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SOLUBILITY ENHANCEMENT OF ALLOPURINOL BY SOLID DISPERSION TECHNIQUE USING SUGAR CARRIERS

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ABSTRACT

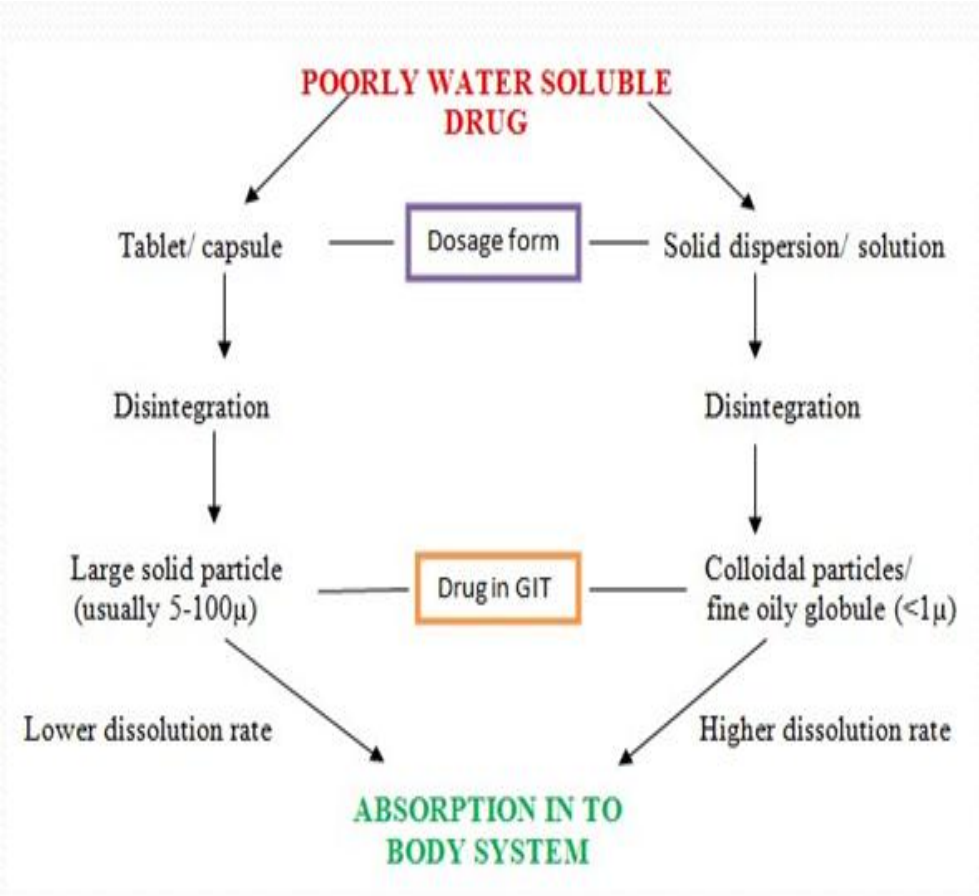
The objective of present study is to enhanced the solubility and dissolution of allopurinol by solid dispersion using sugar carriers. The drug Allopurinol is a Xanthine Oxidase Inhibitor and is used to treat gout and certain types of kidney stones. It is conjointly accustomed stop redoubled acid levels in patients receiving cancer therapy. These patients will have redoubled acid levels because of unharness of acid from the dying cancer cells. Allopurinol works by reducing the quantity of acid created by the body but Allopurinol shows poor-water solubility. The enhancement of the bioavailability of poorly water-soluble drugs is one of the greatest challenges of drug development and several pharmaceutical technologies have been investigated. Solid dispersion is one in all these ways, that was most generally and with success applied to boost the solubility, dissolution rates and consequently the bioavailability of poorly soluble medicine. Some drugs are poorly water soluble and it is difficult to formulate dosage form which gives maximum bioavailability. So the important product not reaching the market. Many of the techniques are there which enhance the solubility of the poorly water soluble drugs, solid dispersion is one of that fruitful technique which enhance solubility, dissolution rates and the bioavailability of poorly soluble drugs Hence, In this project work an attempt will be made to increase the solubility of Allopurinol by solid dispersion using sugar carrier.

KEYWORDS: Solubility Enhancement, Allopurinol, Solid Dispersion, Sugar Carriers''.

