

Fabrication and *in vitro* Evaluation of Allopurinol Fast Dissolving Tablets Using Croscarmellose Sodium, Sodium Starch Glycolate and Crospovidone as Superdisintegrants

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ABSTRACT: The main objective of the study was to formulate fast dissolving tablets of allopurinol to achieve better dissolution rate and further improving the bioavailability to provide a quick onset of action. Nine formulations of fast dissolving tablets of allopurinol were prepared by direct compression technique using croscarmellose sodium (Group A), sodium starch glycolate (Group B) and crospovidone (Group C) as superdisintegrants in different concentrations. All formulations showed satisfactory mechanical strength, uniform weight & drug content, and lesser wetting time & dispersion time. *In vitro* disintegration time, dispersion time, wetting time of all nine formulations were obtained from 11.67±0.88 to 40.67±1.20 seconds, 32.67±0.88 to 65.33±1.45 seconds and 21.67±0.33 to 50.00±1.53 seconds respectively. Amongst all formulations, formulation F-9 prepared by 4.17% crospovidone showed least disintegrating time of 11.67±0.88 seconds along with rapid drug release (98.88% within 15 minutes).

Key words: Fast dissolving tablets, Allopurinol, Superdisintegrants, Disintegration time.

INTRODUCTION

Oral route represents the most preferred way of administration of most therapeutic agents used to produce systemic effects, owing to its numerous advantages and high patient compliance when compared to many other routes.¹ However, many patient groups such as the elderly, children, and patients who are mentally retarded, non-cooperative, nauseated, or on reduced liquid intake/diets have difficulties in swallowing tablet and hard gelatin capsule dosage forms. To overcome these limitations, pharmaceutical scientists have developed innovative drug delivery systems known as Fast Dissolving/Disintegrating Tablets (FDTs) which disintegrate rapidly in saliva, usually in a matter of seconds,

without the need of water or chewing.² The medication can then be absorbed partially or entirely into the systemic circulation from vascular smooth muscle cells than on cardiac muscle blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract.³⁻⁵

Gout is a metabolic disorder which is characterized by hyperuricemia and resultant deposition of monosodium urate in the tissues, particularly the joints and kidneys.^{6,7} Allopurinol, the first strong anti-gout agent, is known as 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one. It is rapidly absorbed from upper GIT after oral administration with a bioavailability varying from 67% to 90% and volume of distribution of about 1.6 L/kg. Plasma half-life is about 2 hr for allopurinol and 18-30 hr for

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oxypurinol (the active metabolite of allopurinol) after an oral dose.

In this study, an attempt has been made to fabricate fast dissolving tablet formulations of allopurinol by direct compression method using croscarmellose sodium, sodium starch glycolate and crospovidone as superdisintegrants. This research was also focused to evaluate the *in vitro* release characteristics, dissolution kinetics and release mechanism of the formulated tablets as well as to evaluate the influence of superdisintegrants level on the release rate.

MATERIALS AND METHODS

Drugs and chemicals. Allopurinol powder, microcrystalline cellulose PH102, lactose, saccharin sodium, talc and magnesium stearate were kindly provided by Incepta Pharmaceuticals Limited (Savar, Dhaka, Bangladesh) as gift samples. Croscarmellose sodium, sodium starch glycolate and crospovidone were obtained from Globe Pharmaceuticals Limited (Begumgonj, Noakhali, Bangladesh). Hydrochloric acid (Merck, Germany, 0.01N) was used as dissolution medium. All solvents and chemicals used were of analytical grade.

Preparation of allopurinol FDTs. The critical parameters to formulate a FDT are the selection of superdisintegrant and optimization of its concentration. Superdisintegrants like croscarmellose sodium, sodium starchglycolate and crospovidone were used in different ratios (2.5, 3.33 and 4.16%, respectively). Tablets each containing 100 mg of allopurinol were prepared as per composition given in Table 1.

Evaluation of powder blends. The powder blend was evaluated for flow properties as follows and presented in Table 2.

