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RESEARCH ARTICLE

PREFORMULATION STUDIES OF MONTELUKAST SODIUM WITH SPECIAL REFERENCE TO DEVELOPMENT OF ANALYTICAL METHODS VIA UV-VISIBLE SPECTROPHOTOMETER AND DRUG- EXCIPIENTS INTERACTION STUDIES

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ABSTRACT

The main objective of this work was to develop the preformulation studies of Montelukast Sodium. Preformulation study was mainly performed to develop simple, accurate, precise and cost effective UV-VIS Spectrophotometric method for the estimation of Montelukast Sodium, an anti asthmatic drug, in bulk and pharmaceutical dosage form. Various parameters like melting point, scanning of the drug and preparation of standard curve in different solvent systems, solubility studies and drug polymers compatibility studies were carried out. The solvent used were Distilled water, Acid buffer, pH 1.2 and Phosphate Buffer, pH 6.8 and the λ_{max} or the absorption maxima of the drug in all these three solvent systems were found to be 349nm. The regression co-efficient obtained from the standard plots were nearly about 1.0 and which proved the linearity of the analytical methods. Calibration curves followed the linear regression. This method can be used for the determination of Montelukast Sodium in quality control of formulation without interference of the excipients. It has been seen that the drug solubility was maximum in water compare to that in Acid buffer, pH 1.2 and Phosphate Buffer, pH 6.8. The FTIR spectrum of pure drug (MLS), Pullulan, Gelatin, METHO E5P, Maltodextrin and POLYOX WSR N80 were recorded. The characteristic peaks of Montelukast sodium were compared in these spectra. As there was no shifting, deleting and broadening of the peak observed in the spectrum, it was concluded that no chemical interactions occurred.

Keywords: Montelukast Sodium, drug excipients compatibility studies and particle size distribution, UV-Vis Spectro photometry, solubility studies.

INTRODUCTION:

Oral route of drug administration has been one of the most convenient and accepted route of drug delivery and amongst it the intraoral route is the most preferred due to its convenience and rapid onset of action. Intraoral dosage forms have evolved as an alternative to conventional tablets, capsules and liquid preparations [1-3]. Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Many pharmaceutical dosages are administered orally in the form of pills that include tablets and capsules. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance [2-6]. Asthma is a chronic lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing (a whistling sound when one breaths), chest tightness, shortness of breath, and coughing. Montelukast sodium is a selective, high affinity, competitive leukotriene receptor antagonist specifically the cysteinyl leukotriene (cyst-LT1) receptor. It suppresses both early and late bronchoconstrictor responses to inhaled antigens or irritants and is used in prevention and long-term symptomatic management of asthma. Montelukast sodium is a selective, high affinity, competitive leukotriene receptor antagonist specifically the cysteinyl leukotriene (cyst-LT1) receptor. It suppresses both early and late bronchoconstrictor responses to inhaled antigens or irritants. Peak plasma concentrations of montelukast sodium are achieved in 2-

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4 hrs after oral administration. The mean oral bioavailability is 64%. Montelukast sodium is >99% bound to plasma proteins. It is extensively metabolized in the liver by cytochrome P-450 isoenzymes CYP3A4, CYP2A6 and CYP2C9, and is excreted principally in the feces via the bile. The t½ of montelukast sodium is between 3-6 hrs. Metabolism was reduced and the elimination t½ prolonged in patients with mild to moderate hepatic impairment. Adverse effects of montelukast sodium include edema, agitation and restlessness, allergy including anaphylaxis, angioedema and urticaria, chest pain, tremor, dry mouth, vertigo and arthralgia. Further suspected adverse events included nightmares, sedation, palpitations and increased sweating. Churg-Strauss syndrome has been reported in association with montelukast sodium [4, 5-10].

The main objective of this work was to develop the preformulation studies of Montelukast Sodium. Preformulation study was mainly performed to develop simple, accurate, precise and cost effective UV-VIS Spectrophotometric method for the estimation of Montelukast Sodium, an anti asthmatic drug, in bulk and pharmaceutical dosage form. Various parameters like melting point, scanning of the drug and preparation of standard curve in different solvent systems, solubility studies and drug polymers compatibility studies were carried out. This UV-VIS Spectrophotometric method was deleloped to determine of Montelukast Sodium in quality control of formulation without interference of the excipients, because this technique is very easy, cheapest compare to the HPLC method.

MATERIAL AND METHODS

CHEMICALS AND REAGENTS USED

Montelukast Sodium was obtained from Ind-Swift, Baddi, India. Pullulan was purchased from Gangwal Chemicals Pvt. Ltd., Mumbai, India, Gelatin was purchased from CDH, India, METHO E5P was collected from Colorcon Asia Pvt. Ltd., Goa, India, Maltodextrin was purchased from Ind-Swift, Baddi, India and POLYOX WSR N80 was purchased from Colorcon Asia Pvt. Ltd., Goa, India. Water was glass-double distilled and further purified from Milli Q water purification system. All the other chemicals were used in analytical grades.

METHODS

The purpose of Preformulation study was to establish physicochemical parameters of drug, physical characteristics & compatibility with common excipients. Preformulation study was mainly performed to develop simple, accurate, precise and cost effective UV-VIS Spectrophotometric method for the estimation of Montelukast Sodium, an anti asthamatic drug, in bulk and pharmaceutical dosage form. Various parameters like melting point, solubility and drug excipients compatibility studies were carried out.