INTRODUCTION

Solid dispersion

Solid dispersion is one of the methods of solubility enhancement, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs.[1] In solid dispersion the drug is dispersed in an inert water-soluble carrier at solid state.



Diagrammatic representation of Poorly Water Soluble Drug

The term solid dispersion describes to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed, in amorphous particles (clusters) or in crystalline particles. Solid dispersion is defined as dispersion of one or more active ingredients (hydrophobic) in an inert carrier (hydrophilic) at solid state prepared by fusion method, solvent evaporation physical mixing kneading method hot melt method spray drying, co-grinding, lyophilization, melt agglomeration, super critical.

MATERIAL AND METHOD

MATERIAL

Table 5.1: Equipments and suppliers name.

S.no	Equipments	Company Name
1	UV/VIS Double Beam Spectrophotometer	Shimadzu
2	pH meter	MKVI
3	Electronic Balance	Contech
4	Melting Point Apparatus	Rolex
5	Magnetic stirrer	Scitech
6	Ultra Sonicator	PCI Analytics
7	FTIR	Shimadzu 8300
8	Dissolution Apparatus	DBK Instruments
9	X-Ray Diffractor	D8 Advance XRD
10	Shaking Incubator	Tanco
11		Tanco

Table 5.2: Chemicals and suppliers name.

S. No.	Chemicals	Company name
1	Allopurinol	Piramal Healthcare Ltd
2	Lactose	SdFine-chem
3	Mannitol	SdFine-chem
4	Sodium Hydroxide (NaOH)	HiMedia Laboratories
5	Hydrochloric acid (HCL)	Molychem
6	Octanol	HiMedia Laboratories
7	Chloroform	Molychem
8	Ethanol	SDFCL
9	Methanol	HiMedia Laboratories

MATERIALS

Allopurinol was obtained as a gift sample from Piramal healthcare limited, Pithampur, Dhar (MP). Lactose and Mannitol are procured from SdFine-chem. limited (Mumbai). All the reagents used in the study were of analytical grade and the solutions were prepared using double distilled water.

RESULT AND DISCUSSION

A. Determination of λ max

The resulting solution shows maximum absorbtion at 245nm and minimum absorbtion at 230nm as shown in figure 5.1. It shows that the drug is pure.

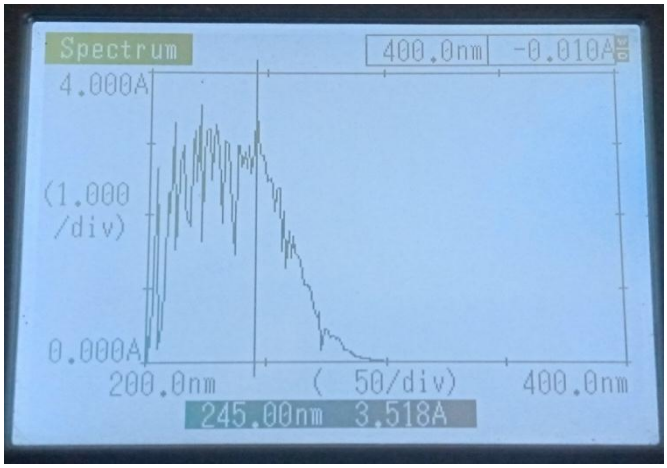


Figure 5.1: λ max of Allopurinol.

B. Melting point determination

The melting point of drug sample was determined by using melting point apparatus. The melting point was found between the range of 344-355°C.

Table 5.3 Melting Point.

S. No.	Melting Point	Average
1.	344-355℃	344℃-355℃
2.	340-352℃	
3.	348-360℃	

C. Partition Coefficient

The logP value of Allopurinol was found to be in the range of 2.04 to 2.51 indicating the lipophilic nature of drug.

D. Solubility studies

Quantitative solubility analysis of allopurinol determined in different solvents and the results were illustrated in table. The allopurinol drug was found to be more soluble in NaOH solution, chloroform and Methanol. The solubility of allopurinol in various solvents are shown in table 5.4.

Table 5.4: Quantitative solubility.

S. No.	Solvents	Solubility mg/ml
1	Methanol	0.612
2	Chloroform	0.750
3	Octanol	0.375
4	Ethanol	0.575
5	Water	0.316
6	NaOH	0.911

E. Fourier transforms infrared spectroscopy (FTIR)

The characteristic peak attributable to various functional groups present in the molecule of drug was assigned to establish the identity of drug. The results suggested that there was no interaction of between allopurinol and excipients. The IR Spectra of spure drug, carrier and formulations are shown in figure 5.2, 5.3, 5.4, 5.5.

