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ORIGINAL ARTICLE

'A Novel Approach to Increasing the Bioavailability of Anti-Gout Drugs through ANOVA Analysis

Yuvraj L. Pandhre*[1], Sandesh R. Sul[1], Mahadev H. Parab[1], Sourabh D. Thakur[1], Manohar D. Kengar[2]
[1]Shree Pushpasen Sawant College of Pharmacy, Jaywant Nagar, Humarmala, Tal. Kudal, Dist- Sindhudurg, Maharashtra, India, Pin: 416812.
[2]Nootan College of Pharmacy, Kavathemahankal, Tal. Kavathemahanka, Dist-Sangli, Maharashtra, India, Pin: 416405.
Corresponding Author Email id- yuvraj8382@gmail.com

ABSTRACT
The objective of this study is to investigate and optimize the bioavailability of anti-gout drugs using a novel approach based on ANOVA analysis, with the aim of enhancing their effectiveness in treating gout. Gout is a common form of inflammatory arthritis caused by the deposition of uric acid crystals in the joints, leading to severe pain, swelling, and impaired mobility. ANOVA analysis allows researchers to evaluate the impact of various factors, such as drug formulation, patient characteristics, and environmental conditions, on drug bioavailability. This experimental study was conducted in Shree Pushpasen Sawant College of Pharmacy, Jaywant Nagar, Humarmala. Study duration was 12 weeks. Subjects were selected by simple random sampling method. The subjects were selected based on Novel Approach to Increasing the Bioavailability. All chemicals and solvents were procured from commercial sources were purified and sterilized using standard procedures from literature whenever required. This study demonstrated the possibility of improving Febuxostat solubility and dissolution performance by the formulation of solid dispersions by spray drying technique using hydrophilic polymer.
Keywords: *Bioavailability, Febuxostat, Gout, PVP-K30, Solid dispersion.*

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INTRODUCTION

Gout is a form of inflammatory arthritis that occurs when high levels of uric acid in the blood lead to the formation of urate crystals in the joints. These crystals cause sudden and severe pain, swelling, redness, and tenderness in the affected joint, commonly the big toe, although other joints can also be affected. Gout attacks can be debilitating and recurrent if not managed effectively.[1] Febuxostat is used to lower hyperuricemia (high uric acid in the blood) in patients with gout who have been treated with allopurinol that did not work well or cannot be treated with allopurinol. Bioavailability of a drug refers to the extent and rate at which the active ingredient of the drug is absorbed and becomes available in the bloodstream for therapeutic action. This is a critical factor in determining the effectiveness of a medication, as it directly impacts the amount of drug that reaches its target site in the body. According to IUPAC, solubility is defined as "The analytical composition of a saturated solution, expressed in terms of the proportion of a designated solute in a designated solvent, is the solubility of that solute. The solubility may be expressed as a concentration, molality, mole fraction, mole ratio, etc."[2-3] Solubility 2, 3 is explained in term of parts of solvent required for 1 part of solute[4], which is shown in Table 1.

Table 1: Definition of Solubility.

Definition	Parts of solvent required for one part of solute
Very Soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly	100 – 1000
Very slightly soluble	1000 -10,000
Insoluble	> 10000

Solubility behavior of a drug is the key determinant of its oral bioavailability. Potential bioavailability problems are prevalent with extremely hydrophobic drugs due to erratic or incomplete absorption from GIT. Therefore; to increase the bioavailability and dissolution rate of the poorly soluble drugs after oral administration is one of the most crucial challenges in modern pharmaceutics. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Recently more than 40% New Chemical Entities (NCEs) developed in Pharmaceutical Industry are practically insoluble in water. These water insoluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. Poor solubility leads to poor absorption, bioavailability, and the need for high drug dosage to be administered, leading to increased side effects[5]. The result is the withdrawal of drugs from the market and/or the return of drugs to be reformulated at the minimum, costing time, money, and energy.[6]

Concept behind BCS:

The in-vivo performance of orally administered drugs depends upon their solubility and tissue permeability characteristics. The release rate or solubility of the drug substance will not be a governing parameter if the absorption of the drug is permeation rate limited and in such cases the in-vitro dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through in vitro - in vivo correlation (IVIVC). Such a drug substance is a good candidate for controlled delivery provided they qualify in terms of their pharmacokinetics and pharmacodynamics for controlled release development.[7] Spray drying is a commonly used technique in the pharmaceutical industry to produce solid dosage forms, such as powders, granules, and microspheres, from liquid formulations. When combined with hydrophilic polymers, spray drying can be particularly effective in enhancing the bioavailability of drugs by improving solubility, stability, and absorption characteristics.[8]

MATERIAL AND METHOD

Chemicals: All chemicals and ingredients were procured from commercial sources were purified and sterilized using standard procedures from literature whenever required.

Preparation of solid dispersions of Febuxostat[9-10]

Solid dispersion of Febuxostat with PVP-K30 and β-cyclodextrin as carrier in combinations and individually were prepared by spray drying technique with different ratios. The composition of solid dispersion is shown in table no. 2

Table No. 2: Composition of Solid dispersion.

Sr.No	Batch Code	Febuxostat(g)	β-cyclodextrin(g)	PVP-K30 (g)	Drug: Carrier
1	B1	1	3	0	1:3:0
2	B2	1	2	0	1:2:0
3	B3	1	1	2	1:1:2
4	B4	1	2	1	1:2:1
5	B5	1	0	2	1:0:2
6	B6	1	0	3	1:0:3

Experimental design for the Febuxostat fast dissolving tablets:

In the present work, 2^2 factorial designs shown in table no. 3 were used to optimize the concentrations of two types of disintegrating agents. A two factor and two levels (2^2) full factorial design was used and four experimental runs were performed. Statistical models with interaction terms were derived to evaluate the influence of Croscarmellose sodium(X_1) and sodium starch glycolate (X_2) on tablet % Friability (Y_1) and Disintegration time (Y_2). All the prepared tablets were characterized for hardness and disintegration time. 2^2 full

factorial designs were used to prepare Febuxostat fast dissolving tablet. The amount of variables for factorial design of tablet formulations is shown in table no.4.

Table No. 3: Design layout for 2^2 factorial designs.

BatchNo.	Coded Value.		Actual Values.	
	X_1	X_2	Cross carmelloseSodium (mg)	Sodium Starch Glycolate (mg)
F_1	-1	+1	15	10
F_2	+1	+1	20	10
F_3	-1	-1	15	5
F_4	+1	-1	20	5

INDICATES -1= LOW LEVE +1= HIGH LEVEL.

Where, independent variables are: X_1 = Cross carmellose sodium.X_2 = Sodium starch glycolate.

Table No. : 4. Amount of variables in 2^2 factorial design batches.

Coded levels	-1	+1
Cross carmellose sodium (X_1)	**15**	**20**
Sodium starch glycolate (X_2)	**5**	**10**

RESULT

Authentication of Drug

Melting point: Temperature was noted at which solid drug changes into liquid. It was found to be 208°C. (std. – 208-210°C)

Spectroscopic analysis: Determination of λmax the standard solution of Febuxostat of concentration 10 µg/ml showed maximum absorbance at the wavelength of 315 nm. Hence the λmax of Fobuxostat was found to be 315nm.

Saturation solubility of solid dispersions in various solvents:

Table No.5: Solubility studies of prepared solid dispersion.

Sr. No.	Batch Code	Polymerused	Drug: Polymer ratio	Solubility in Distilled water* (mg/ml)	Increase in Solubility In Distilled Water (no. of folds)	Phosphate buffer (Ph 6.8)*	Increase in Solubility in phosphate buffer (no. of folds)
1	B1	β-CD	1:1	0.0565±0.213	1.569	0.307±0.123	2.79
2	B2		1:2	0.0667±0.432	1. 852	0.554±0127	5.03
3	B3	β-CD:PVP-K30	1:1:2	0.0798±0.132	2.216	0.723±0.187	6.57
4	B4	β-CD: PVP-K30	1:2:1	0.0677±0.301	1.880	0.681±0.201	6.19
5	B5	PVP-K30	1:2	0.0616±0.421	1.711	0.420±0.311	3.81
6	B6		1:3	0.0656±0.404	1.822	0.563±0.240	5.11

***Values are of (n±SD), n=3.**

Table No. 6: Percent Drug content of Febuxostat in solid dispersion batches.

