Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)

AJPRD

Open Access Available online at http://ajprd.com/index.php Research Article

DEVELOPMENT AND EVALUATION OF DISINTEGRATION CONTROL MATRIX TABLETS OF FEBUXOSTAT BY USING 2^3 FACTORIAL DESIGN

Kanke Pralhad*[1], Sawant Pankaj[1], Md. Rageeb Md. Usman[2], Baviskar Kiran[3]

*[1,3]Dept. of Pharmaceutics, Smt S. S. Patil College of Pharmacy, Chopda, Maharashtra, India
[1]Dept. of PDL, Unichem Lab Pvt. Ltd. Goa
[2] Dept. of Pharmacognosy, Smt. S. S. Patil College of Pharmacy, Chopda, Maharashtra, India

ABSTRACT

Disintegration control matrix tablet (DCMT) is a new approach for poorly water soluble drugs which successfully sustain therelease up to 24hrs by controlling the disintegration rate of tablet. DCMT mainly forms the granules containing drug febuxostat and disintegrant sodium alginate which controls the release of febuxostat by controlling the rate of disintegration in wax coating plays an important role. The sustained release of drug is maintained by increasing the wax coating or decreasing the amount of disintegrant.The release of drug from tablet is uniform throughout till all the drug releases from tablet and it is justified by in-vitro dissolution studies.DCMT increases the solubility of drug and improves the bioavailability without disturbing gastrointestinal transit.

Key Words:-DCMT, Wax, Disintegrating agent, Solid dispersion, Febuxostat.

Article Info: Received 25 July, 2018; **Review Completed** 14 Aug 2018; **Accepted** 18 Aug 2018

Cite this article as:

Kanke Pralhad, Developmen and Evaluation Of Disintegration Control Matrix Tablets Of Febuxostat By Using 2^3 Factorial Design, Asian Journal of Pharmaceutical research and Development.**2018;6 (4): 12-20**

DOI: http://dx.doi.org/10.22270/ajprd.v6.i4.392

***Address for Correspondence**
Pralhad Kanke, Department. of Pharmaceutics, Smt S. S. Patil College of Pharmacy, Chopda, Maharashtra, India

INTRODUCTION

Disintegration control matrix tablet (DCMT):

DCMT is the novel approach employed for sustaining the drug release and increasing the solubility and bioavailability of drug. The drug release is controlled by the penetration of water in the matrix which is the rate determining step for dissolution of the DCMT. It contains water soluble matrix forming polymer HPMC, disintegrating agent sodium alginate, and carnauba wax which is insoluble or hardly soluble in aqueous body fluids and the release of drug is controlled by means of resistance of coating layer or matrix against the diffusion of drug therein[1,2,4]. Febuxostat is poorly water soluble drug belongs to BCS Class-II which is used in the treatment of gout [3]. Poor solubility of drug is an issue in the formulation so it is firstly prepared with the solid dispersion which helps to enhance the solubility of drug upto some extent, the SD is prepared with HPMC and sodium alginate which after SD coated with carnauba wax, Febuxostat is chemically 2- [3- cyano-4- (2- methlypropoxy) phenyl]- 4- methlythiazole- 5 carboxylic acid. It is a non purine selective inhibitor of xanthine oxidase that is indicated for use in the treatment of hyperuricemia and gout [4-7]

MATERIALS AND METHODS

Materials

Febuxostat is provided as a gift sample by Ajanta Pharma Ltd., Aurangabad. The HPMC and magnesium st is provided by Colorcon, mumbai as gift sample.

Remaining excipients are purchased from Dipa chemicals Aurangabad.

Preparation of DCMT

The disintegration controlled matrix tablet of febuxostat can be prepared in the steps as follows:

- Preparation of solid dispersion
- Wax coating of solid dispersion
- Tablet compression

Preparation of solid dispersion

The solid dispersion is prepared by physical mixing of drug and excipients, the accurately weight quantity of febuxostat and HPMC and sodium alginate taken i.e. 40mg ,90mg ,25mg and mixed thoroughly in polybag however the quantity is taken in multiple of ten.

Preparation of wax coated granules

The granules where prepared by hot melt extrusion method in which the carnauba wax is melted and the solid dispersion mixture is incorporated in the melted wax. On molted state the molten mass is pass through sieve 22 to form uniform size granules.

Tablet compression

Finally 500mg tablet were compressed using 8mm in diameter flat punch using Rotary Tablet Compression Machine[7,8]

Analytical method development

Selection of media: phosphate buffer pH 6.8 is selected as media for method development by UV spectroscopy as the drug is found to be stable and soluble in this media.