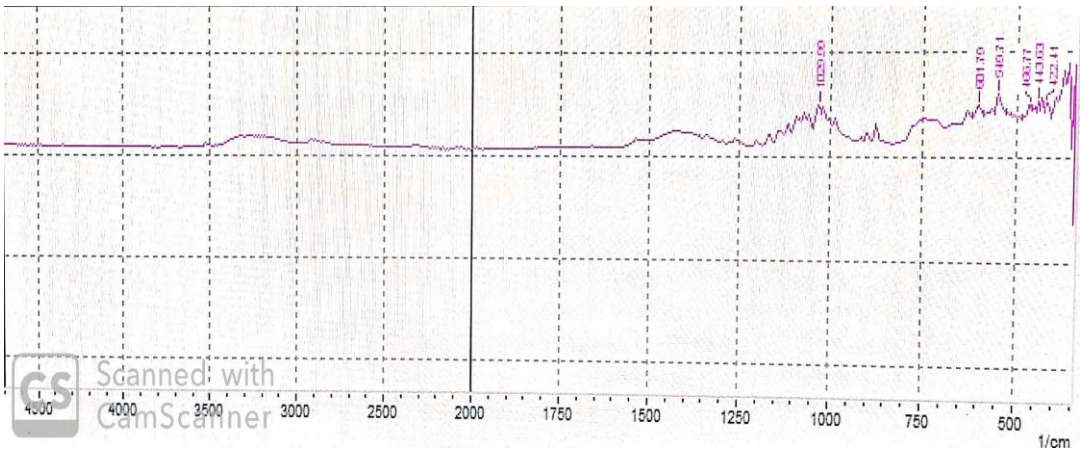


Figure 5.2: FTIR of Lactose.

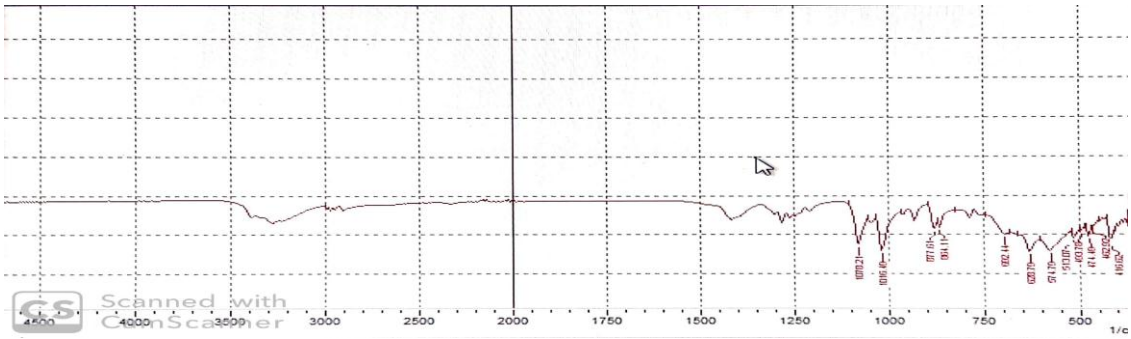


Figure 5.3: FTIR of Mannitol.