Sr. No.	Batch code	% drug content
1	B1	82.36
2	B2	84.63
3	B3	90.42
4	B4	88.62
5	B5	86.91
6	B6	81.33

Table No. 7: Cumulative percentage drug release of Febuxostat and Spray dried Solid dispersion of Febuxostat.

Sr. No	Time (mins)	Pure Drug*	% Cumulative drug release					
			B1*	B2*	B3*	B4*	B5*	B6*
1	0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
2	10	2.21±0.008	30.37±0.05	32.30±0.06	40.36±0.05	34.28±0.03	35.01±0.03	32.07±0.03
3	20	4.61±0.109	38.97±0.06	43.34±0.03	47.80±0.02	43.81±0.01	40.58±0.03	41.34±0.02
4	30	7.63±0.03	51.75±0.05	54.16±0.02	62.86±0.03	60.22±0.03	56.75±0.01	52.36±0.06
5	40	9.20±0.118	72.72±0.04	74.38±0.03	76.98±0.03	75.09±0.03	74.90±0.02	73.70±0.03
6	50	12.39±0.101	79.38±0.06	80.41±0.03	83.63±0.01	86.93±0.01	82.37±0.01	81.83±0.04
7.	60	13.39±0.002	85.59±0.04	87.61±0.01	97.67±0.03	92.45±0.03	89.18±0.03	86.31±0.06

***Values are of (n±SD), n=3**

DSC studies of Pure Drug and optimized Solid dispersion batch (B3):

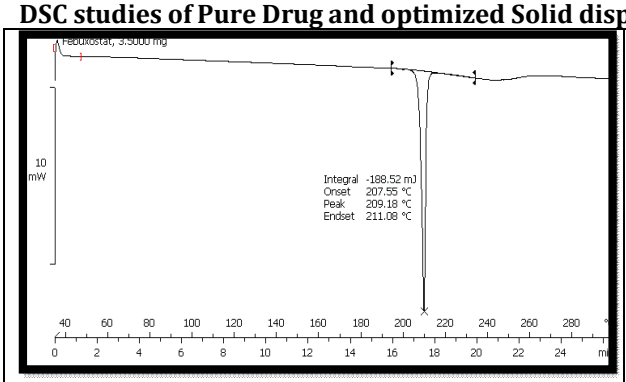


Fig No.1: DSC Thermogram of Febuxostat.

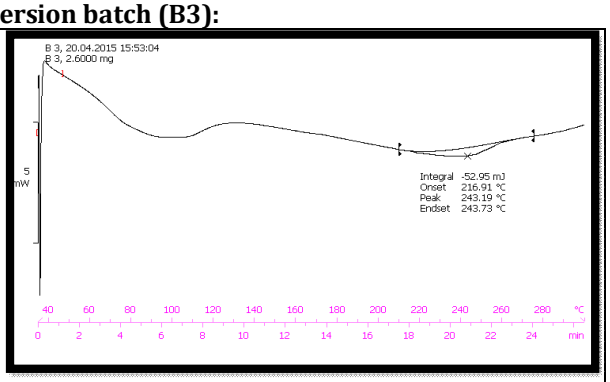
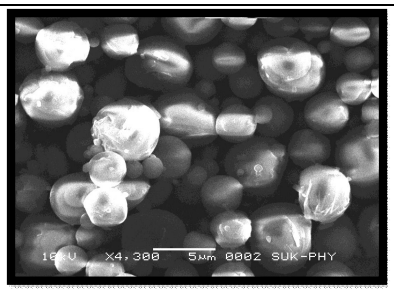
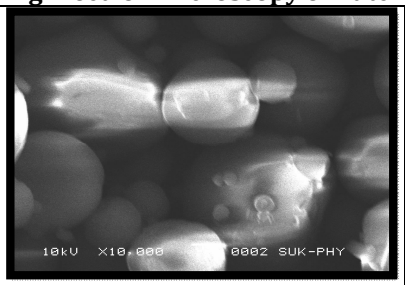


Fig No. 2: DSC Thermogram of Optimized solid dispersion batch.