Preparation of Standard Stock Solution: Standard drug solution of Febuxostat was prepared by dissolving 25 mg in 25 ml of deionized water the resultant solution obtained is 1000µg/ml used as stock solution for further dilutions.

UV Spectra: The UV spectrum of Febuxostat solution (08 µg/ml) exhibited wavelength of absorbance maximum at 315 nm which complies with the reported.[1.5]

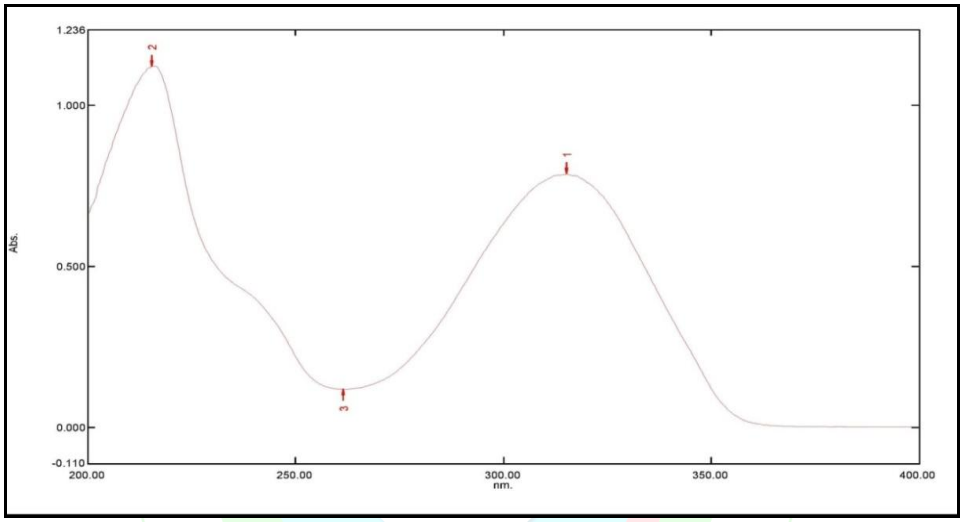

Figure 1: UV Spectrum of Febuxostat

Calibration curve:

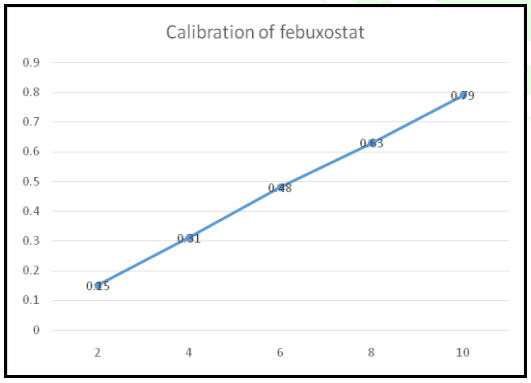

Figure 2: Calibration curve of Febuxostat

Preparation of Standard Dilutions: The serial dilutions from the above stock solution is prepared in the range of 02, 04, 06, 08, 10 µg/ml. The absorption was measured at λ_{max} 315 nm. The data obtained was summarized in table 1

Table 1: Validation Parameters for Febuxostat

Sr no	Parameter		Results
1	Wavelength		315 nm
2	Range (µg/ml)		2-10 (µg/ml)
3	Equation of Linearity		Y=0.07933X-0.00557
4	Correlation coefficient (r^2)		0.99944
5	Accuracy		102.4451
6	Precision	Intraday %RSD	0.332757
		Interday %RSD	0.351395
7	Limit of Detection		0.055693825
8	Limit of Quantification		0.168769167

Fourier Transform Infra-Red Spectra

The FTIR spectrum of Febuxostat was recorded over a range of 4000 cm^{-1} to 400 cm^{-1}. The spectrum obtained

was concordant with the reference as depicted in Figure 2;

Drug Excipient Compatibility Study by FTIR

In all physical mixtures of drug and polymer, there was neither masking of single characteristic peak nor existence of additional peak in the spectra. (Fig 3,4) so we can conclude that drug and polymers are compatible with each other

