calibration curve for the estimation of Montelukast sodium

S. No	Concentration (µg/ml)	Absorbance at 287.3 nm
1.	0.2	0.055
2.	0.4	0.132
3.	0.6	0.215
4.	0.8	0.298
5.	1.0	0.385

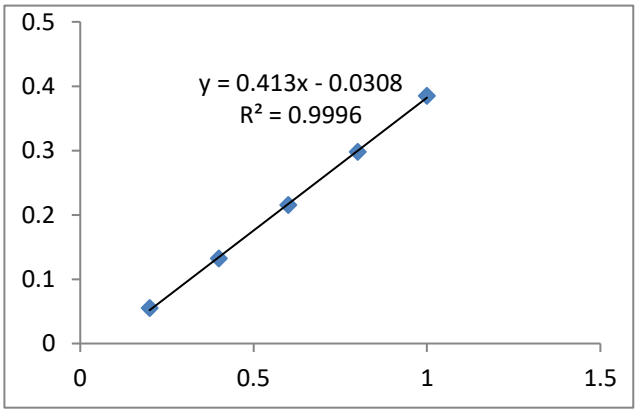

Figure 1: Calibration curve of Montelukast Sodium

Preparation of Montelukast Sodium crystal by using Solvent evaporation method: [8,9]

Crystal preparation using Acetone (Mls-1):

The 0.5g of drug was dissolved in 50 ml of Acetone and check its solubility. To this solution another weighed amount of Montelukast Sodium 2g was added and dissolved with 90 ml of Acetone and kept over water bath for 90 minutes. The solution was filtered through whatmann filter paper and the filtrate was kept at room temperature. The crystals obtained, were collected by filtration, dried under vacuum condition then stored in well closed container.

Crystal preparation from using Cyclohexane (Mls-2):

The 0.5g of drug was dissolved in 50 ml of Cyclohexane and check its solubility. To this solution, another weighed amount 2 g of Montelukast Sodium was added and refluxed with 90 ml of Cyclohexane for 2 hours. The solution was filtered through Whatman filter paper and kept it at room temperature. The crystals obtained were collected by filtration, dried under vacuum and kept aside stored in well closed container.

Crystal preparation from using Ethanol (Mls-3):

The 0.5g of drug was dissolved in 50 ml of Ethanol and check its solubility. To this solution another weighed amount of 2 g of Montelukast Sodium was added and refluxed with 90 ml of Ethanol. The solution was filtered through Whatman filter paper and the filtrate was kept at room temperature. The crystals obtained were collected and dried under vacuum at room temperature and stored in well closed container.

Crystal preparation using Distilled water (Mls-4):

The 0.5 g drug was dissolved in 50 ml of Distilled water to check its solubility. To this solution, another weighed amount 2 g of Montelukast Sodium was added and refluxed with 90 ml Distilled water. The solution was filtered through whatmann filter paper and kept for crystallization at room temperature. The crystals obtained were collected and dried under vacuum and stored in well closed container.

Characterization of Crystals

1. Compound Microscopy:

Microscopy is a popular tool in the pharmaceutical industry, where it is used to examine shape and size as well as identify the solid state form of the sample. Different types of microscopes are currently used for the characterization of pharmaceutical crystals. The crystals were visualised with 10X and 45X lenses. The crystals' shape characteristics were observed.

2. Percentage yield:

All batches of prepared crystals were accurately weighed. The measured weight of prepared crystals was divided by the total amount of all the solvents and drugs used in the preparation of the crystals, which gave the total percentage yield of crystals.

3. Melting Point analysis: [10]

Melting point measured by Capillary tube method in an oil bath-melting-point apparatus, A few crystals of the compound are placed in a thin-walled capillary tube 10-15 cm long, about 1 mm in inside diameter, and closed at one end. The capillary, which contains the sample, and a thermometer are then suspended so they can be heated

slowly and evenly. The temperature range over which the sample is observed to melt is taken as the melting point.

4. FT- IR Spectroscopy: [11]

The crystal samples were triturated with dried potassium bromide using agate mortar and pestle. These quantities were usually sufficient to give a disc of 13 mm diameter and a spectrum of suitable intensity. The mixture after grinding into a fine powder was spread uniformly in a suitable die and compressed into a pellet form at a pressure of about 10kg/cm1 for three minutes by using hydraulic press. The resultant pellet was mounted in a suitable holder in the FT-IR spectrophotometer and full range spectra of all crystals were recorded form 4000 cm^{-1} to 400 cm^{-1}.