Bulk density.^{8,9} Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (W) was determined. The bulk density (ρ_b) was calculated using the formula: $\rho_b = W/V_b$

Tapped density.¹⁰ A measuring cylinder containing a known mass of blend (W) was tapped

for a fixed time (100 tapping). The minimum volume (V_t) occupied in the cylinder and weight of the blend (W) was measured. The tapped density (ρ_t) was calculated using the following formula: $\rho_t = W/ V_t$

Compressibility index.¹¹ The simplest method of measurement of free flow of powder is compressibility, given by compressibility index (I), which is calculated as follows: $CI = \{(\rho_t - \rho_b) / \rho_t\} \times 100$

Hausner's ratio.¹² This is an indirect index of ease of powder flow. It is calculated by the following formula: Hausner's Ratio = ρ_t/ρ_b

Angle of repose.¹³ Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated using the following formula: $\theta = \tan^{-1}(h/r)$

Evaluation of tablets. The tablets were evaluated for the following parameters:

Thickness and diameter test.⁹ Five tablets were taken and their thickness and diameter was measured using Vernier callipers. Five trials for each formulation were made and are expressed in mm (table3).

Weight variation.¹⁴ Ten tablets from each formulation were randomly selected and average weight was determined (Table3).

$$\% \text{ weight variation} = \{(\text{Average weight} - \text{Individual weight}) / \text{Average weight}\} \times 100$$

Friability test.¹⁴ Three tablets were initially weighed and placed to a friabilator, operated at 25 rpm for 4 min or run upto 100 revolutions and dropping the tablets at a height of 6 inches in each revolution. Tablets were de-dusted using a soft muslin cloth, re-weighed and the loss in weight (friability) was determined as follows:

$$\% \text{ Friability} = \{(\text{initial weight} - \text{final weight}) / (\text{initial weight})\} \times 100$$

Hardness test.¹⁵ Three tablets were randomly picked and hardness of tablets was determined by

using a hand operated hardness test apparatus (Electrolab EH-01P). It is expressed in Kgf (Table 3).

***In vitro* disintegration time.**¹⁶ The disintegration time for all formulations was determined by using disintegration test apparatus containing 900 ml of 0.01N HCl solution (Table 3).

***In vitro* dispersion time.**¹⁷ One tablet was placed in a beaker containing 10 ml of 0.01N HCl solution at $37 \pm 0.5^\circ\text{C}$ and the time in seconds required to complete dispersion was determined. Three trials for each formulation were performed (Table3).

Table 1. Proposed formulations for allopurinol fast dissolving tablets.

Ingredients (mg)	Group A			Group B			Group C		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Allopurinol	100	100	100	100	100	100	100	100	100
Croscarmellose sodium	6	8	10	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	6	8	10	-	-	-
Crospovidone	-	-	-	-	-	-	6	8	10
Microcrystalline cellulose PH102	60	60	60	60	60	60	60	60	60
Lactose	64	62	60	64	62	60	64	62	60
Saccharin Sodium	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Total weight (mg)	240	240	240	240	240	240	240	240	240

Table 2. Granule properties of proposed formulations of allopurinol FDTs.

Formulation code	Bulk density (gm/ml)	Tap density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose
Group A	F-1	0.513	0.719	28.651	42.34°
	F-2	0.493	0.702	29.772	42.60°
	F-3	0.499	0.712	29.916	43.67°
Group B	F-4	0.518	0.740	30.000	41.47°
	F-5	0.531	0.752	29.388	42.93°
	F-6	0.511	0.739	30.853	42.98°
Group C	F-7	0.506	0.692	26.879	43.99°
	F-8	0.490	0.675	27.407	44.34°
	F-9	0.489	0.670	27.015	44.36°

Table 3. Tablet properties of the different formulations of allopurinol FDTs.