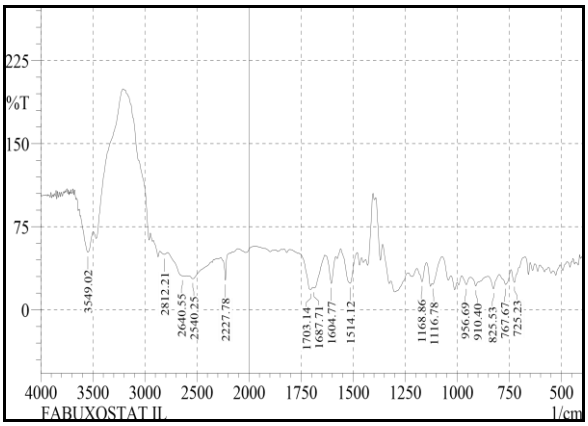

Figure 3: FTIR spectrum of Febuxostat

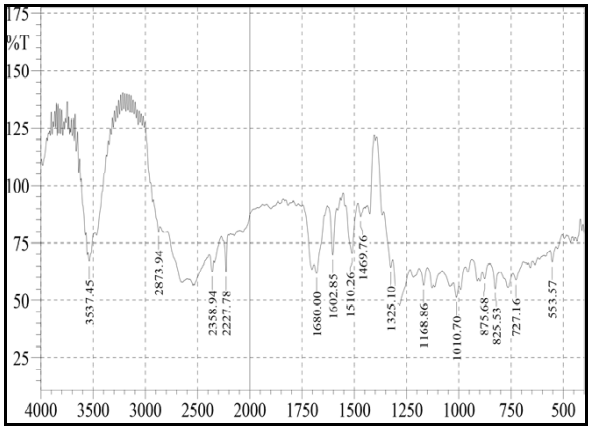

Figure 4: IR Spectrum of Physical Mixture

Evaluation of Flow Properties of Powder Blends of Factorial Batche

The characterization of flow properties of powder blends is important in tablet compression. The powder blends with good flow properties gives uniform die fill and consequently it gives the uniform tablet weight as shown in below table.2

Table 2: Powder Flow properties of factorial batches

Batch	Bulk Density*	Tapped Density*	Carr's Index*	Hausner's Ratio*	Angle of Repose* (^{0})
F1	0.423 ± 0.003	0.512 ± 0.003	17.38 ± 0.68	1.21 ± 0.046	27.12 ± 0.886
F2	0.419 ± 0.003	0.499 ± 0.003	16.32 ± 0.7	1.19 ± 0.02	29.24 ± 0.831
F3	0.437 ± 0.002	0.567 ± 0.001	22.92 ± 0.356	1.24 ± 0.044	25.36 ± 1.333
F4	0.417 ± 0.001	0.494 ± 0.01	16.59 ± 0.668	1.18 ± 0.02	25.12 ± 0.72
F5	0.413 ± 0.003	0.497 ± 0.004	16.9 ± 0.344	1.2 ± 0.079	26.42 ± 0.524
F6	0.42 ± 0.007	0.527 ± 0.001	20.3 ± 0.603	1.25 ± 0.036	28.54 ± 0.813
F7	0.431 ± 0.005	0.521 ± 0.003	17.27 ± 0.882	1.2 ± 0.05	27.18 ± 1.006
F8	0.428 ± 0.002	0.535 ± 0.008	20 ± 0.96	1.25 ± 0.046	29.36 ± 0.584

All values are mean ± SD, * =3

Formulation batches of febuxostat

Table 3: Amount of excipients in 2^3 factorial design (optimized) batches

Batch Code	F1	F2	F3	F4	F5	F6	F7	F8
Febuxostat	40	40	40	40	40	40	40	40
HPMC K100M	90	90	90	102	102	102	90	102
Sodium Alginate	15	15	25	25	15	25	25	15
Carnauba Wax	185	151	185	185	185	151	151	151
Lactose	150	184	140	128	138	162	174	172
Mg. Stearate	20	20	20	20	20	20	20	20
Total Wt.	500	500	500	500	500	500	500	500

Evaluation of Febuxostat DCMT

The tablets from the factorial batches were evaluated for different evaluation parameters of table no.4.

Physical Appearance

The tablets from all factorial batches were light Yellowish, circular. The surface texture was smooth. The thickness of tablets of factorial batches was 3.13 to 3.22 mm and it was found to be within limit of deviation from average value.

Weight Variation

For tablet weighing 500 mg or more, not more than two tablets differ from the average weight by 5% deviation. The percent deviation in weight variation from average value for all formulation of factorial design batches were within limit (Table 4). The weight variation within limits indicates uniformity in tablet compression and consequently content of drug in a unit.

Hardness

The hardness is important characteristics to be evaluated for handling and transportation properties of the tablets. The hardness of tablets was found to be 4-5 Kg/cm^2 which indicate good handling and transportation characteristics.

Friability

The friability is important characteristics to be evaluated for handling and transportation properties of the tablets. The friability of tablets was less than 0.7% which indicates good handling and transportation characteristics.

Drug Content

The drug content of the eight formulations was found to be between 97.22 to 101.89 % (i.e. variation of ±4%). The value ensures good uniformity of the drug content in the tablet.

Thus all the physical parameters of the compressed matrices were found to be practically within control. As shown in the following table 4.