5. Dissolution study: [12]

The 100 mg drug equivalent crystals are passed through sieve number 100, and the crystals filled in capsule then placed in USP type-1 basket dissolution test apparatus in 900ml of dissolution media (pH- 7.4) at 50 rpm and 37±0.5°c temperature. 1 ml of sample solutions were withdrawn at 5, 10, 15, 30, 45, 60 minutes time intervals. 1 ml of 0.1 N Hcl was added immediately after each withdrawal to maintain the sink conditions. The withdrawn sample was filtered through whatmann filter paper to exclude any undissolved particle. From this solution 2ml of the solution was pipetted out and the absorbance of solutions was determined by UV spectrophotometrically at 287.3 nm after making appropriate dilutions using the same medium.

RESULTS AND DISCUSSION

Preparation and Characterization of Crystal Forms

Crystal preparation using Acetone solvent (Mls-1):

The Microscopic evaluation shows the formulated crystals are like Prism shape. It is shown in figure 2.

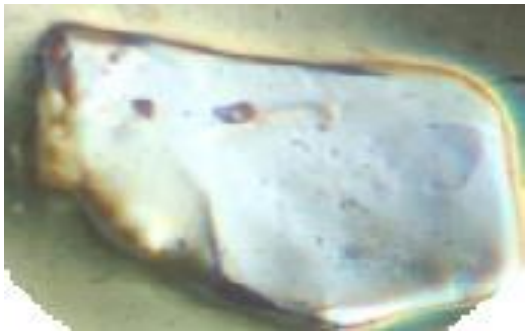

Figure 2: Prism shape crystals obtained by using Acetone solvent – Microscope view

Crystal preparation using Cyclohexane (Mls-2):

The Microscopic evaluation shows the formulated crystals are like Cubic shape. It is shown in figure 3.

Figure 3: Cubic shape crystals obtained by using Cyclohexane solvent – Microscope view

Crystal preparation using Ethanol (Mls-3):

The microscopic evaluation shows the formulated crystals are like Needle shape. It is shown in figure 4.

Figure 4: Needle shape crystals obtained by using Ethanol solvent – Microscope view

Crystal preparation using Distilled Water (Mls-4):

The Microscopic evaluation shows the formulated crystals are like Prism shape. It is shown in figure 5.

Figure 5: Prism shape crystals obtained by using Distilled water solvent – Microscope view

Percentage of yield

The percentage yield of formulated crystals was found to be the range of 71.4% to 79.4% which is shown in table no.2. All the formulation was in acceptable range of yield.

Melting point evaluation

The Melting point of prepared crystals are found to be 78°C and 95°C. It is shown in table no 2. The formulation Mls-2 and Amlo-3 are nearer to the pure drug melting point, it indicates the stable form of polymorph. The formulation Mls-1 and Mls-4 are higher than the pure drug melting point it indicates that the crystals are in metastable form of polymorph.

Fourier Transform Infrared Spectroscopic studies

FT-IR spectrum of the Mls-1, Mls-2, Mls-3 and Mls-4 showed all characteristic peaks of pure drug, which indicates that there is no modification or interaction. It is shown in Figure 6-10.

Dissolution Studies

The prepared crystals of montelukast sodium dissolution profile of 60 minutes. The range from 48.79% - 77.36%. The dissolution drug release rate was found to be comparatively less in pure drug. The maximum drug release rate was absorbed with Mls-1 (77.36%) and Mls-2 (65.76%), fewer dissolution profile was found in Mls-3 (61.67%) and Mls-4 (48.79%) (The results shown in table no: 4 and figure: 11). This study indicated that, the enhanced amount of drug release (Mls-1 and Mls-2) because of the conversion of Meta stable form crystals. The formulation Mls-1 was produce better drug release rate than other formulations.

