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RESEARCH ARTICLE

SOLUBILITY ENHANCEMENT OF ALLOPURINOL BY SOLID DISPERSION USING SUGAR CARRIERS

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ABSTRACT

The objective of research work is to enhance the solubility and dissolution of allopurinol by solid dispersion using different concentration of sugar carriers (lactose and mannitol). The allopurinol solid dispersions were prepared by kneading method using lactose and mannitol with different ratio of drug and carrier such as 1:1, 1:3, 1:5 and after the formulation all the physiochemical properties were examined. All the formulations were found within the permissible pharmacopoeial limits for various physicochemical parameters. The pre-formulation studies, like Fourier, transform infrared spectroscopy (FTIR) showed the absence of drug-excipient interactions. The solubility and dissolution profiles of the sample were increased with increasing the concentration of allopurinol solid dispersions. Kneading method was proved to be a successful technique for the development of stable solid dispersion of allopurinol. The dissolution amount percentage of allopurinol formulations was found between 89.43 to 98.43% within 60 min. Hence, from the all evaluation studies, it was evident that F5 formulation was the better formulation. F5 formulation (Allopurinol: Mannitol in the ratio of 1:3), 98.43% drug released within 60 min.

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INTRODUCTION

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 (Ketan, 2012). In solid dispersion the drug is dispersed in an inert water-soluble carrier at solid state. 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.

Classification of solid dispersion on the basis of recent advancement

First generation solid dispersion: This solid dispersions are prepared by using crystalline carriers. Urea and sugars were the first carrier used in the preparation of solid dispersions. This has a disadvantage of being thermodynamically unstable and they do not release drug at a faster rate.

Second generation solid dispersion: In these solid dispersions are prepared using amorphous carriers instead of crystalline carriers. The drug is molecularly dispersed in the polymeric carrier. The polymeric carriers are divided into two groups:

- Synthetic polymer–povidone, polyethylene glycols and polymethacrylates.
- Natural polymers – hydroxyl propyl methyl cellulose, ethyl cellulose, starch derivatives like cyclodextrin.

Third generation solid dispersion: In these solid dispersions contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These shows the highest degree of bioavailability for the drugs that are having poor solubility. The surfactants being used in the third generation solid dispersion are such as insulin, poloxamer 407 etc.

Fourth generation solid dispersion: The fourth generation solid dispersion is also known as controlled release solid dispersion (CRSD), here we use poorly water-soluble drugs having short biological half-life. It contains two objectives namely solubility enhancement and extended release in a controlled manner. In this generation, the dispersion of drug in a carrier will improve the solubility whereas use of water swellable polymers can delay the drug release. The polymers which are used include ethyl cellulose, hydroxypropyl cellulose, Eudragit RS, RL, poly (ethylene oxide) and carboxyvinyl polymer (Singh, Kaur, 2017).

MATERIALS AND METHODS

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.

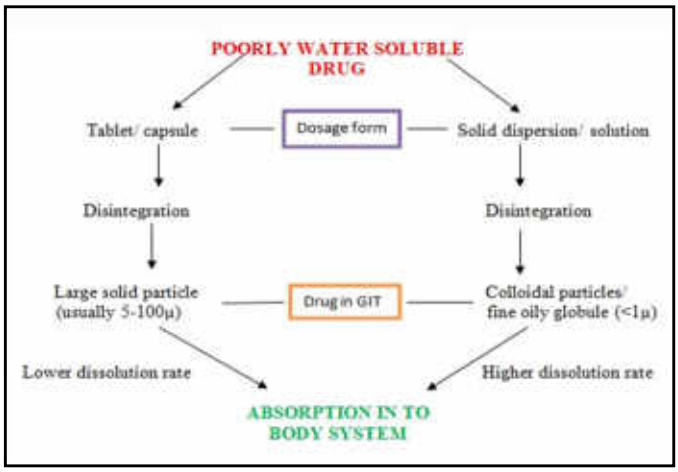

Figure 1. Diagrammatic Representation of Poorly Water Soluble Drug

Method

Determination of λ max: For the determination of λ max, Stock solution of drug was prepared by dissolving 100mg of drug in 0.1M HCL and make up the volume to 100ml (conc.1000 µg/ml). 10ml of stock solution was diluted to 100ml of 0.1M HCL and then 10ml of this solution was diluted to 100ml with 0.1M HCL. The resulting solution was examined in the range of 360nm to 230nm by UV-visible spectrophotometer. The resulting solution was showed maximum absorptions shown in Figure no. 2.