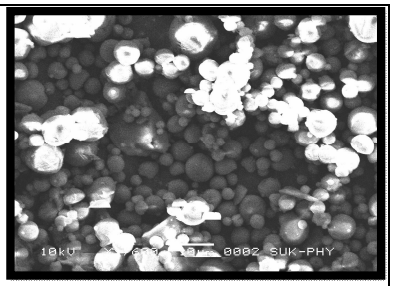
Scanning Electron Microscopy of Batch B3:



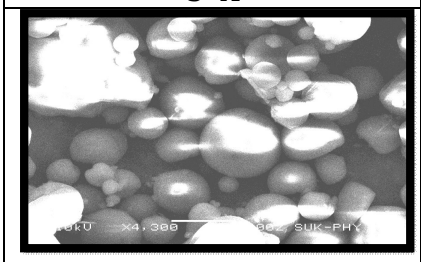
3- A



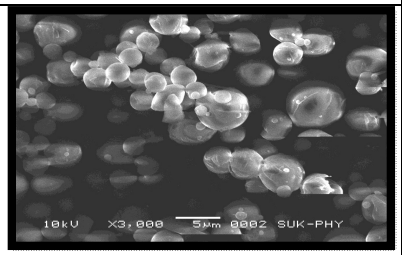
3- B



3- C



3- D



3- E

Fig No. 3(A to E): Images of SEM photomicrographs of optimized batch of prepared solid dispersion.

Data Analyses of Formulations:

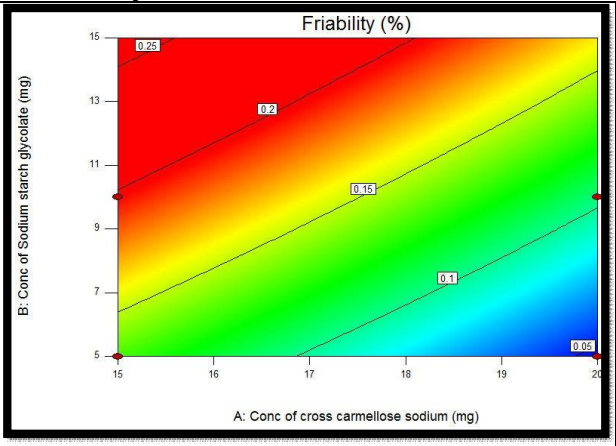


Fig No.4: Contour plot for Friability.

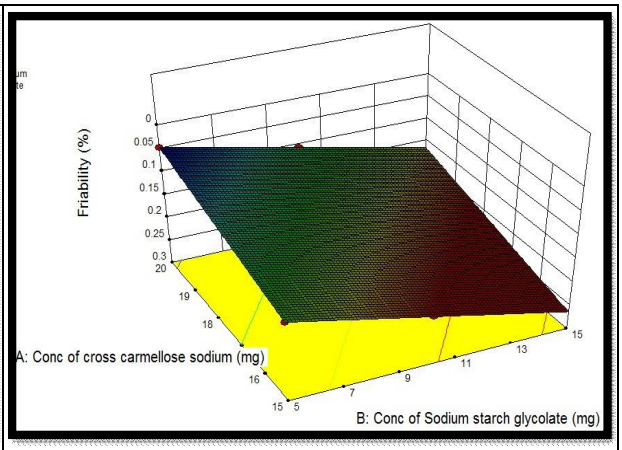


Fig No. 5: Surface plot for Friability.