MELTING POINT

The melting point of MLS was determined using melting point apparatus.

SCANNING OF THE DRUG (Montelukast sodium)

Montelukast sodium was scanned in the following solvent and buffers-

i) Distilled water
ii) Acid buffer, pH 1.2
iii) Phosphate buffer, pH 6.8

i) Scanning of the drug in distilled water:

50 mg of drug was dissolved in distilled water in 100 ml in volumetric flask, and volume was made to 100 ml with distilled water. 2 ml of this stock solution was further diluted to 50 ml to get concentration of 20 µg/ml. This solution was scanned in UV-spectrophotometer and characteristic peak was observed at 349 nm.

ii) Scanning of the drug in acid buffer, pH 1.2:

50 mg of drug was dissolved in acid buffer, pH 1.2 in 100 ml in volumetric flask, and volume was made to 100 ml with same solvent. 2 ml of this stock solution was further diluted to 50 ml to get concentration of 20 µg/ml. This solution was scanned in UV-spectrophotometer and characteristic peak was observed at 349 nm.

iii) Scanning of the drug in phosphate buffer, pH 6.8:

50 mg of drug was dissolved in phosphate buffer, pH 6.8 in 100 ml in volumetric flask, and volume was made to 100 ml with same solvent. 2 ml of this stock solution was further diluted to 50 ml to get concentration of 20 µg/ml. This solution was scanned in UV-spectrophotometer and characteristic peak was observed at 349 nm.

PREPARATION OF STANDARD CURVE

i) Standard plot of Montelukast sodium in distilled water

50 mg of Montelukast sodium was dissolved in distilled water and volume was made up to 100 ml by same solvent. This gave the concentration of 500 µg/ml (stock solution). 1, 2, 3, 4, 5 and 6 ml of this stock solution was further diluted to 100 ml to get different concentrations (µg/ml): 5, 10, 15, 20, 25 and 30. Absorbances were measured at the wave-length of 349 nm.

ii) Standard plot of Montelukast sodium in acid buffer, pH 1.2

50 mg of Montelukast sodium was dissolved in acid buffer, pH 1.2 and volume was made up to 100 ml by same solvent. This gave the concentration of 500 µg/ml (stock solution). 1, 2, 3, 4, 5 and 6 ml of this stock solution was further diluted to 100 ml to get different

concentrations (µg/ml): 5, 10, 15, 20, 25 and 30. Absorbances were measured at the wave-length of 349 nm.

iii) Standard plot of Montelukast sodium in phosphate buffer, pH 6.8

50 mg of Montelukast sodium was dissolved in phosphate buffer, pH 6.8 and volume was made up to 100 ml by same solvent. This gave the concentration of 500 µg/ml (stock solution). 1, 2, 3, 4, 5 and 6 ml of this stock solution was further diluted to 100 ml to get different concentrations (µg/ml): 5, 10, 15, 20, 25 and 30. Absorbances were measured at the wave-length of 349 nm.

FTIR STUDIES

The FTIR spectrum of pure drug (MLS), Pullulan, Gelatin, METHO E5P, Maltodextrin and POLYOX WSR N80 were recorded in potassium bromide using Shimadzu FTIR – 8400 S(CE). Then, after preparing the films, IR spectrum of physical mixture of ingredients were also recorded. The range of scanning was 400 cm^{-1}–4000 cm^{-1}. The characteristic peaks of Montelukast sodium were compared in these spectra.

SOLUBILITY STUDIES

Solubility of Montelukast sodium was determined using shake flask method.

RESULT AND DISCUSSIONS

The melting point of Montelukast sodium was found to be 274^0 C – 277^0 C, which is same as documented (275.9^0 C).