Melting point determination: Melting point of Allopurinol was determined by using open capillary method. The capillary was filled with small amount of drug powder and and it was placed along with thermometer in melting point apparatus. The temperature was noted using thermometer. The average of three values was considered as the melting point of drug as shown in Table no. 2.

Solubility studies: An allopurinol was added to 10ml of different solvents. The solutions were sonicated for 1 hr at room temperature. The solutions obtained were filtered through a filter paper and the filtrate was diluted with distilled water. The diluted solutions were measured spectrophotometrically at a λ max of 250 nm using the same medium as a blank and the resulting solubility is shown in the Table 3.

Fourier transforms infrared spectroscopy (FTIR): Samples of 1-2 mg of drug alone, each excipient alone, physical mixtures of allopurinol with the investigated excipients (1:1, w/w) prepared by physical and perfect mixing and solid dispersion were scanned from 4,000-400 cm^{-1}. The spectrophotometer was of shimadzu. The results suggested that there was no interaction of between allopurinol and excipients. The IR Spectra of pure drug, carrier and formulations are shown in Figure no.3, 4, 5, 6.

Determination of flow properties of solid dispersion

1. **Bulk density:** Bulk density is the mass of bulk solid that occupies a unit volume of a bed, including the volume of all interparticles voids. The bulk density of the formulation F1, F2, F3, F4, F5, F6 is shown in the table no.4.
2. **Tapped density:** The tapped volume was measured by tapping the formulations to constant volume. The tapped density of the formulation F1, F2, F3,F4 ,F5 ,F6 is shown in the table no. 4.
3. **Carr's index:** 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 no.4.
4. **Hausner's ratio:** It is an indirect index of ease of flow of formulations. The Hausner ratio of the formulation F1, F2, F3, F4, F5, F6 is shown in the table no. 4.
5. **Angle of Repose (θ):** The friction forces in a loose powder can be measured by the angle of repose (θ). It is defined as maximum angle possible between the surface of pile of powder and the horizontal plane. The angle of repose of the formulation F1, F2, F3, F4, F5, F6 is shown in the table no. 4.

Preparation of standard calibration curve of allopurinol: Standard calibration curve of allopuinol is prepared by taking accurately weighed 100ml of allopurinol and dissolved in 100 ml of 0.1 N sodium hydroxide then make up the volume upto1000 ml with 0.1 N sodium hydroxide. Then 1,2,3,4,5,6,7,8,9, and 10 ml of these solution was taken in 10ml volumetric flask and make up the volume with 0.1 N sodium hydroxide upto 10ml. The dilutions were analysed by UV spectrophotometer at 250nm and absorbance was noted. The standard curve was plotted with absorbance values against drug concentration as shown in Figure no.7.

Preparation of solid dispersion of Allopurinol using sugar carriers: The drug Allopurinol and the carriers, lactose and mannitol were mixed and wetted with double distilled water and kneaded thoroughly for 45 mins in the mortar pestle. The paste formed was dried for 24 hours. Dried powder was passed through sieve no.40 and kept in the dessicator until further evaluation.

Table 1. 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
F6	100	-	500	600

Drug content in solid dispersions: An amount equivalent to 10 mg of allopurinol was weighed from each resultant solid dispersion (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 no. 7.1.

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. The in vitro release of various formulations are shown in figure no.9, 10.

Powder X-ray diffractometry: Powder X-ray diffraction (PXRD) patterns were traced employing Xray diffractometer (Philips PW 1729 Netherlands.) for the all samples, using Ni filter, CuK (α) radiation, a voltage of kV, a current of 20 mA and receiving slit of 0.2 in. The samples were analyzed over 2θ range of 5° to 60°, with scan step size of 0.020° (2θ) and scan step time of 1 second. The X-ray diffraction of pure drug, lactose and mannitol are shown in figure no. 11, 12, 13, 14.

RESULT AND DISCUSSION

Determination of λmax: The resulting solution shows maximum absorbtion at 245nm and minimum absorbtion at 230nm as shown in Figure no. 2.