Table 4: Evaluation of Febuxostat DCMT

Batch	Appearance	Weight Variation* mg ± SD	Hardness (Kg/cm^2) ±SD	Friability# %	Thickness (mm) ±SD	Drug content (%mg) ±SD
F1	Yellowish white, circular	500±0.74	4.2±0.28	0.81±0.03	3.20±0.12	99.13± 0.14
F2	Yellowish white, circular	500±0.41	4.7±0.5	0.69±0.07	3.19±0.220	98.03± 1.11
F3	Yellowish white, circular	500±0.97	4.1±0.31	0.82±0.03	3.18±0.03	100.09±0.45
F4	Yellowish white, circular	500±1.24	4.5±0.21	0.52±0.03	3.21±0.13	99.5±0.79
F5	Yellowish white, circular	500±0.47	5.0±0.28	0.60±0.06	3.24±0.11	99.5±0.49
F6	Yellowish white, circular	500±1.24	4.9±0.5	0.62±0.09	3.20±0.12	98.1± 0.49
F7	Yellowish white, circular	500±0.94	4.0±0.28	0.61±0.06	3.18±0.25	97.89± 0.83
F8	Yellowish white, circular	500±0.81	4.6±0.5	0.63±0.02	3.17±0.15	98.22± 0.36

*** n=20, #n=10,All values are mean ± SD**

Disintegration Study

The disintegration study of the optimized F7 batch was studied as the Japanese pharmacopeia. The disintegration test was carried out by a modified disintegration test of Japanese Pharmacopoeia (JP) using the disintegration apparatus listed in JP at a frequency of 30 cycles per minute. One tablet was tested in 900 mL of JP first medium (pH 1.2), which were maintained at 37.5 °C. The tablet was dried at 30 °C for 12 h, and the disintegration ratio (% disintegrated) was calculated by the following equation.

$$\%disintegrated = W_i - W_t / W_i * 100$$

Where, Wt is the weight of tested DCMT sampled at time t and Wi is the initial weight of DCMT.

Before the test was carried out the initial weight were noted down. The tablets were disintegrated for the 2Hrs, 4Hrs, 6Hrs, and 8Hrs for the study of penetration of the dissolution media. The test was carried out in the 0.1 N HCl and pH 6.8 phosphate buffer. After each reading the final weight of the tablet was obtained. Using the initial and final weight of the tablet % disintegration was calculated for the 2Hrs, 4Hrs, 6Hrs and 8Hrs.

Table 5:- % Disintegration of the tablet

DISINTEGRATION STUDY			
Time	Initial weight	Final weight	% Disintegrated
2 Hrs	499	458	08.21
4 Hrs	501	425	15.16
6 Hrs	503	386	23.26
8 Hrs	500	321	35.80
10 Hrs	501	285	43.11

In Vitro Drug Release Studies

The rate of drug dissolution may be directly related to the efficacy of the tablet product, as well as the bioavailability differences between the formulations. This test of dissolution is most of the times useful to specific types of dosage forms such as; sustained release, time dependent, targeted etc. to know the approximate drug release behavior of dosage form in the GIT.

In vitro drug release study was carried out using USP dissolution apparatus I in 0.1N HCl for first 2Hrs and then buffer pH 6.8 for a period of remaining 22 Hrs. However drug is practically insoluble in 0.1N HCL so there were no release and release is checked in pH 6.8 buffer for 24 hr.