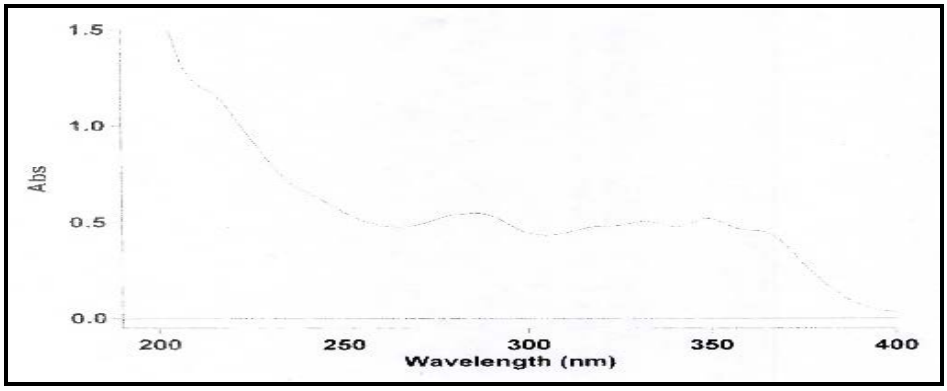

Figure 1: UV spectrum of MLS in distilled water

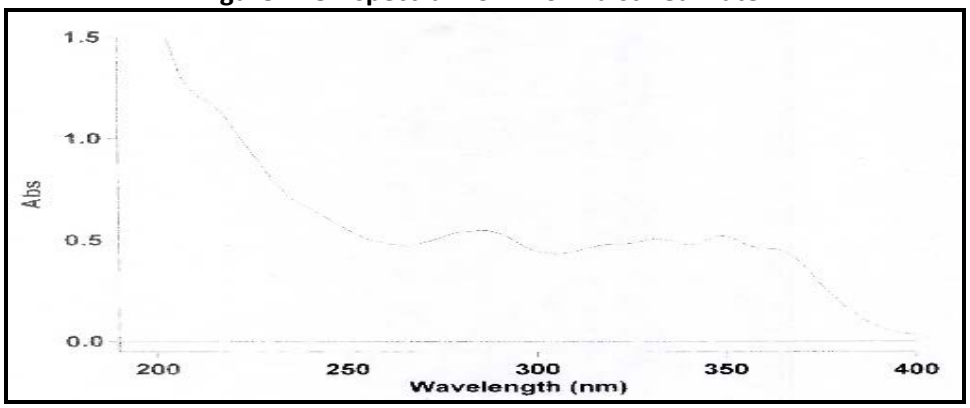

Figure 2: UV spectrum of MLS in acid buffer, pH 1.2

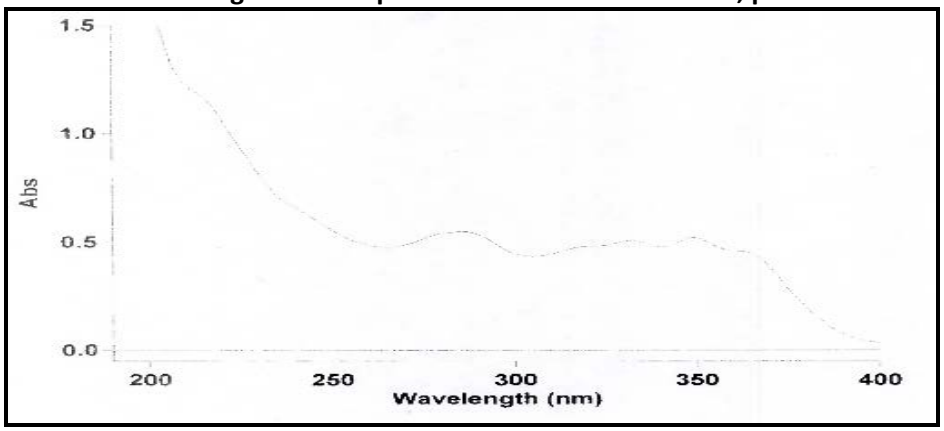

Figure 3: UV spectrum of MLS in phosphate buffer, pH 6.8

Table 1: Summary of the scanning of Montelukast sodium in various solvents

S. No.	Amount of Montelukast sodium (mg)	Solvent used to make up volume	Final volume (ml)	Conc. of stock solution (µg/ml)	Conc. of scanning solution (µg/ml)	Scanning range (nm)	Characteristic peak, λ_{max} (nm)
1	50	Distilled water	100	500	20	200 – 400 nm	349
2	50	Acid Buffer, pH 1.2		500	20		349
3	50	Phosphate Buffer, pH 6.8		500	20		349

The solvent used were Distilled water, Acid buffer, pH 1.2 and Phosphate Buffer, pH 6.8 and the λ_{max} or the absorption maxima of the drug in all these three solvent systems were found to be 349nm.

STANDARD PLOTS

Standard Plot of Montelukast sodium in distilled water

Concentration of stock solution = 500 µg/ml, Drug = Montelukast sodium
Maximum wave-length (λ_{max}) = 349 nm, Solvent = distilled water

Table 2: UV Absorbance of Montelukast sodium in distilled water

S. No.	Conc. of Drug (µg/ml)	Absorbance (Mean± S.D.*)
1	0	0.0±0.000
2	5	0.125±0.007
3	10	0.250±0.009
4	15	0.377±0.006
5	20	0.503±0.008
6	25	0.628±0.004
7	30	0.740±0.005

* S. D. = Standard Deviation, n=3

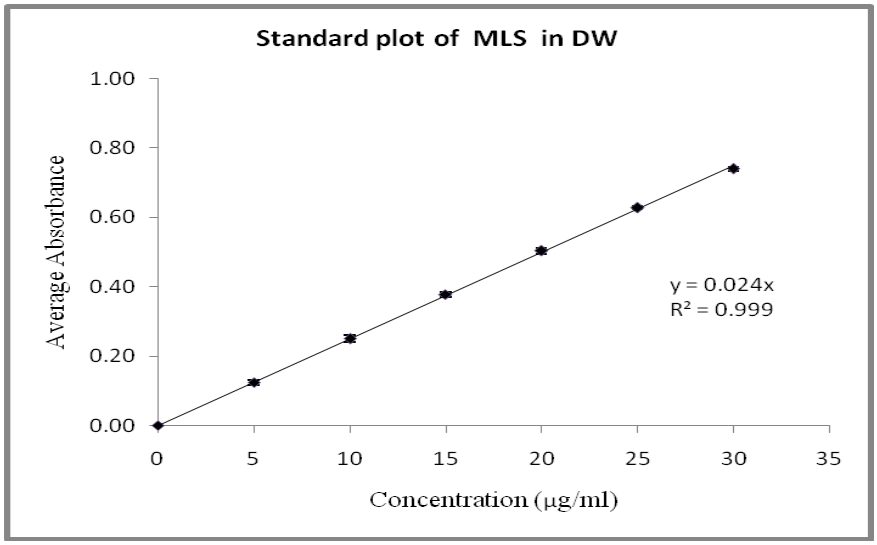

Figure 4: Average UV-absorbance of Montelukast sodium in distilled water±S.D. (n=3)