Code	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Thickness* (mm)	3.15±0.02	3.19±0.02	3.15±0.02	3.11±0.03	3.17±0.03	3.15±0.04	3.18±0.03	3.13±0.02	3.14±0.02
Diameter* (mm)	8±0	8±0	8±0	8±0	8±0	8±0	8±0	8±0	8±0
Weight variation* (%)	0.26±0.09	0.35±0.09	0.37±0.14	0.37±0.09	0.45±0.10	0.43±0.15	0.39±0.14	0.51±0.08	0.41±0.11
Hardness** (Kgf)	3.20±0.05	3.11±0.02	3.01±0.04	3.04±0.05	3.15±0.06	2.97±0.05	3.04±0.04	3.19±0.06	3.10±0.04
Friability** (%)	0.56±0.02	0.62±0.02	0.73±0.01	0.53±0.01	0.45±0.03	0.69±0.01	0.61±0.01	0.41±0.01	0.48±0.01
<i>In vitro</i> disintegration time** (sec)	34.67±1.20	27.67±1.45	19.00±0.58	40.67±1.20	25.00±1.53	18.00±1.00	19.33±0.67	15.33±1.45	11.67±0.88
<i>In vitro</i> dispersion time** (sec)	61.33±0.88	54.00±1.15	48.67±1.33	65.33±1.45	60.00±1.53	50.67±0.67	53.33±1.33	44.00±0.58	32.67±0.88
Wetting time** (sec)	45.67±1.20	36.33±0.88	28.33±1.33	50.00±1.53	45.33±0.67	34.33±1.20	37.33±0.88	27.67±1.20	21.67±0.33
Water absorption Ratio** (%)	99.11 ± 0.24	105.92 ± 0.58	121.20 ± 0.20	95.78 ± 0.41	101.16 ± 0.68	111.91 ± 0.42	103.05 ± 0.38	116.67 ± 0.36	127.78 ± 0.21
Drug content** (%)	98.65 ± 0.74	98.97 ± 0.75	100.24 ± 1.10	98.04 ± 0.80	100.89 ± 1.13	99.60 ± 1.32	98.96 ± 0.46	100.25 ± 0.48	100.97 ± 1.16

All values are expressed as Mean ± SEM; * and ** indicates n=5 and n=3 respectively.

Wetting time.¹⁸ Three trials for each formulation were performed (Table3).

Water absorption ratio.¹⁹ Water absorption ratio (R) was determined by using the following equation-

$$R = \{(W_a - W_b)/W_a\} \times 100$$

Where, W_a = weight of tablet after water absorption and W_b = weight of tablet before water absorption (Table 3).

Drug content.²⁰ The percentage of drug content by the following equation for five tablets:

Percent drug content =

$$\frac{A_{\text{spl}} \times W_{\text{std}} \times \text{Average Weight} \times P_{\text{std}}}{A_{\text{std}} \times W_{\text{spl}} \times \text{Label Claimed Value}}$$

Where, A_{spl} = absorbance of sample, W_{std} = weight of standard, P_{std} = potency of standard (99.003%), A_{std} = absorbance of standard and W_{spl} = weight of sample.

In vitro dissolution study. The release rate of allopurinol from fast dissolving tablets was determined using the USP Type II (Rotating paddle method) dissolution test apparatus. It was performed using 900 ml of 0.01 N HCl as dissolution medium (according to USP), at $37 \pm 0.5^\circ\text{C}$ and 75 rpm. A sample solution (5 ml) was withdrawn from the dissolution apparatus at predetermined time intervals of 0.5, 2, 4, 6, 8, 10, 12 and 15 minutes. The same volume of dissolution medium is replaced to maintain sink condition. Samples withdrawn were filtered through Whatmann filter paper (no.41) and suitably diluted with 0.01N HCl. Absorbance of these solutions was measured at 250 nm using a UV-1800 SHIMADZU UV spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve. Dissolution rate was studied for all formulations.

RESULTS AND DISCUSSION

Nine formulations of fast dissolving tablets of allopurinol were prepared with varying concentration

of croscarmellose sodium, sodium starch glycolate and crospovidone. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained in table2. The results of loose bulk density and tapped bulk density ranged from 0.489 to 0.531 and 0.670 to 0.752, respectively. Using above two density data, compressibility index and Hausner's ratio were calculated. Compressibility index of the prepared blends falls in the range of 26.879 to 30.853% and this is also supported by Hausner's values which were in the range of 1.368 to 1.446.

The mean thickness and diameter was ($n = 5$) almost uniform in all the formulations and values ranged from 3.11 ± 0.03 to 3.19 ± 0.02 mm and 8 ± 0 , respectively. The standard error mean values indicated that all formulations were within the range. Table 3 shows that all the formulated tablets exhibited low weight variation that differed between 0.26 ± 0.09 to $0.51 \pm 0.08\%$ from different batches with acceptable limit as per pharmaceutical specifications. The hardness was found in the range of 2.97 ± 0.05 to 3.20 ± 0.05 kgf. The loss in total weight of the tablets due to friability was between 0.41 ± 0.01 to $0.73 \pm 0.01\%$ which was absolutely below 1% indicating a good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling.