Table 6: Percent cumulative drug release of formulation F1 to F8

Time	F1	F2	F3	F4	F5	F6	F7	F8
1	16.47± 0.906	16.53± 0.477	14.69 ± 0.607	15.01 ± 0.779	14.54 ± 0.442	12.05 ± 1.015	15.36 ± 0.947	15.51 ± 0.932
2	**20.91 ± 0.892**	**21.97 ± 0.948**	**19.49 ± 0.835**	**19.73 ± 0.562**	**18.02 ± 0.957**	**16.53 ± 0.671**	**19.10 ± 0.872**	**19.36 ± 0.769**
3	25.55 ± 0.965	25.56 ± 1.521	23.84 ± 0.502	23.63 ± 0.331	21.46 ± 0.608	20.91 ± 0.397	22.67 ± 0.674	23.78 ± 0.492
4	30.94 ± 0.968	32.56 ± 0.311	27.68 ± 1.631	28.49 ± 0.131	25.39 ± 0.154	24.14 ± 0.547	27.82 ± 1.315	27.87 ± 0.695
5	36.50 ± 0.841	38.78 ± 0.924	32.82 ± 0.751	33.21 ± 0.927	29.39 ± 0.599	28.62 ± 0.784	32.58 ± 0.756	31.37 ± 0.549
6	40.76 ±0.915	42.79 ± 1.968	36.25 ± 0.725	37.64 ± 0.656	33.83 ± 0.562	32.50 ± 1.232	35.88 ± 1.110	35.75 ±0.574
7	45.53 ± 0.663	46.88 ± 0.389	40.76 ± 0.335	41.26 ± 1.999	37.50 ± 1.846	36.51 ± 0.973	40.13 ± 0.742	38.50 ± 0.812
8	50.25 ± 0.946	49.39 ± 0.271	44.70 ± 0.978	45.25 ± 0.208	41.19 ± 0.495	40.78 ± 701	43.65 ± 0.778	41.60 ± 0.674
9	52.78 ± 0.294	52.77 ± 0.479	48.38 ± 0.598	47.71 ± 0.584	44.32 ± 0.772	44.88 ± 0.571	46.31 ± 1.543	44.86 ± 0.318
10	56.05 ± 0.976	55.60 ± 0.662	50.25 ± 0.646	52.21 ± 0.715	49.81 ± 0.967	48.66 ± 0.721	50.05 ± 1.238	48.61 ±0.994
11	59.71 ± 0.627	59.71 ± 0.842	55.87 ± 0.699	57.00 ± 0.677	51.12 ± 0.733	53.58 ± 0.671	55.34 ± 0.671	52.95 ± 0.741
12	**63.01 ± 0.947**	**61.67 ± 0.437**	**58.93 ± 0.674**	**57.92 ± 0.688**	**52.92 ± 0.977**	**57.23 ± 0.699**	**59.80 ± 0.794**	**54.67 ± 0.554**
24	**92.91 ± 0.991**	**92.91 ± 0.786**	**93.30 ± 0.594**	**98.12 ± 0.740**	**96.75 ± 0.457**	**98.70 ± 0.774**	**93.69 ± 0.795**	**95.17 ± 1.745**

All values are mean ± SD, n=3

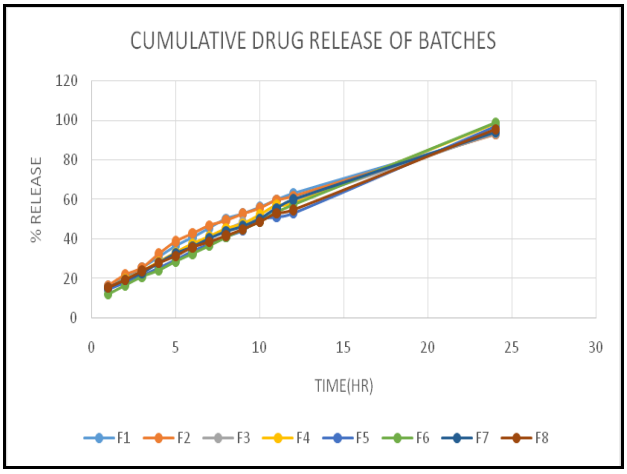

Figure 5: Percent cumulative drug release of formulation F1 to F8

From the release pattern of formulations containing HPMC and Carnauba wax it could be concluded that, the combination of these polymers worked well. HPMC K 100M reported gelling agent as well as sustained / controlled release agent, for decreased initial burst release wax is used for avoiding the penetration of water and sodium alginate as disintegrating agent. The 2^3 factorial designed batches were formulated and in vitro drug release was studied. The formulation batches from F1 to F8 is evaluated for the in-vitro drug release and found that the batch F3-F8 gives optimum release and batch F7 is selected for optimization with lower polymer content.

Kinetics Of Drug Release

Under certain conditions it can be used as a surrogate for the assessment of bioequivalence. Several theories or a kinetic model describes drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is a function of t (time) related to the amount of the drug dissolved from the pharmaceutical dosage system.The quantitative interpretation of the values obtained in dissolution assay is facilitated by the usage of generic equation that mathematically translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms.[9,10]

In most cases the theoretical concept does not exist and some empirical equations have proved to be most accurate or appropriate. The kind of drug, its polymorphic form, crystallinity, particle size, solubility and amount in that pharmaceutical dosage form can influence the release kinetics.