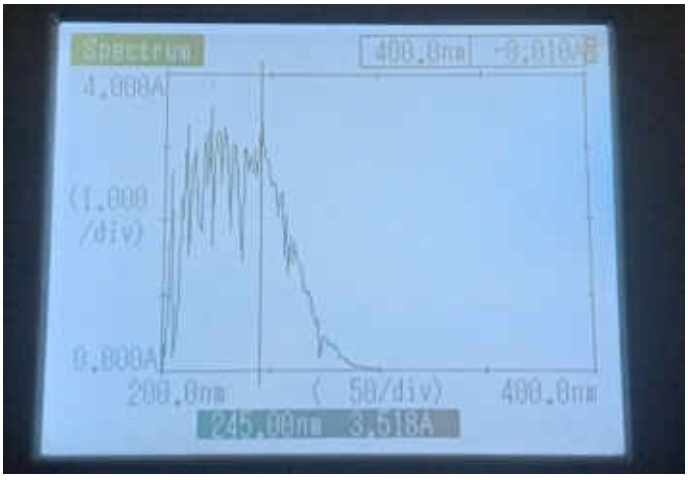

Figure 2. Lamda max of Allopurinol

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 2. Melting Point

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

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 no. 3.

Table 3. 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

Fourier transforms infrared spectroscopy (FTIR): 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 no. 3, 4, 5, 6.

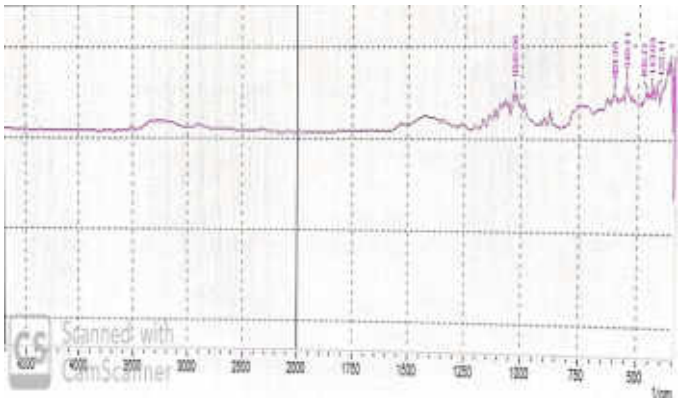

Figure 3. FTIR of Lactose

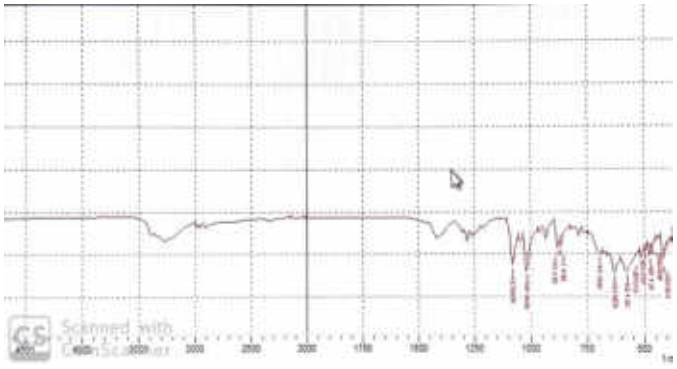

Figure 4. FTIR of Mannitol

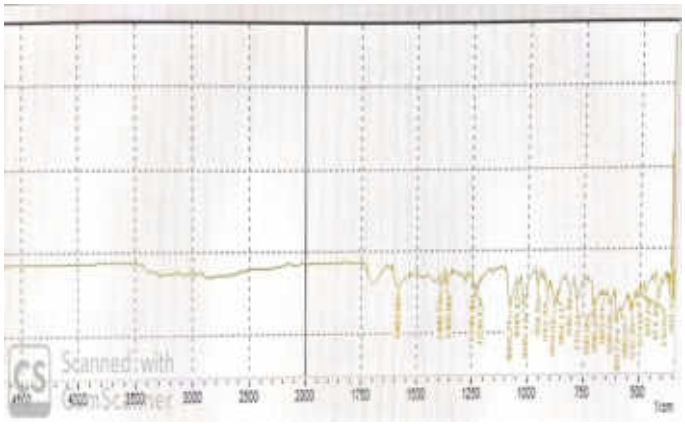

Figure 5. FTIR of Formulation 5 (Allopurinol + Mannitol)