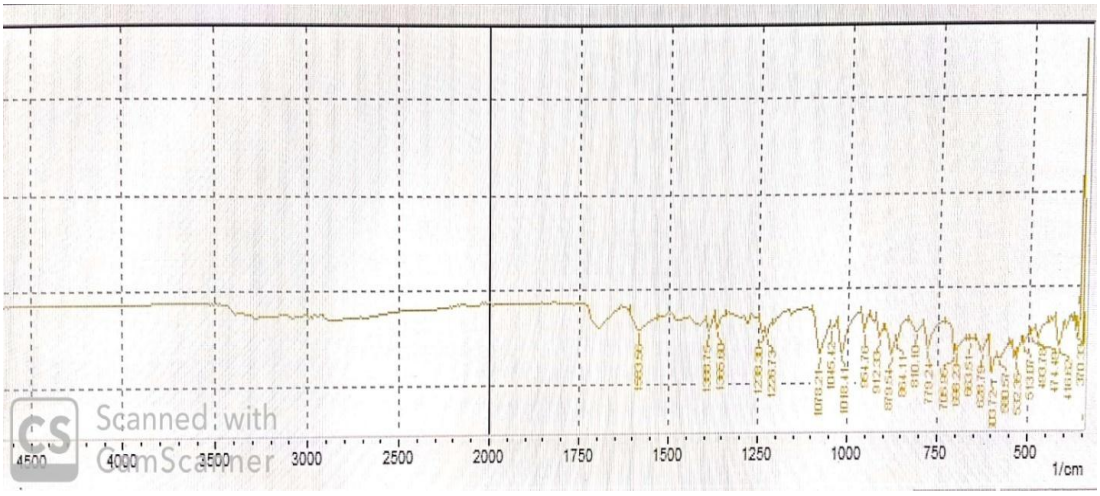


Figure 5.4: FTIR of Formulation 5 (Allopurinol + Mannitol).

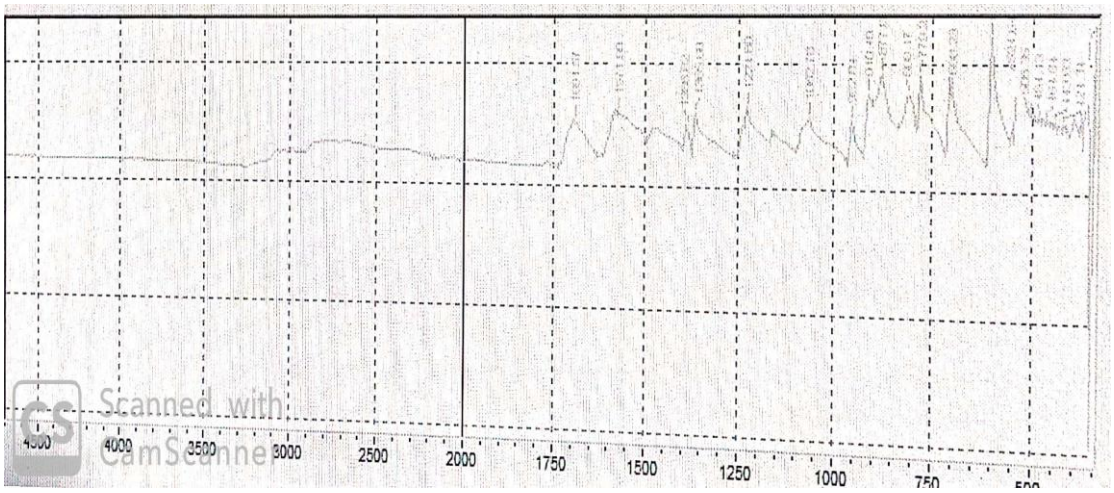


Figure 5.5: FTIR of Allopurinol.

F. Preparation of standard calibration curve of allopurinol

The standard curve was plotted with absorbance values against drug concentration as shown in figure.5.6. which shows the linear standard curve of Allopurinol.

Table 5.5 Absorbance data of Allopurinol in 0.1N NaOH for preparation of calibration curve, at 245.5nm.

S. No.	Concentration (in microgram/ ml)	Absorbance (in nm)
1	1	0.152
2	2	0.245
3	3	0.325
4	4	0.388
5	5	0.461
6	6	0.541
7	7	0.627
8	8	0.716
9	9	0.801

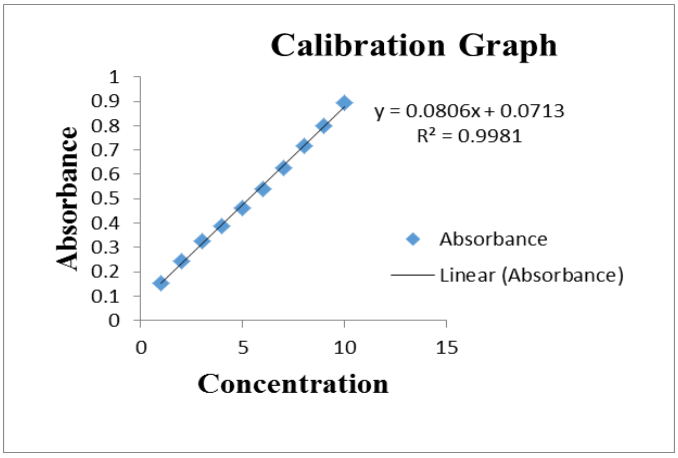


Figure 5.6: Calibration curve of Allopurinol in 0.1N NaOH.