The results of *in vitro* disintegration were within the specified limit and comply with the criteria for fast dissolving tablets, the value were with 11.67 ± 0.88 to 40.67 ± 1.20 seconds. Effect of concentration of superdisintegrants on disintegration time is shown in figure 1. It revealed that disintegration time increased with increase in the concentration of superdisintegrants. The *in vitro* dispersion time is measured by the time taken to undergo uniform dispersion. Rapid dispersion was observed in the range of 32.67 ± 0.88 to 65.33 ± 1.45 seconds. Wetting time is closely related to the inner structure of the tablet which showed that wetting process was very rapid (21.67 ± 0.33 to 50.00 ± 1.53 seconds) in almost all formulations. The order of enhancement of the disintegration, dispersion and wetting time with

various superdisinte grants found to be sodium starch glycolate > croscarmellose sodium > crospovidone.

Water absorption ratio of all formulations ranged from 95.78±0.41 to 121.20±0.20 sec.

Table 4. Percent drug release of different batches of allopurinol FDTs.

Time (min)	Percent drug release								
	Group A			Group B			Group C		
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
0.5	22.07	26.14	31.39	24.21	26.68	30.54	27.96	31.5	36.75
2	45.44	63.79	67.25	44.17	53.61	57.71	56.41	60.6	67.38
4	66.16	73.46	79.3	62.74	74.37	80.53	68.93	74.01	82.86
6	73.49	87.69	85.84	72.3	78.53	90.29	77.35	82.56	90.5
8	80.75	90.31	87.71	77.73	87.43	91.43	82.38	83.98	93.78
10	83.01	91.88	91.51	82.55	90.8	93.22	84.33	88.51	96.01
12	85.29	93.34	94.04	84.61	92.37	94.79	87.36	90.06	97.6
15	90.25	95.67	98.08	90.21	94.37	97.24	91.05	95.69	98.88

Table 5. *In vitro* drug release kinetics for proposed allopurinol FDTs.

Formulation code	Zero order regression co-efficient (R ²)	1 st order regression co-efficient (R ²)	Higuchi regression co-efficient (R ²)	Korsmeyer-Peppas regression co-efficient (R ²)	Hixson-Crowell regression co-efficient (R ²)
Group A	F-1	0.772	0.951	0.949	0.490
	F-2	0.678	0.933	0.892	0.437
	F-3	0.661	0.956	0.881	0.413
Group B	F-4	0.795	0.968	0.962	0.491
	F-5	0.731	0.955	0.928	0.459
	F-6	0.676	0.939	0.893	0.431
Group C	F-7	0.715	0.937	0.919	0.439
	F-8	0.695	0.951	0.905	0.424
	F-9	0.642	0.981	0.871	0.399

Table 6. *In vitro* drug release mechanism for proposed formulations of allopurinol FDTs using Korsmeyer-Peppas model.

Formulation code	Diffusion exponent (n)	Release type
Group A	F-1	Fickian
	F-2	Fickian
	F-3	Fickian
Group B	F-4	Fickian
	F-5	Fickian
	F-6	Fickian
Group C	F-7	Fickian
	F-8	Fickian
	F-9	Fickian

Determination of release mechanism from multiple coefficients. The release kinetics parameters of all formulations are presented in table 5. Based on highest regression co-efficient value (R²) the best-fit model for all nine formulations seemed following first-order model. When the data were plotted according to a first-order equation, the

formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8 and F-9 showed a fair linearity, with regression co-efficient values of 0.951, 0.933, 0.956, 0.968, 0.955, 0.939, 0.937, 0.951 and 0.981, respectively.

The dissolution data was also fitted to the well-known exponential equation (Korsmeyer-Peppas

equation²¹), which is often used to describe the drug release mechanism:

$$M_t / M_\infty = kt^n$$

Where M_t/M_∞ is fraction of drug released, k is kinetic constant, t is release time and n is the diffusional exponent for drug release which gives an indication of the release mechanism. As indicated in

table-6, the n values ranging from 0.289 to 0.416 indicated that the drug release for all the formulations was found to follow Fickian's release. This value ($n \leq 0.45$) indicates the diffusion mechanism and suggested that the drug release was controlled by only one process.