Table 3: characterization parameters

Crystal form	Solvent used	Percentage of yield	Shape [Microscope]	Melting point (°C)
Pure drug	-	-	-	86
Mls-1	Acetone	71.4%	Prism	94
Mls-2	Cyclohexane	79.4%	Cubic	86
Mls-3	Ethanol	76.7%	Needle	78
Mls-4	Distilled water	74.8%	Prism	95

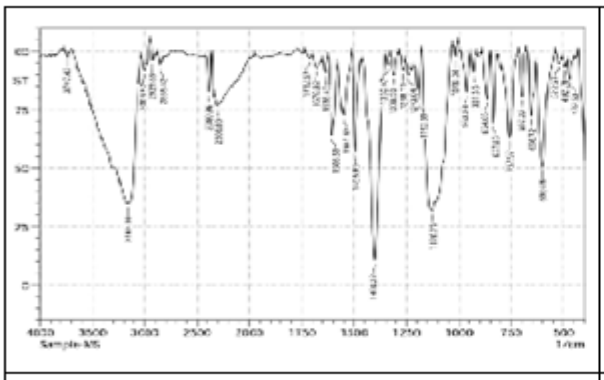

Figure 6, FT-IR of Montelukast sodium

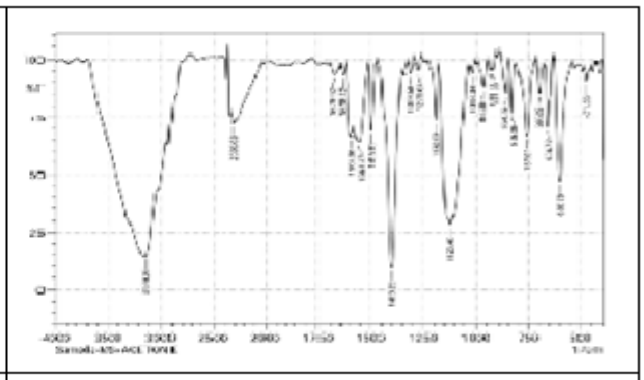

Figure 7, FT-IR of Mls-1

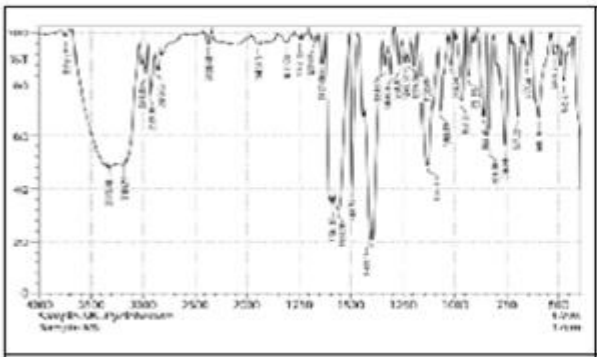

Figure 8, FT-IR of Mls-2

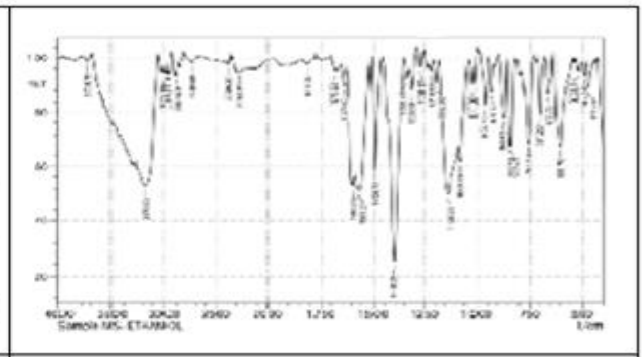

Figure 9, FT-IR of Mls-3

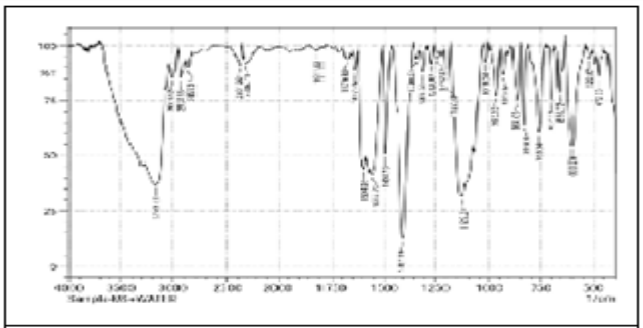

Figure 10, FT-IR of Mls-4

Table 4: Dissolution profile of the crystal forms of Montelukast sodium.