Standard Plot of Montelukast sodium in Acid buffer, pH 1.2

Concentration of stock solution = 500 µg/ml, Drug = Montelukast sodium

Maximum wave-length (λ_{max}) = 349 nm Solvent = Acid buffer, pH 1.2

Table 3: UV Absorbance of Montelukast sodium in acid buffer, pH 1.2

S. No.	Conc. of Drug (µg/ml)	Absorbance (Mean± S.D.*)
1	0	0.0±0.000
2	5	0.113±0.003
3	10	0.236±0.004
4	15	0.374±0.002
5	20	0.489±0.008
6	25	0.613±0.008
7	30	0.733±0.009

* S. D. = Standard Deviation, n=3

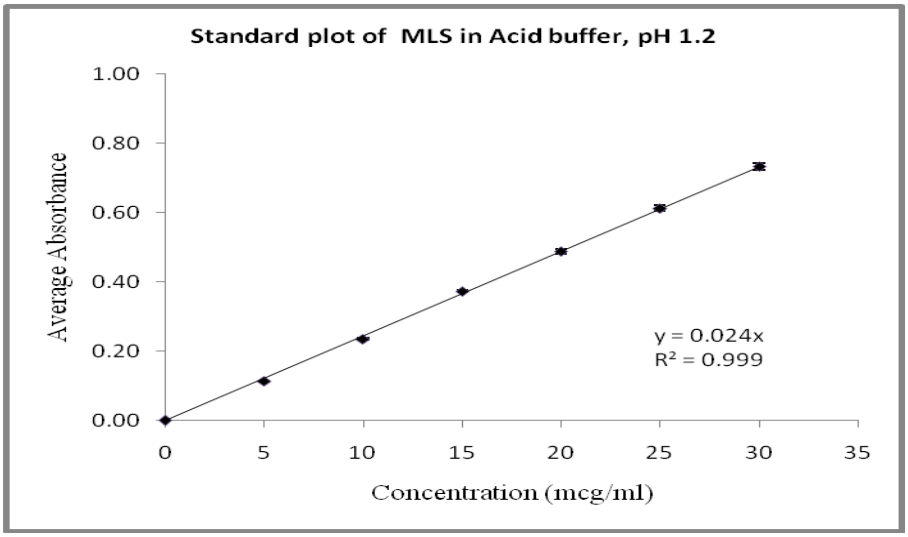

Figure 5: Average UV-absorbance of Montelukast sodium in acid buffer pH, 1.2±S.D. (n=3)

Standard Plot of Montelukast sodium in Phosphate buffer, pH6.8

Concentration of stock solution = 500 µg/ml, Drug = Montelukast sodium

Maximum wave-length (λ_{max}) = 349 nm, Solvent = Phosphate buffer, pH 6.8

Table 4: UV Absorbance of Montelukast sodium in phosphate buffer, pH 6.8

S. No.	Conc. of Drug (µg/ml)	Absorbance (Mean± S.D.*)
1	0	0.0±0.000
2	5	0.120±0.004
3	10	0.245±0.006
4	15	0.386±0.005
5	20	0.499±0.007
6	25	0.639±0.006
7	30	0.746±0.006

* S. D. = Standard Deviation, n=3

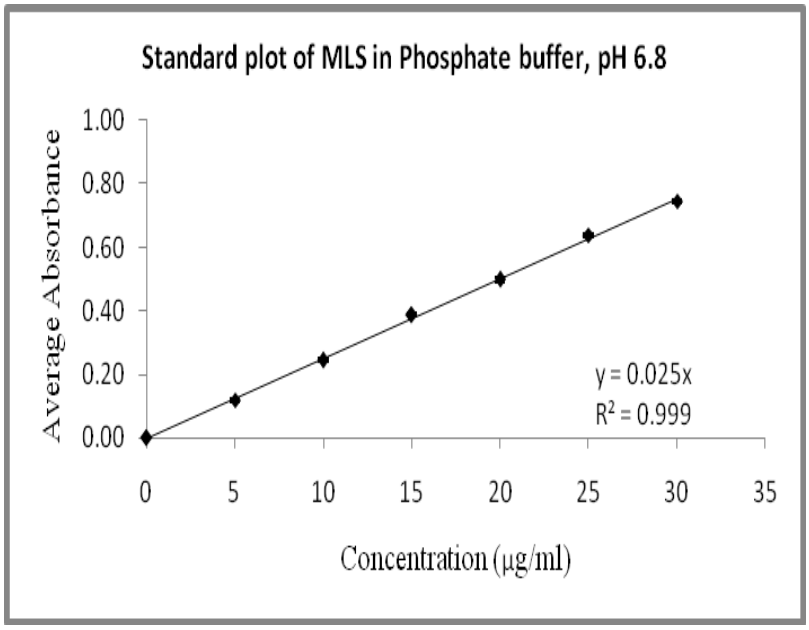

Figure 6: Average UV-absorbance of Montelukast sodium in phosphate buffer pH, 6.8±S.D. (n=3)

From the standard curve in different solvent system it can be concluded that all the R^2 values were nearly 1, means it was followed linearity. The drug followed Lambert-Beer's law in the UV region. Also, no interaction was observed between the drug and excipients.