Formulation Of Allopurinol Solid Dispersion By Kneading Method Composition of Solid dispersion

Formulation Code	Drug (in mg)	Lactose (in mg)	Mannitol (in mg)	Net amount (in mg)
F1	100	100	-	200
F2	100	300	-	400
F3	100	500	-	600
F4	100	-	100	200
F5	100	-	300	400

EVALUATION OF OPTIMIZED SOLID DISPERSION FORMULATIONS

A. Bulk characterization of solid dispersion

Flowability is an important bulk powder characteristic. The term "Flowable" means an irreversible deformation of a powder to make it flow due to the application of external energy.

1. Carr's index

The Carr index (also: Carr's index or Carr's Compressibility Index) is an indication of the compressibility of a powder. It is named after the scientist Ralph J. Carr, Jr. It indicates the ease with which a material can be induced to flow. The carr's index of the formulation F1, F2, F3, F4, F5, F6 is shown in the table 6.5.

It is expressed in percentage and is given by:

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table 6.2: Flow properties of Carr's Index.

CARR'S INDEX (%)	TYPE OF FLOW
5-15	Excellent
12-18	Good
18-23	Fair to passable
23-35	Poor
35-38	Very poor
>40	Extremely poor

2. Hausner's ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner. The Hausner ratio of the formulation F1, F2, F3, F4, F5, F6 is shown in the table 6.5.

It is an indirect index of ease of flow of formulations. It is measured by

Hausner's ratio = $\frac{\text{Tapped density}}{\text{Bulk density}}$

Table 6.3: Flow properties of Hausner's Ratio.

HAUSNER RATIO	TYPE OF FLOW
<1.25	Good
1.25 - 1.5	Moderate
>1.5	Poor

3. Angle of Repose (θ)

The formulation were allowed to flow through a funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of formulation formed. The angle of repose of the formulation F1, F2, F3, F4, F5, F6 is shown in the table 6.5.

Table 6.4: Flow properties of Angle of Repose.

<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

5Bulk characterization and flow properties of formulation

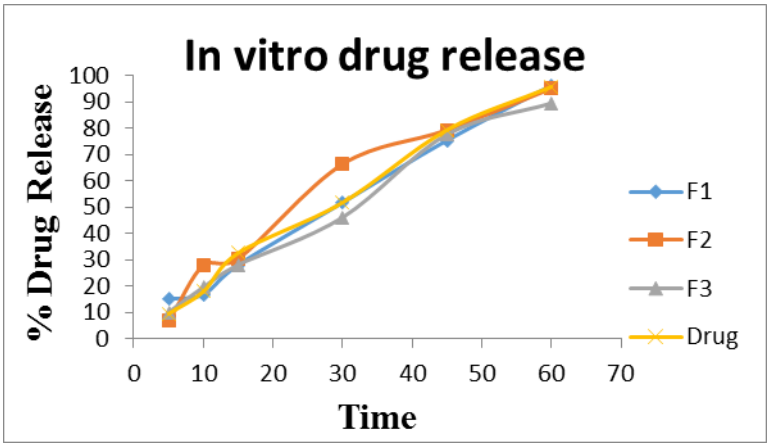
Formulation Code	Bulk Density	Tapped Density	Hausner's Ratio	Carr's Index	Angle of repose
F1	0.34	0.58	1.70	41.37	26.4°
F2	0.51	0.71	1.39	28.16	30.06°
F3	0.70	0.95	1.35	26.31	25.4°
F4	0.33	0.55	1.66	40.00	26.95°
F5	0.55	0.79	1.43	30.37	27.6°
F6	0.69	0.95	1.37	27.36	26.3°

Drug Content

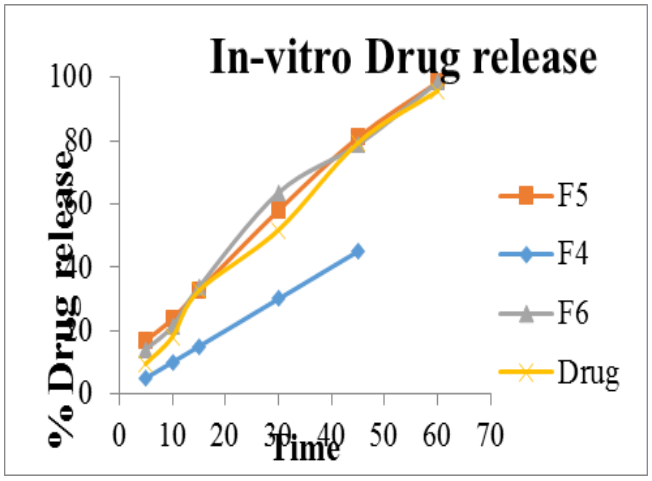
Formulation Code	%Drug Content
F1	87.09%
F2	91.20%
F3	90.30%
F4	93.60%
F5	96.30%