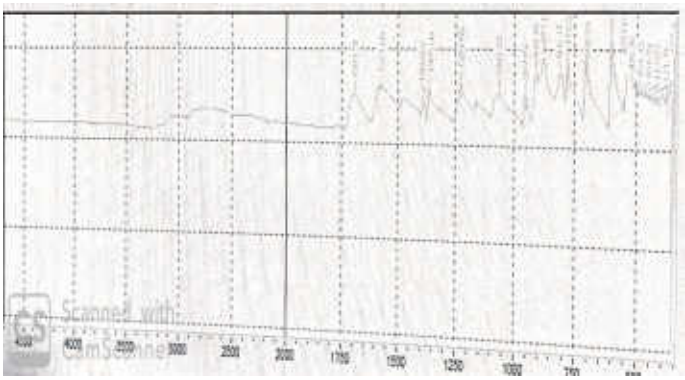

Figure 6. FTIR of Allopurinol

Determination of flow properties of solid dispersion: The flow ability of the formulation can be shown in the Table no.4.

Table 4. Bulk 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	26.3^0

Preparation of standard calibration curve of allopurinol: The standard curve was plotted with absorbance values against drug concentration as shown in Figure no.7.

Table 5. Absorbance data of Allopurinol in 0.1N NaOH for preparation of calibration curve, at 245.5nm

S. No.	Concentration (in µg / 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
10	10	0.892

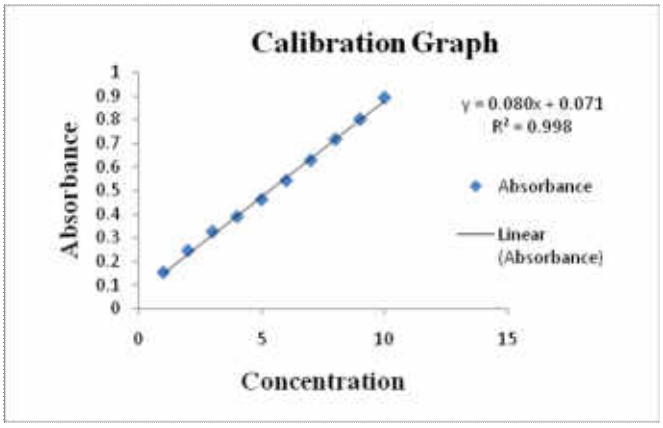

Figure 7. Calibration curve of Allopurinol in 0.1N NaOH

Drug content in solid dispersions: The drug content estimation was performed to ensure uniform distribution of drug. The drug content of solid dispersion of Allopurinol was performed for all the prepared formulations. The result indicates that the drug content in all the formulations was found uniform between 87% to 96% which was analysed spectrophotometrically at λ max 250nm. The drug content of various formulations are shown in Table no. 6.

Table 6. Drug content of various formulation

Formulation Code	% Drug Content
F1	87.09%
F2	91.20%
F3	90.30%
F4	93.60%
F5	96.30%
F6	94.26%

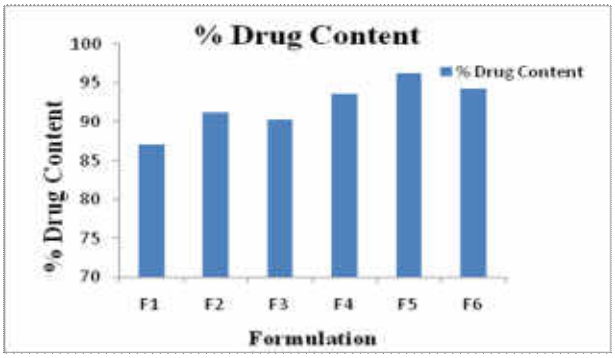

Figure 8. Comparison of percentage drug content and formulations

In vitro dissolution of allopurinol from solid dispersions: The in vitro drug release profile of pure drug Allopurinol, solid dispersion in dissolution medium are shown in figure (8.1, 8.2). Solid dispersion of Allopurinol showed a significant increase in the drug release as compared with pure Allopurinol. In the formulations F1 and F2 showing 96.18% and 95.6% drug release, F3 and F4 showing 89.43% and 97.31% drug release, and F5 and F6 showing 98.43% and 98.43% drug release respectively. All the formulation showed improved drug release rate as compared to pure Allopurinol. The in vitro release of various formulations are shown in Figure no.9, 10.