INTERPRETATION OF IR SPECTRA

The FTIR spectrum of pure drug (MLS), Pullulan, Gelatin, METHO E5P, Maltodextrin and POLYOX WSR N80 were recorded in potassium bromide using Shimadzu FTIR – 8400 S(CE). Then, after preparing the films, IR spectrum of physical mixture of ingredients were also recorded. The characteristic peaks of Montelukast sodium were compared in these spectra.

Table 5: Preparation of physical mixture (PM) of MDF using various polymers

Code / Ingredients	PM01	PM02	PM03	PM04	PM05
PULLULAN (mg)	550	-	-	-	-
GELATIN (mg)	-	600	-	-	-
METHO E5P (mg)	-	-	500	-	-
MALTODEXTRIN (mg)	-	-	-	600	-
POLY N80 (mg)	-	-	-	-	500
MLS (mg)	131	131	131	131	131
Sorbitol (mg)	100	-	100	-	75
Propylene glycol (mg)	-	100	-	125	-
Aspartame (mg)	25	25	-	25	-
Sucralose (mg)	-	-	25	-	25
Citric acid (mg)	25	25	25	25	25

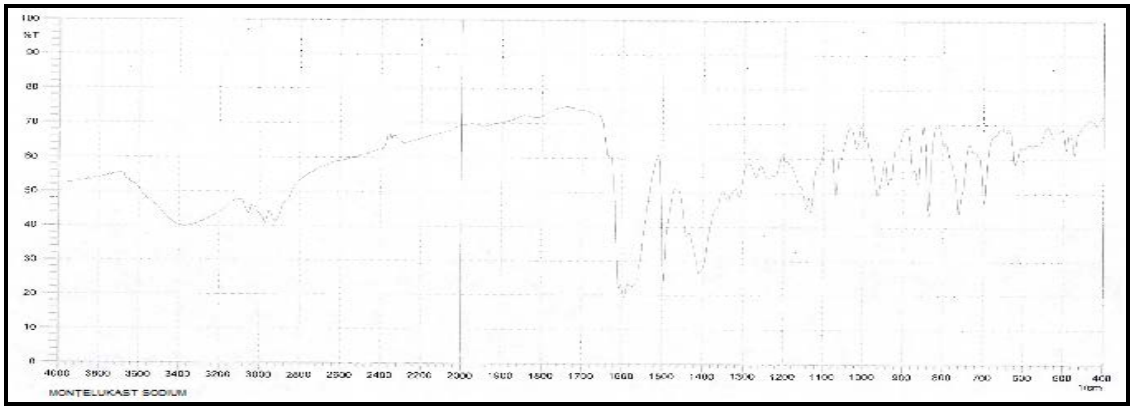

Figure 7: FTIR spectrum of Montelukast sodium

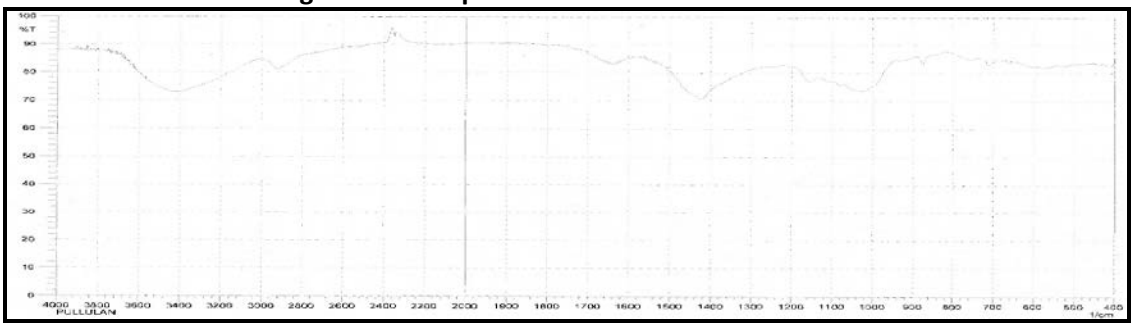

Figure 8: FTIR spectrum of Pullulan

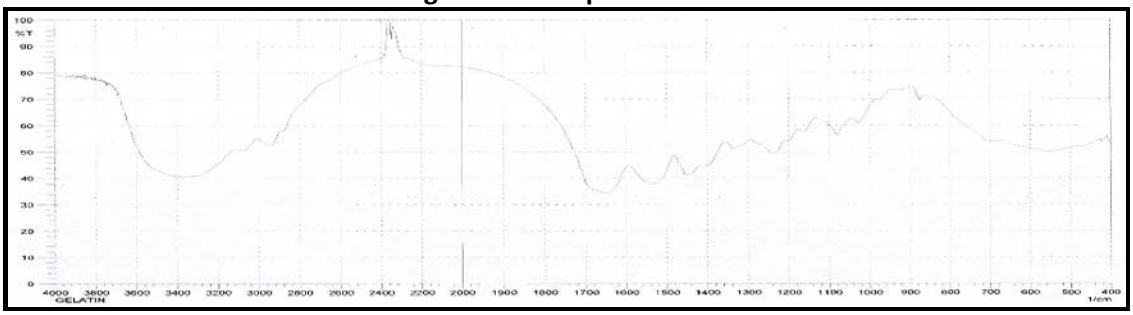

Figure 9: FTIR spectrum of Gelatin

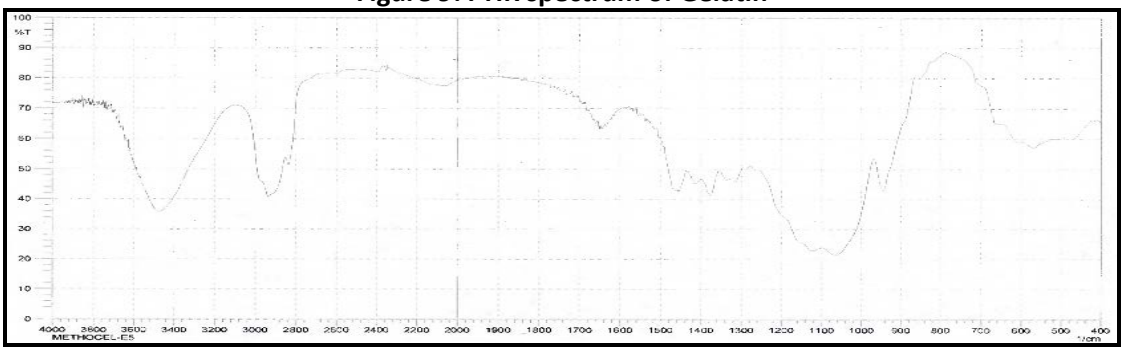

Figure 10: FTIR spectrum of METHO E5P

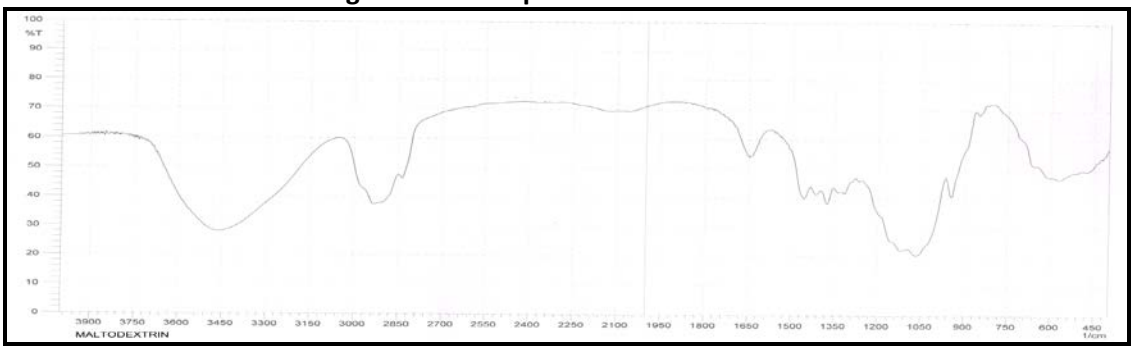

Figure 11: FTIR spectrum of Maltodextrin

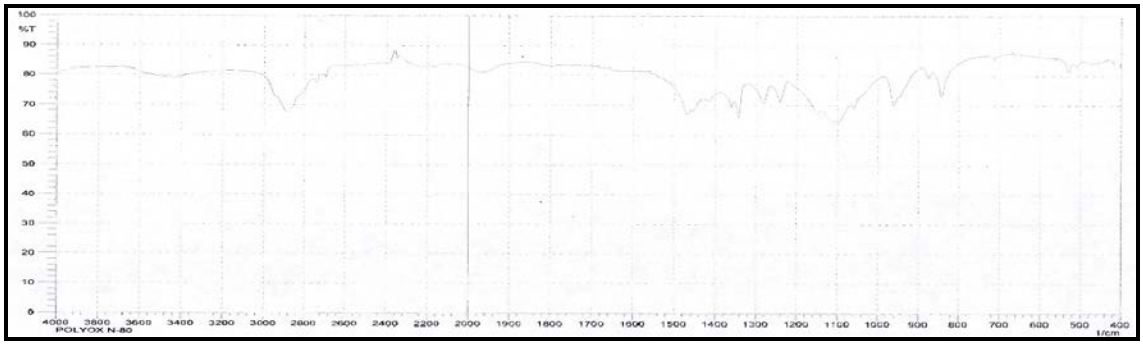

Figure 12: FTIR spectrum of POLY N80

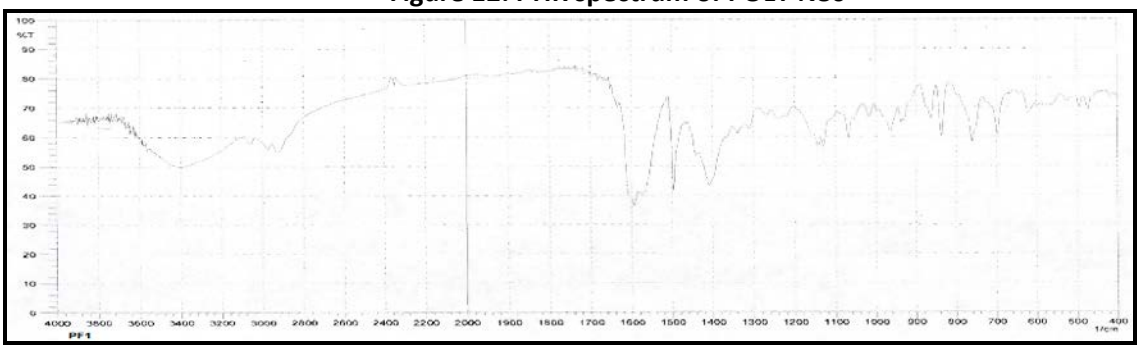