In the present study, the drug release was analyzed by DD Solver software to study the kinetics of drug release mechanism. The results showed that the factorial design batches followed Korsemeyer Peppas model. The R value of Korsemeyer Peppas was found close to one as shown in Table 7. The rate of drug release from the matrix tablet is rapid initially followed by progressively slow drug release through the matrix. The slow release of the drug from the matrix may be due to the carnauba wax which is coated over the granules. [10,11]

Table 7: Model fitting data of DCMT of Febuxostat

Batch code	R2				
	Zero	First	Korsemeyer Peppas	Higuchi	Hixson
F1	0.7232	0.9168	0.9606	0.9372	0.9073
F2	0.9000	0.9333	0.9738	0.8681	0.9447
F3	0.6406	0.8986	0.9474	0.9547	0.8821
F4	0.6488	0.8986	0.9856	0.9429	0.8694
F5	0.5539	0.9393	0.9710	0.9429	0.9069
F6	0.7380	0.9963	0.9835	0.9446	0.9205
F7	0.8025	0.9134	0.9923	0.9127	0.9175
F8	0.8062	0.8995	0.9774	0.8988	0.9040

The % drug release of the optimized batch F7 follows the Korsemeyer Peppas kinetic model the graph as shown below:

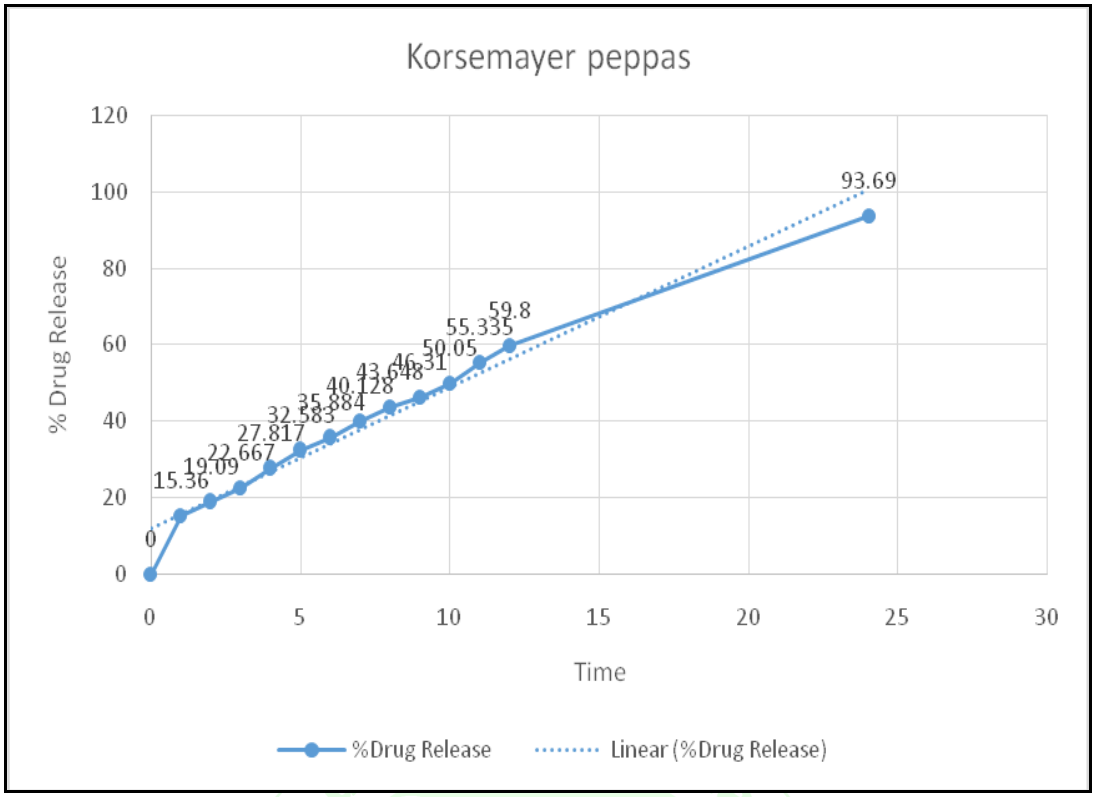

Figure 6: %Drug Release profile of the Optimized Batch F7

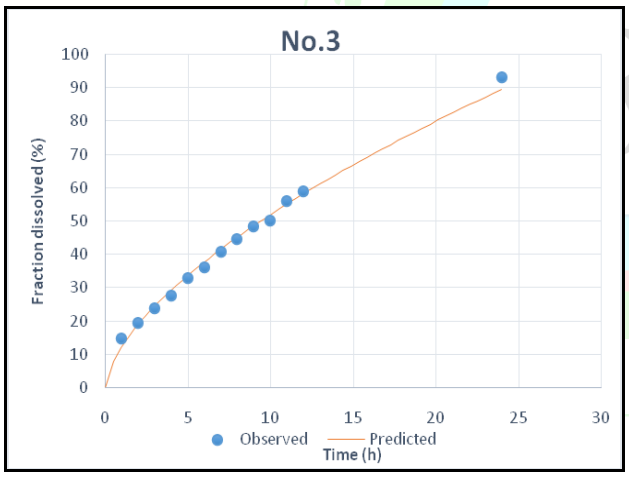

Figure 7: F7 Korsemeyer Peppas Model

Statistical Analysis By Design Expert Software

Experimental design can be defined as the strategy for setting up experiments in such a manner that the information required is obtained as efficiently and precisely as possible. The factorial design can serve as an essential tool to understand the complexity of mechanisms of pharmaceutical formulations. The polynomial equations are used to evaluate the statistical significance of the obtained responses. The 2^3 full factorial designs were selected to study the effect of independent variables Sodium Alginate (X1), HPMC K 100M (X2), and Carnauba wax (X3) on dependent variables Q_2, Q_{12}, Q_{24}.