Table 7. In vitro dissolution of allopurinol from various formulations

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

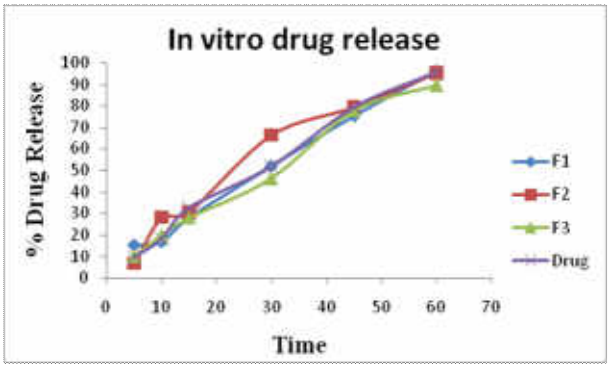

Figure 9. Comparison of drug release profile of pure Allopurinol & F1, F2, F3 Batches

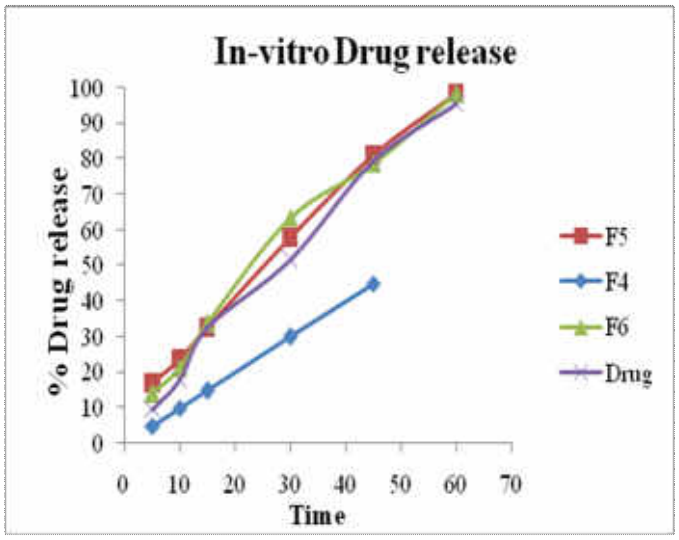

Figure 10. Comparison of drug release profile of pure Allopurinol & F4,F5,F6 Batches

Powder X-ray diffractometry: The X-ray diffraction of pure drug, lactose and mannitol are shown in Figure no. 11, 12, 13, 14.