Invitro dissolution of allopurinol from solid dispersion

Time	F1	F2	F3	F4	F5	F6	Drug
5	15.18	6.75	10.12	12.93	16.87	14.06	9.56
10	16.87	28.12	19.68	27.00	23.62	21.37	18.00
15	28.12	30.37	28.12	29.81	32.62	33.75	32.62
30	51.75	66.37	46.12	51.75	57.93	63.56	51.75
45	75.37	79.31	77.62	77.62	81.0	78.75	79.31
60	96.18	95.06	89.43	97.31	98.43	97.43	95.66



Comparison of drug release profile of pure Allopurinol & F1,F2,F3 Batches



Comparison of drug release profile of pure Allopurinol & F4,F5,F6 Batche

Powder X-ray diffractometry

The X-ray diffraction of pure drug, lactose and mannitol are shown in figure 6.4, 6.5, 6.6, 6.7. It shows that the crystalline form of the drug was converted in the amorphous form.

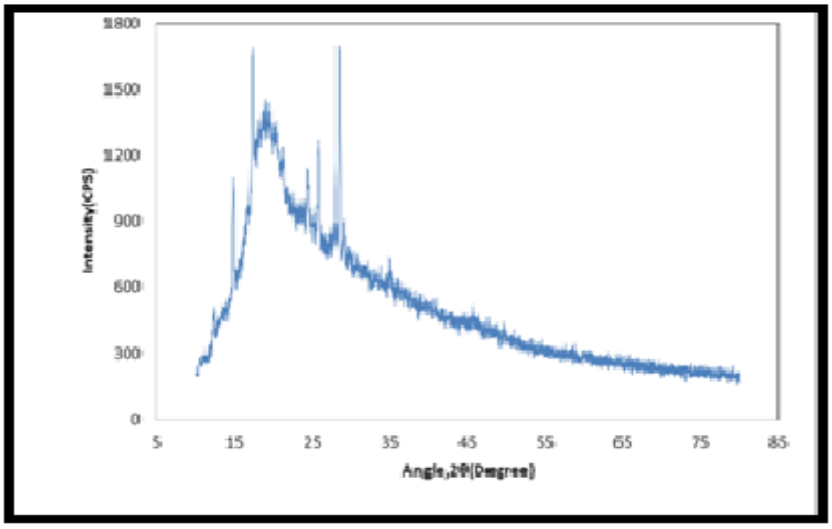


Figure 6.4: X-Ray diffraction of Allopurinol.

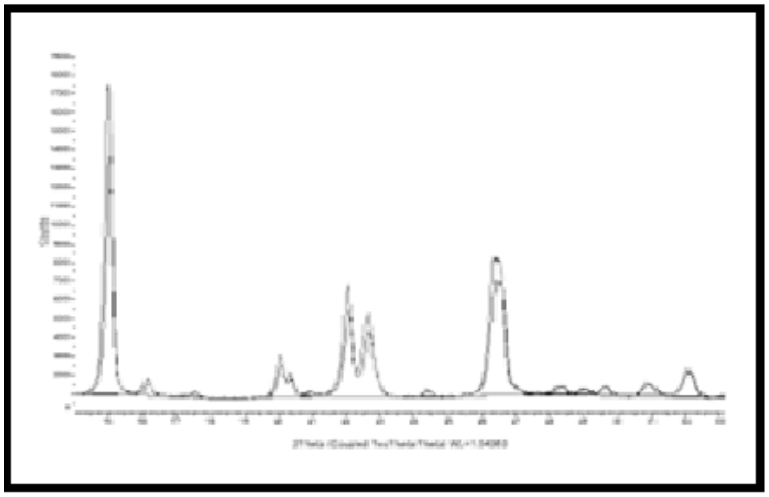


Figure 6.6: X-Ray diffraction of Mannitol.