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

The Q_2, Q_{12}, Q_{24} for batches F1-F8 showed a wide variation. The data clearly indicates that the Q_2, Q_{12}, Q_{24} values are strongly dependent on the selected independent variables. The fitted regression equations relating the responses Q_2, Q_{12}, Q_{24} are shown in the equations, respectively.

The equation conveyed the basis to study the effects of variables. The regression coefficient values estimates the model fitting. The r^2 was high indicating the adequate fitting of the linear model.

The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e. positive or negative. The coefficient of variable X1, X2, X3 i.e. HMPC K100 M,Sodium alginate, and Carnauba wax in case of responses Q_2, Q_{12} and Q_{24} indicates that as the HMPC K100 M,Sodium alginate, and Carnauba wax concentration was increased, the Q_2, Q_{12} and Q_{24} value decreased. [12,13]

Response Surface Plot

The linear model obtained from the regression analysis used to build a 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. The response surface plot were generated using Design Expert 7.1.6 software presented in Fig.8, 9, 10 to observe the effects of independent variables on the response studied such as Q_2, Q_{12}, Q_{24}.

Graphical presentation of the data helped to show the relationship between the response and the independent variables. The information given by graph was similar to that of mathematical equations obtained from statistical analysis. The response surface plots showed that various combinations of independent variables X_1, X2 and X3 may satisfy any specific requirement (i.e. maximum drug release upto 24 Hrs and minimum burst release in 3 Hrs) while taking into consideration of various factors involved in dosage form[14,15]