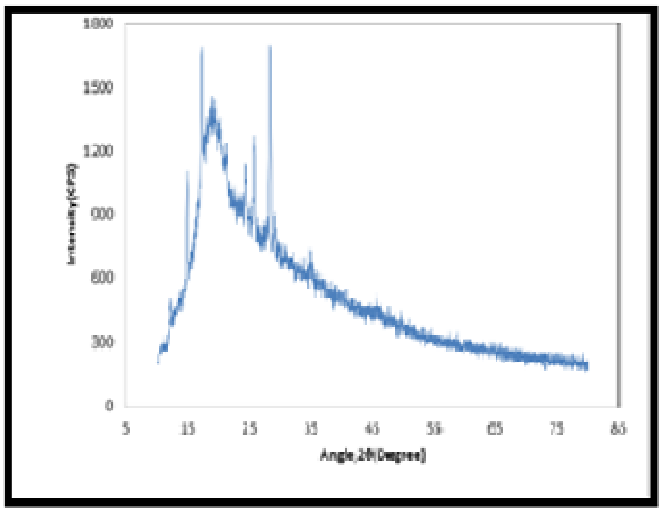

Fig. 11. X-Ray diffraction of Allopurinol

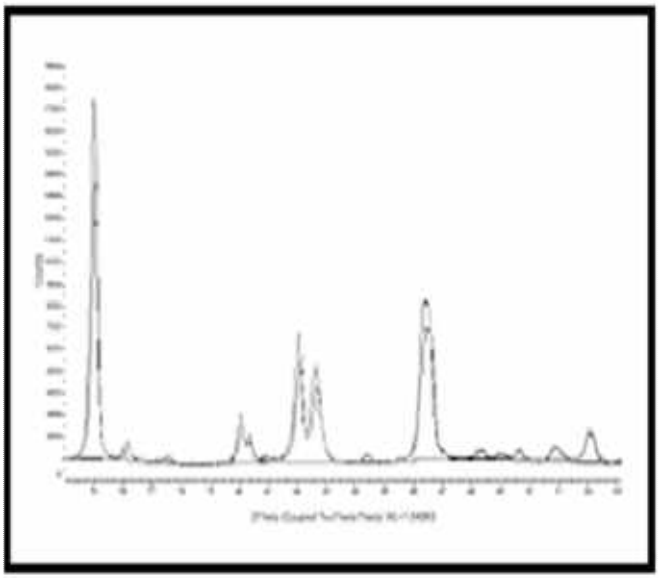

Fig. 12. X-Ray diffraction of Lactose

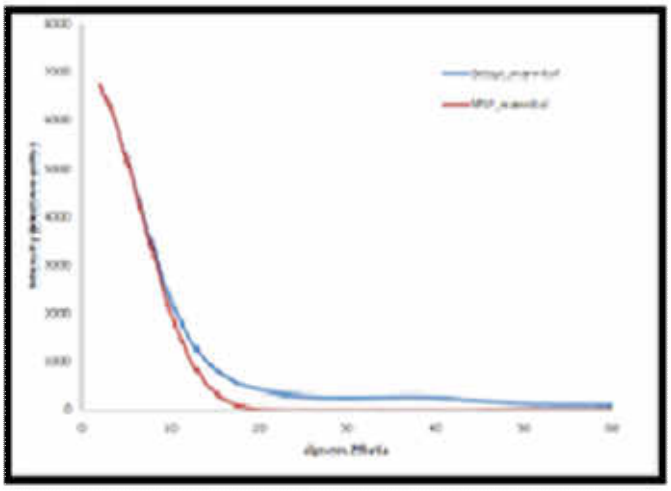

Fig. 13. X-Ray diffraction of Mannitol

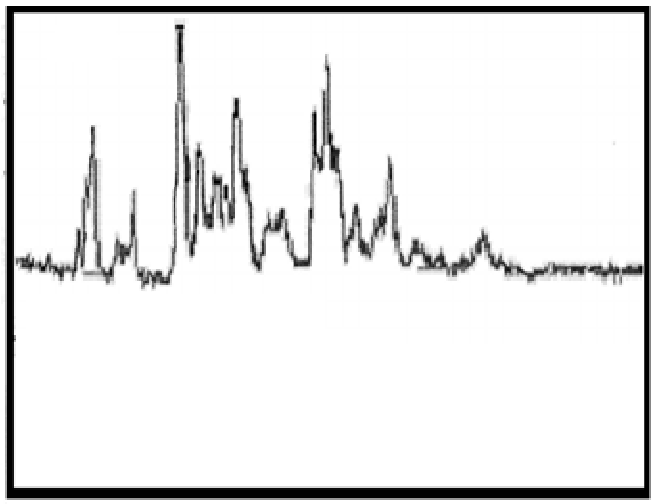

Fig. 14 X-Ray diffraction of F5

Conclusion

The study done reveals that the water solubility, dissolution rate of allopurinol can be enhanced and ultimately the bioavailability of allopurinol will also be increased by using sugar carrier with allopurinol for solid dispersion. The drug allopurinol is in crystalline form which is converted to amorphous form to enhance the solubility by solid dispersion .This might be due to solubilising effect of carriers or amorphous state of the drug in solid dispersion or entrapping the drug in molecular state by the carrier. Lactose and mannitol are used as a carrier in the formulation of solid dispersion in different concentration such as 1:1, 1:3, 1:5. As the concentration of the carriers increased, it also improved the solubility of the drug. The nature and amount of carrier used plays an important role in the enhancement of the dissolution rate. The increased solubility and dissolution rate of allopurinol provided the rapid onset of action .The carrier used is easily available, feasible to use and have low cost .Thus the formulation will be the cost effective. From the above study it was concluded that the kneading technique is useful for the preparation of solid dispersion of allopurinol.

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REFERENCES

A. A. H. Sathali and J. Jayalakshmi : Enhancement of Solubility and dissolution rate of olmesartan medoxomil by solid dispersion technique, *Journal of Current Chemical and Pharmaceutical Sciences,* 3(2), 2013, 123-134.

Abhishekh Das, Amit Kumar Nayak, Biswaranjan Mohanty, and Satyabrata Panda, Solubility and Dissolution Enhancement of Etoricoxib by Solid Dispersion Technique Using Sugar Carriers, International Scholarly Research Network, Volume 2011, Article ID 819765.

Akiladevi D, Shanmugapandiyan P, Jebasingh D ,J. Pharm. Sci vol 3 (2011).

Ankit Gupta1 , Mahesh Kumar Kataria , Ajay Bilandi, Formulation and evaluation of solid dispersion of Glipizide for solubility and dissolution rate enhancement , International Journal of Pharmaceutical and drug analysis, Vol: 2 Issue:2 Page:74-87.