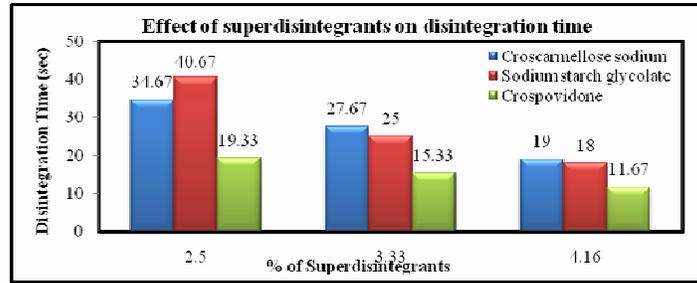


Figure 1. Effect of concentration of superdisintegrants on disintegration time.

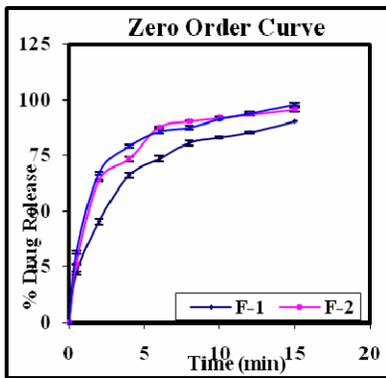


Figure 2. Zero order release model of allopurinol FDTs of group A formulations containing croscarmellose sodium (F-1, F-2 and F-3).

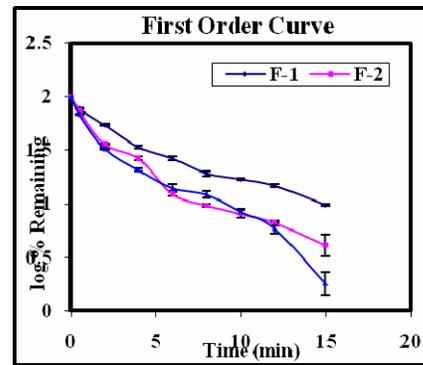


Figure 3. First order release model of allopurinol FDTs of group A formulations containing croscarmellose sodium (F-1, F-2 and F-3).

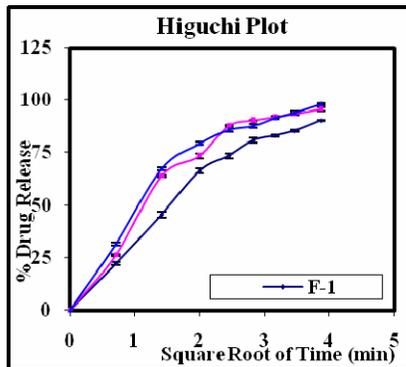


Figure 4. Higuchi release model of allopurinol FDTs of Group A formulations containing croscarmellose sodium (F-1, F-2 and F-3).

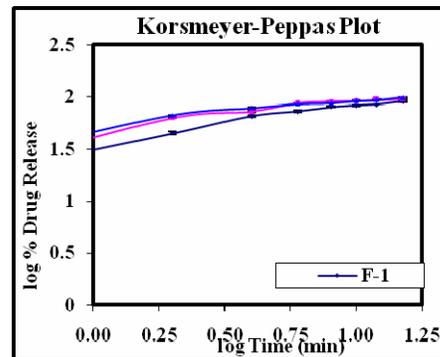


Figure 5. Korsmeyer-Peppas release model of allopurinol FDTs of Group A formulations containing croscarmellose sodium (F-1, F-2 and F-3).

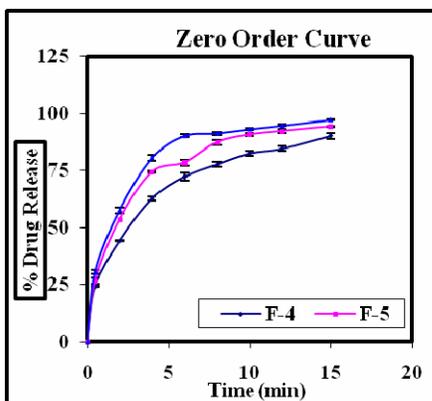


Figure 6. Zero order release model of allopurinol FDTs of Group B formulations containing sodium starch glycolate (F-4, F-5 and F-6).

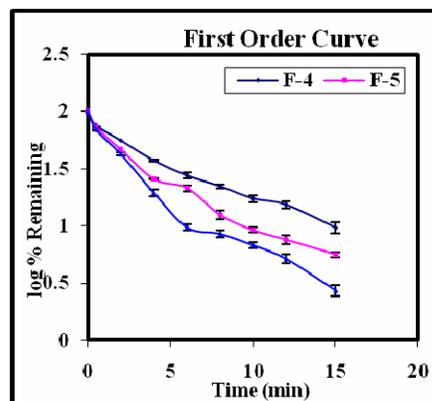


Figure 7. First order release model of allopurinol FDTs of Group B formulations containing sodium starch glycolate (F-4, F-5 and F-6).