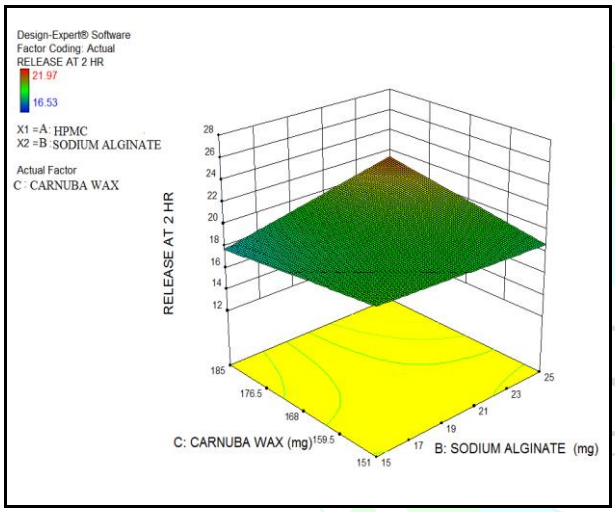

Figure 8: Response surface plot for Q2

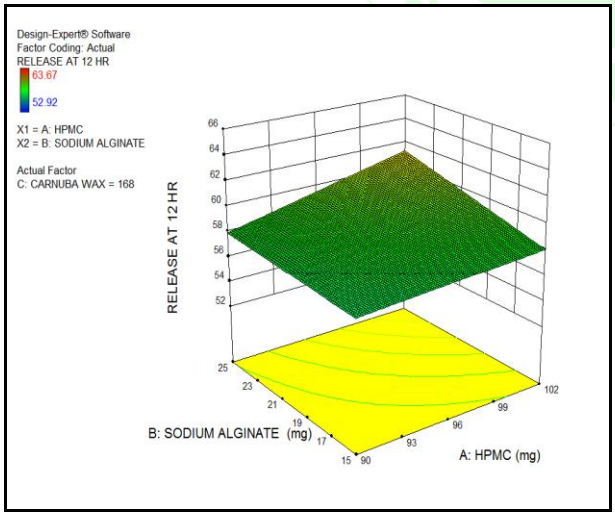

Figure 9: **Response surface plot for Q12**

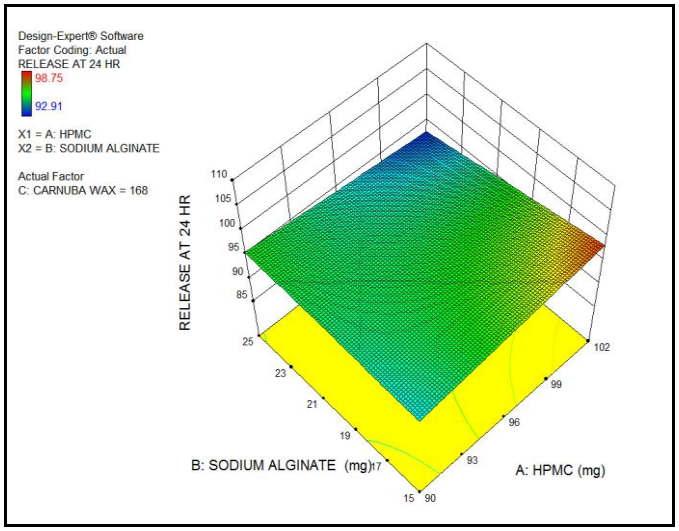

Figure 10: Response surface plot for Q24

CONCLUSION

The popularity of DCMTis tremendously increasing since the last decade. The number of drugs that are being formulated into DCMT is also increasing with a higher pace. DCMT is sustained release formulation that releases the drug in zero order kinetics with increase in solubility and bioavailability of poorly water soluble drugs. DCMT achieves the complete absorption of drugs without disturbing the gastrointestinal transit as in case of geriatrics patients. This is completely new approach for poorly water soluble drug as sustain release formulation which sustains the drug upto 24hrs.Drugs that are photo unstable are good candidates for formulation into DCMT. The potential for such dosage forms is promising and has a strong market acceptance.

ACKNOWLDGEMENT

The authors express gratitude to Ajanta Pharma Ltd., for providing gift sample of Febuxostat Aurangabad (India), Wockhardt Research Center, Aurangabad (India) and also Colorcon, mumbai for providing gift sample of various polymer and Govt. college of pharmacy, Aurangabad for providing various instrument for performing my research work.

REFERENCES

1. *Patent: Toshinobo U, Kiyohide H, Fujisava pharmaceutical Co.Ltd. Sustained release tablet EP 0168044 B1.*
2. *U. Deokate, J.Wavhale, Disintegration control matrix tablet: A review, Int. J. of Pharm. Res. Scholars, 2015, l-4 (2),411-416.*
3. *Angelo L G, Kenneth G Saag, Febuxostat: The Evidence For Its Use In The Treatment Of Hyperuricemia And Gout, Core evidence, 2009, 4, 25 – 36.*
4. *Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ibuki R, et al. Development Of Novel Sustained-Release System, Disintegration-Controlled Matrix Tablet (Dcmt) With Solid Dispersion Granules Of Nilvadipine (II): In vivo evaluation.,J Control Release,2006,112, 51–56.*
5. *CH Harmonised Tripartite Guideline : Validation of analytical procedures., 2005, 1-13.*

6. *Silverstein R.M, Webster F.X, Spectroscopic Identification of Organic Compound,VII edition, John Wiley & Sons,New Jersy, 2005,76-81.*
7. *Skoog DA, Holler, F. J. and Timothy, A. N.,Principles of Instrumental Analysis.,V Edi.,Saunders College Publishing. Harcourt Brace College, Publishers.Sweden, 2005, 74-95.*
8. *Ministry of Health andWelfare Ministerial Notification No. 104 1994,Japanese Pharmacopoeia, PMDA Publishers, Japan,2011,1–1654.*
9. *Dash S, Murthy PN, Nath L, Chowdhury P., Kinetic modeling on drug release from controlled drug delivery systems., Acta Pol Pharm, 2010, 67(3), 217–22.*
10. *Kim H, Fassihi R. Application of binary polymer system in drug release rate modulation. 2. Influence of formulation variables and hydrodynamic conditions on release kinetics. J Pharm Sci 1997;86:323*
11. *Bhargava. Oral sustained release dosage form: Opportunity to prolong the release of drugs. Int J Adv Res Pharm Biosci 2013;3:7–14.*
12. *Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ibuki R, et al. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine (II): In vivo evaluation. J Control Release 2006;112:51–6*
13. *Rowe R, Sheskey P OS, editor. Handbook of Pharmaceutical Excipients. Fifth Edit. Pharmaceutical Press; 2006*
14. *Arjun S, Ritika S, Faraz J. Sustained Release Drug Delivery System : a Review. Int Res J Pharm 2012;3:21–4*
15. *Rathore AS, Jat RC, Sharma N, Tiwari R, Ram S, Of C, et al. An Overview : Matrix Tablet As Controlled Drug Delivery System. Int J Res Dev Pharm Life Sci 2013;2:482–92*
16. *Sciences H, Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm 2010;67:217–23.*