Time (minutes)	Mls-1±SD	Mls-2±SD	Mls-3±SD	Mls-4±SD	Pure drug±SD
0	0	0	0	0	0
5	12.90±**0.041**	10.24±**0.022**	9.80±**0.062**	9.02±**0.013**	6.49±**0.033**
10	24.49±**0.053**	21.68±**0.037**	19.65±**0.033**	12.79±**0.013**	9.65±**0.029**
15	41.49±**0.057**	30.26±**0.029**	28.59±**0.061**	20.65±**0.037**	18.78±**0.070**
30	54.76±**0.045**	43.84±**0.033**	41.57±**0.062**	28.74±**0.021**	27.88±**0.061**
45	67.59±**0.045**	58.25±**0.049**	50.09±**0.074**	41.62±**0.012**	40.18±**0.039**
60	77.36±**0.049**	65.76±**0.017**	61.67±**0.041**	48.79±**0.017**	45.99±**0.033**

*All values are expressed as mean ± standard deviation n=3.

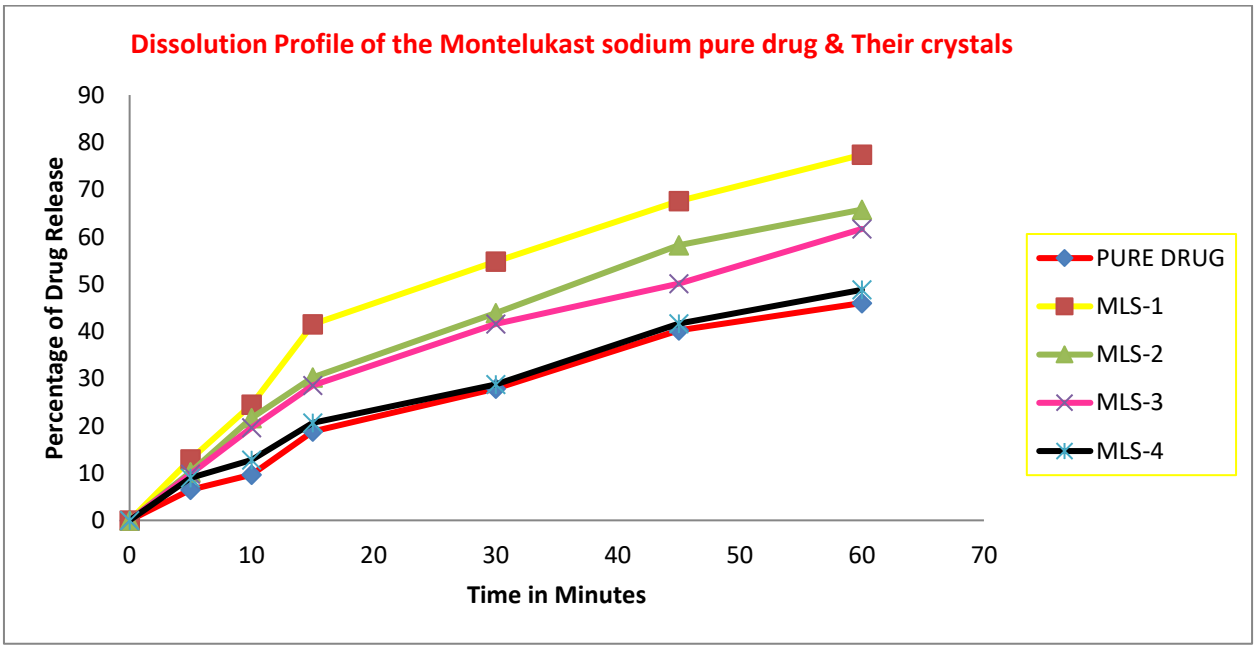

Figure 11: Dissolution Profile of the Montelukast sodium pure drug & their crystals

CONCLUSSION

The Montelukast sodium polymorphism study establishes the existence of polymorphism based on Compound Microscope, Percentage yield, Melting point, FT-IR analysis and Dissolution study. Prepared polymorphs have shown differences in their Melting point, Crystal shape and dissolution profiles. Among the polymorphs Mls-1, Mls-2 was metastable polymorphs it shown much better Dissolution profiles than Mls-3, Mls-4 and Pure drug. The Mls-3 and Mls-4 was stable polymorphs and shows slow dissolution profiles. The dissolution and other parameters would drive the Mls-1 crystals as a best comparatively.

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