Figure 13: FTIR spectrum of physical mixture PM1

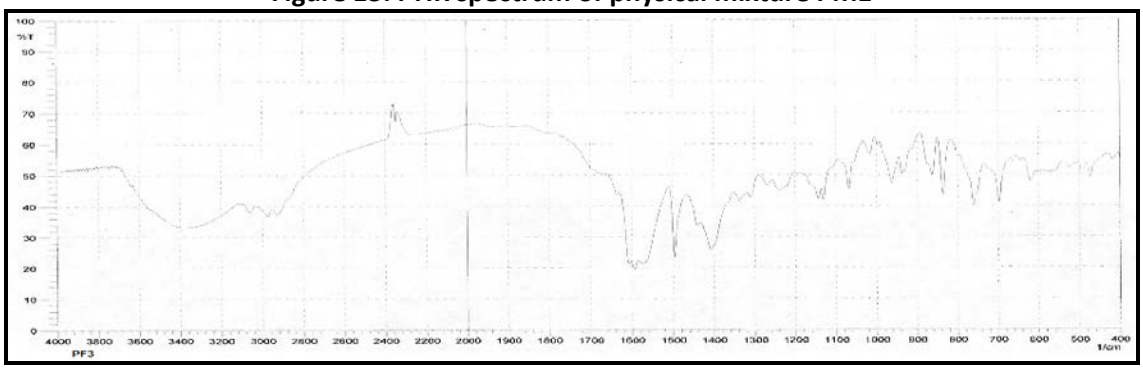

Figure 14: FTIR spectrum of physical mixture PM2

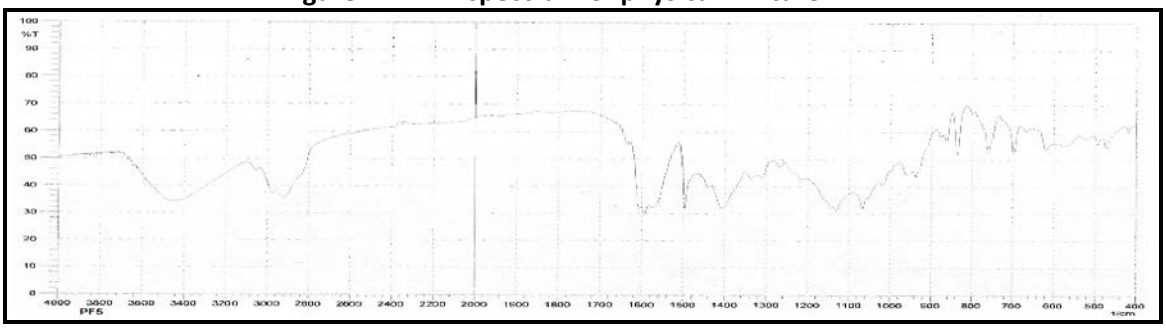

Figure 15: FTIR spectrum of physical mixture PM3

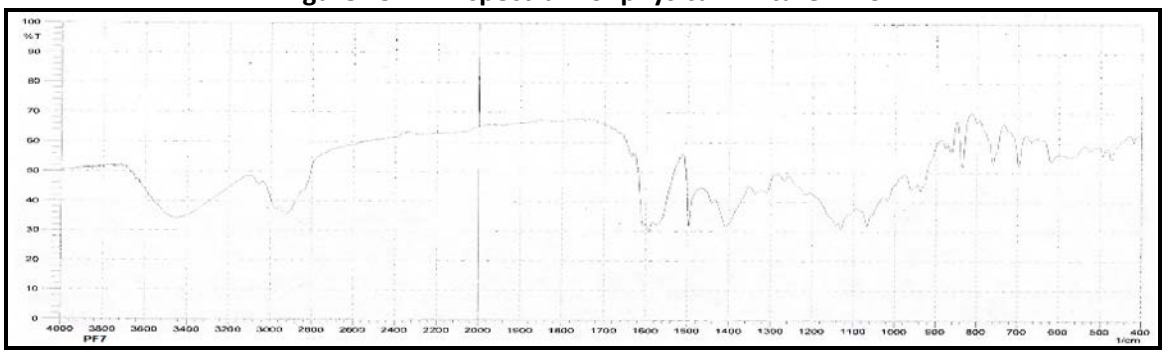

Figure 16: FTIR spectrum of physical mixture PM4

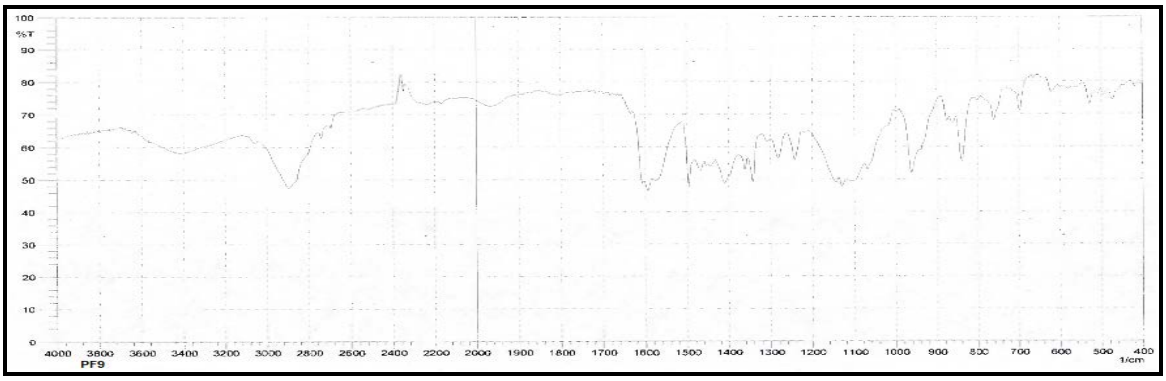

Figure 17: FTIR spectrum of physical mixture PM5

FTIR technique is used to determine any chemical interactions between drug and excipients. The peaks of drug are shown in the table, which match with the peaks mentioned in the literature which confirms the identification of drug with its functional groups.

Table 6: Interpretation of FTIR spectra of Montelukast sodium

FTIR peak as reported in literature (cm^{-1})	FTIR peak shown by drug (cm^{-1})	Interpretation
3396	3393.84	O-H stretching (carboxylic group)
3057	3055.24	Aromatic C-H stretching
1594	1593.16	C=N stretching
1132	1130.81	C-O stretching
1068	1068	Aromatic C-Cl stretching
837	837	Aromatic C-H bending
697	698.18	C-S stretching

The FTIR spectra of pure drug (Montelukast sodium), polymers (Pullulan, Gelatin, METHO E5P, Maltodextrin and POLYOX WSR N80), and physical mixtures were obtained using FTIR Spectrophotometer (FTIR – 8400S (CE), SHIMADZU). FTIR Spectra is shown in Figures and results are tabulated below:

Table 7: Wave- number of different functional groups present in Montelukast sodium

Code	Composition	Peak for Montelukast sodium (cm^{-1})						
		O-H stretching	Aromatic C-H stretching	C=N stretching	C-O stretching	Aromatic C-Cl stretching	Aromatic C-H bending	C-S stretching
MLS	Reported in Literature	3396	3057	1594	1132	1068	837	697
MLS	Montelukast sodium	3393.84	3055.24	1593.16	1130.81	1068	837	698.18

After observing the spectra and above data, it could be concluded that the peak of all the characteristic functional groups of Montelukast sodium are intact in pure drug (Montelukast sodium), and physical mixtures correspondingly. As there was no shifting, deleting and broadening of the peak observed in the spectrum, it was concluded that no chemical interactions occurred.

SOLUBILITY STUDIES

Solubility of Montelukast sodium was determined using shake flask method. The results are tabulated below:

Table 8: Solubility of Montelukast sodium in various solvents

S. No.	Solvent	Solubility of MLS (mg/ml)
	Distilled water	52.5 mg/ml
	Acid buffer, pH 1.2	7.0 mg/ml
	Phosphate buffer, pH 6.8	3.5 mg/ml

From the table 8, it can be clearly concluded that Montelukast sodium is highly soluble in water compare to the Acid buffer, pH 1.2 and Phosphate buffer, pH 6.8. As the pH of the media was changed, immediately the solubility was decreased. Various preformulation studies were performed. These included melting point determination, determination of λ_{max} in various solvents in UV region, preparation of calibration curve in various solvents, FTIR spectral analysis, drug – excipient compatibility (using FTIR), and solubility studies.

CONCLUSION

The solvent used were Distilled water, Acid buffer, pH 1.2 and Phosphate Buffer, pH 6.8 and the λ_{max} or the absorption maxima of the drug in three solvent systems were found to be 349nm. The regression co-efficient obtained from the standard plots were nearly about 1.0 and which proved the linearity of the analytical methods. Calibration curves followed the linear regression. This method can be used for the determination of Montelukast Sodium in quality control of formulation without interference of the excipients. It has been seen that the drug solubility was maximum in water compare to that in Acid buffer, pH 1.2 and Phosphate Buffer, pH 6.8. The FTIR spectrum of pure drug (MLS), Pullulan, Gelatin, METHO E5P, Maltodextrin and POLYOX WSR N80 were recorded. The characteristic peaks of Montelukast sodium were compared in these spectra. As there was no shifting, deleting and broadening of the peak observed in the spectrum, it was concluded that no chemical interactions occurred.

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