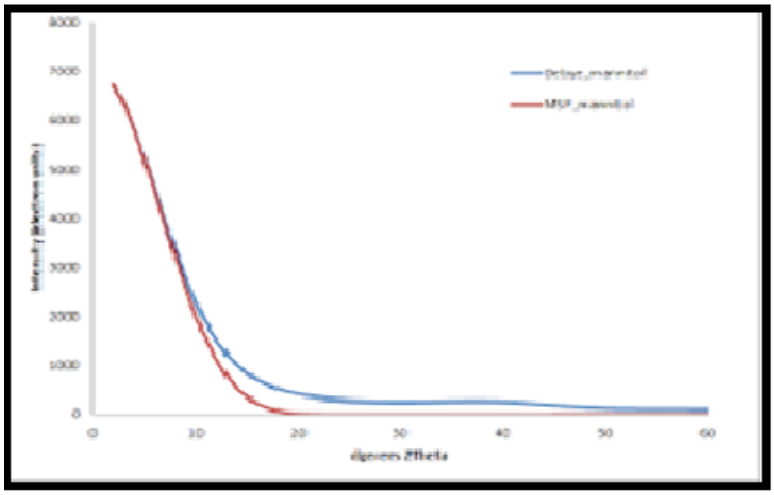


Figure 6.5: X-Ray diffraction of lactose.

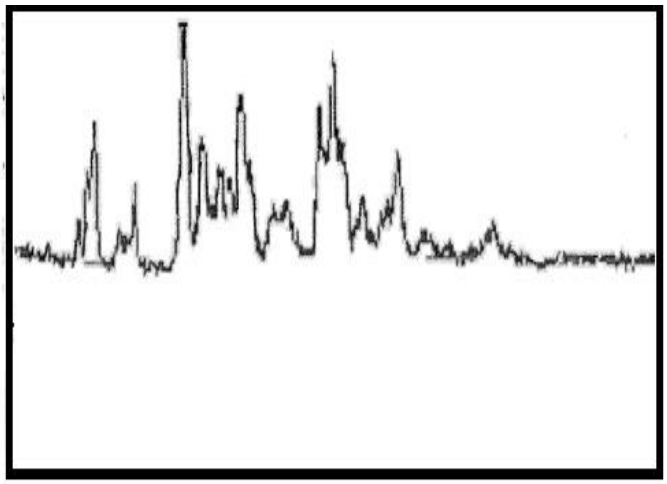


Figure 6.7: X-Ray diffraction of formulate.

A. Determination of saturation solubility

Solubility study was performed according to method reported by Higuchi and Connors. Toevaluate the increase in solubility of allopurinol in solid dispersion F1,F2,F3,F4,F5,F6 wereadded 10 ml distilled water taken in stoppered conical flask and were shaken for 8 hrs at 37°C in incubator shaker. And solution were kept for 24 hrs, after shaker to achieveequilibrium, two ml aliquots were withdrawn at 1 hr intervals and filtered through whatmanfilter paper. The filtered were solution analysed spectrophotometrically at 250 nm against blank.

B. Drug contentin solid dispersions

An amount equivalent to 10 mg of allopurinol was weighed from each resultant soliddispersion (with different carriers) and dispersed in 50 mL 0.1 N sodium hydroxide using a 100 mL volumetric flask and then was stirred for 10 min. The volume obtained was completed to 100 mL with 0.1 N sodium hydroxide and shaken well. 2ml from the previous solution were taken and were completed to 10ml with 0.1N sodium hydroxide. The absorbance was measured using a UV spectrophotometer at 250nm, using 0.1N sodium hydroxide as a blank. The drug content of various formulations are shown in table 6.1.

C. In vitro dissolution of allopurinol from solid dispersions

The rotating basket dissolution apparatus was used for the determination of dissolution rates of allopurinol solid dispersions. An accurately weighed amount of each solid dispersion equivalent to 100 mg of allopurinol was placed into the basket of the dissolution test apparatus. The basket was rotated at 50 rpm in 900 mL of the dissolution medium (0.1 N

HCl) and maintained at a constant temperature (37 ± 0.5°C). Each of 5 mL, were withdrawn from the dissolution medium at time intervals of 5, 15, 30, 45 and 60. The same volume of 0.1 N HCl was used to replace the withdrawn samples. The samples were suitably filtered, diluted, and measured spectrophotometrically at 250 nm. Thein vitro release of various formulations are shown in figure 6.2, 6.3.

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