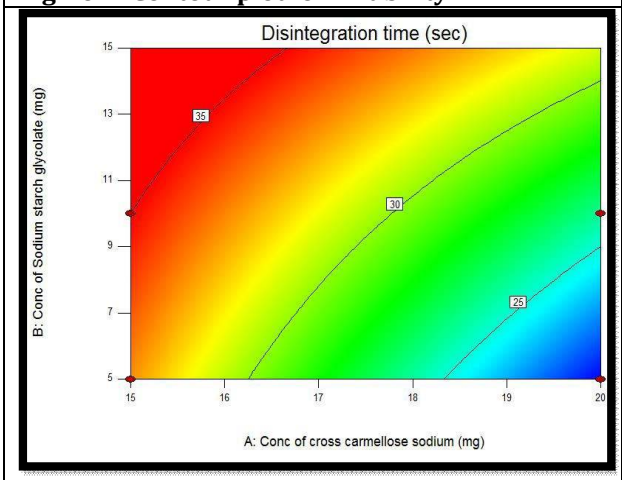


Fig No. 6: Contour plot for Disintegration.

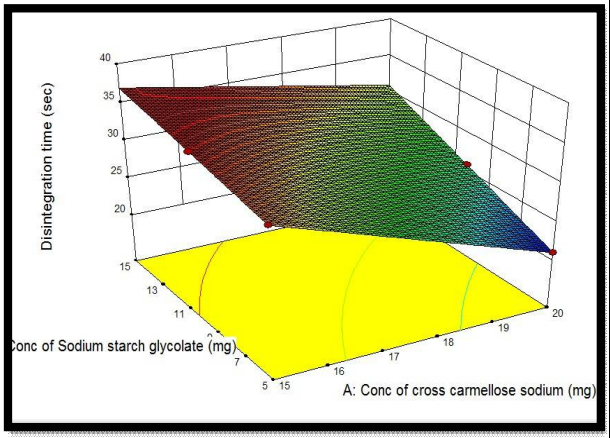


Fig No. 7: Surface plot for Disintegration.

Table No. 8: Values for factorial equation

Response	Factorial Equation.
Friability (%)	$0.15-0.047X_1+0.062X_2-3.500X_1X_2$
Disintegration time (sec)	$30.50-4.50X_1+3.50X_2+1.50X_2X_2$

For response friability (%), negative sign for CCS (X1) and positive sign of SSG (X2) indicates that the friability increases with an increase in the concentration SSG and vice versa. For response disintegration time, the negative sign for CCS (X1) and positive sign of SSG (X2) indicates that disintegration increases, as the amount of SSG increases and CCS decreases.

Response Surface Plot

The response surface model obtained from the regression analysis was used to build up contour and 3-D graphs in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots.

CONCLUSION

This study demonstrated the possibility of improving Febuxostat solubility and dissolution performance by the formulation of solid dispersions by spray drying technique using hydrophilic polymer. The spray drying method of preparing solid dispersions was found to be satisfactory as it produced good product with high drug content. Combination of β-CD and PVP-K30 has given a much higher in the solubility of Febuxostat than is possible with them individually. This may be due to complexation with β-CD and

intermolecular hydrogen bonding PVP-K30 with drug. FTIR study of optimized solid dispersion batches conclude the better hydrogen bonding interaction between drug and polymer has occurred due to spray drying process. Higher dissolution and solubility rate is due to complexation and hydrogen bond. From DSC characterizations it can be concluded that drug might have converted from its crystalline form to amorphous state or molecularly dispersed into polymer matrix during rapid evaporation in spray drying chamber. Comparative in-vitro dissolution studies concluded that faster and rapid dissolution of Febuxostat from optimized batch of tablet than marketed preparation. From Kinetic data of all batches, it is concluded that fast dissolving tablets follows First order as drug release mechanics. From factorial design study, it is concluded that as the concentration of Cross carmellose sodium increases, disintegration time decreases and as the concentration of Sodium starch glycolate increases disintegration time increases.

AUTHOR'S CONTRIBUTIONS:

YLP and MDK: data collection, SRS. : Designing and supervision of experiments, MHP: data analysis and results performed some of the experiments, SDT. : Drafting of manuscript, KMD. : Paper review and improvement. All authors have read and agreed to the published version of the manuscript.

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DATA AVAILABILITY STATEMENT:

Not applicable.

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