Cilurzo F, Minghetti P, Casiraghi A and Montanari L (2002).Characterization of nifedipine solid dispersions. Int. J. Pharm., 242(1-2): 313-317.

G. Singh, Kaur, G. D. Gupta and S. Sharma; "Enhancement of the Solubility of Poorly Water Soluble Drugs through Solid Dispersion: A Comprehensive Review: Indian Journal Pharm Sci 2017;79(5): 674-687.

Ganesh Chaulang, Piyush Patel, Sharwaree Hardikar, Mukul Kelkar, Ashok Bhosale, Sagar Bhise, Formulation and Evaluation of Solid Dispersions of Furosemide in Sodium Starch Glycolate, Tropical Journal of Pharmaceutical Research, 2009; 8 (1): 43-51.

K.Sai Saran, M.Srujan kumar, Dr. K.V. Subrahmanyam, Enhancement of solubility of Ritonavir by using solid dispersion technique, *International Journal of Innovative Pharmaceutical Science and Research* 1(2),2013, 266-280.

Ketan T. Savjani, Anuradha K. Gajjar, and Jignasa K. Savjani; "Drug Solubility: Importance and Enhancement Techniques"; ISRN Pharm. 2012; 195727

Mathew George, Lincy Joseph, Pooran Mal Saini, Jyothi lakshmiV Nair, Enhancing the Bioavailability of Poorly Water Soluble Drug Etoroxib Using Solid Dispersion Technique" Solid Dispersion a Method to Improve Bioavailability of Poorly Water Soluble Drug,. Ijppr. Human, 2016; Vol. 6 (4): 17-51.

Mogal S. A, Gurjar P. N, Yamgar D. S and Kamod A.C.; "Solid dispersion technique for improving solubility of some poorly soluble drugs"; Der Pharmacia Lettre, 2012, 4 (5):1574-1586.

Ms. Fainaz M. Chaudhari, Ms. Trusha Y. Puttewar, Dr. Ravindra Y. Patil, Solubility Enhancement of Aspirin by Solid Dispersion Method, *International Research Journal of Pharmacy and Pharmaceutical Research*, 2015; Vol. 5 (1): 208-218.

Nagasamy Venkatesh D, Arun Radhakrishna, S. Saraswathi, M. S. Padma Priya, N. Imran Khan, N. Kathirulla , S. Sruthi, Dissolution enhancement of Diacerein using water soluble carrier by using solid dispersion technology, 2017; 7(5):33-41.

NL Prasanthi, N Rama Rao, SS Manikiran, Studies on dissolution enhancement of poorly water soluble drug using water soluble carriers, *Asian Journal of Pharmaceutica and Clinical Research,* Vol.3 Issue 2, 2010, 94-97.

P. Radhika Reddy, P. Manjusha Reddy and A. Siva Koti Reddy, Enhancement of bioavailability of carbamazepine by solid dispersion techniques, International research journal of pharmacy and chemistry, 2013, 3(1), 54-56.

Pekamwar S.S ,Kankudte A.D. ,Kale G.K. ,Formulation and evaluation of solid dispersion of lopinavir by using different techniques, International research journal of pharmacy, 2015,6 (9).

Prasanth VV , Abhilash M , Shanth Kumar , Rinku Mathappan , Sourav Tribedi and Sam T Mathew, Formulation and Evaluation of Solid Dispersion of Melitracen, International Journal of Pharmaceutical and chemical sciences, Vol. 2 (3), 2013,1426-1434.

S.Muralidhar, G.Devala Rao, M. Krishna Murthy, K.Kiran Kumar, K. Kranthi Teja, Syed Khaja Nawaj, T.V.Narayana, Enhancement of dissolution rate of etoricoxib through solid dispersion technique, Journal of Applied Pharmaceutical Science 01 (05), 2011, 129-132.

Sachin K. Gawai, Subhash V. Deshmane, R. N. Purohit, Kailash R. Biyani, In Vivo-In Vitro Evaluation of Solid Dispersion Containing Ibuprofen, *American Journal of Advanced Drug Delivery,* 2013, 066-072.

Shinde Sunita S , Patil Manisha V Amol Shete S , Disouza JI Atpadikar Pranit, Solid Dispersions of Poorly Water Soluble Drug Using Spray Drying Technique, International Journal of Drug Delivery 5 , 2013, 323-330.

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