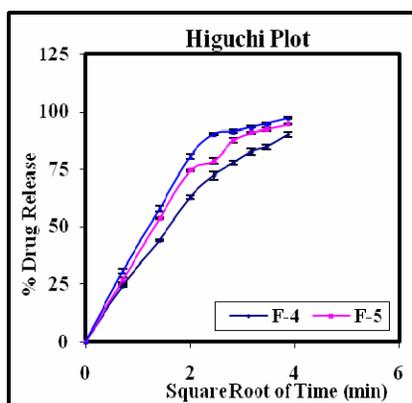


Figure 8. Higuchi release model of allopurinol FDTs of Group B formulations containing sodium starch glycolate (F-4, F-5 and F-6).

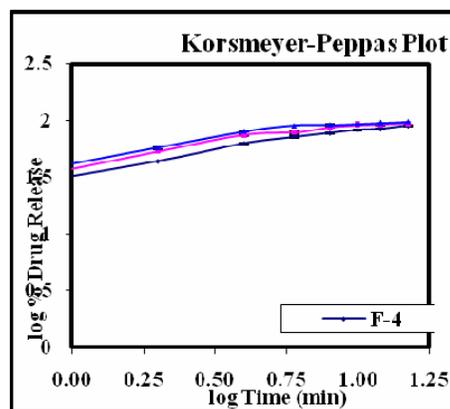


Figure 9. Korsmeyer-Peppas release model of allopurinol FDTs of Group B formulations containing sodium starch glycolate (F-4, F-5 and F-6).

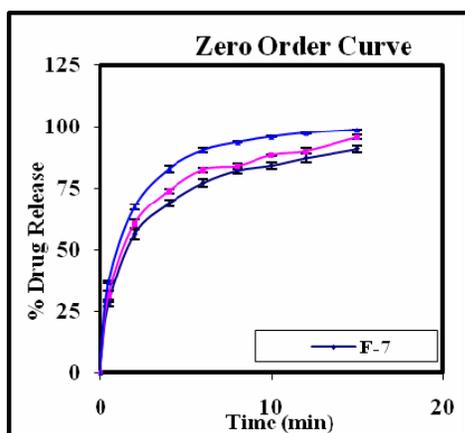


Figure 10. Zero order release model of allopurinol FDTs of Group C formulations containing crospovidone (F-7, F-8 and F-9).

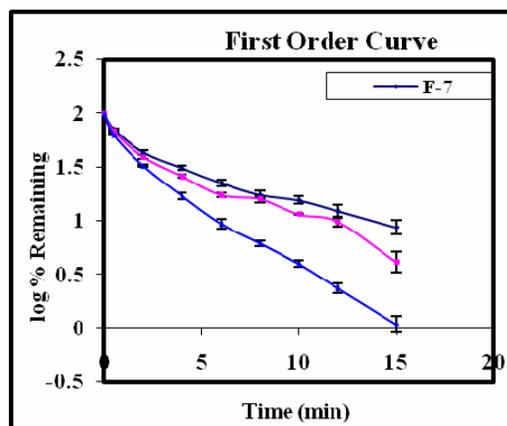


Figure 11. First order release model of allopurinol FDTs of Group C formulations containing crospovidone (F-7, F-8 and F-9).

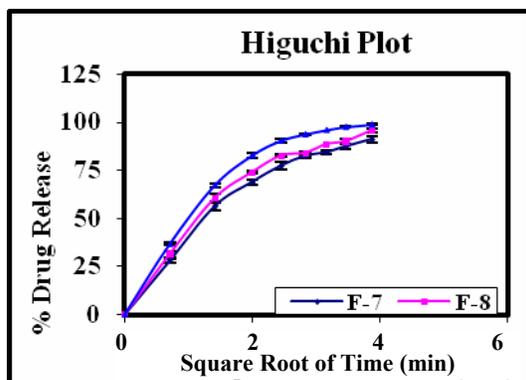


Figure 12. Higuchi release model of allopurinol FDTs of Group C formulations containing crospovidone (F-7, F-8 and F-9).

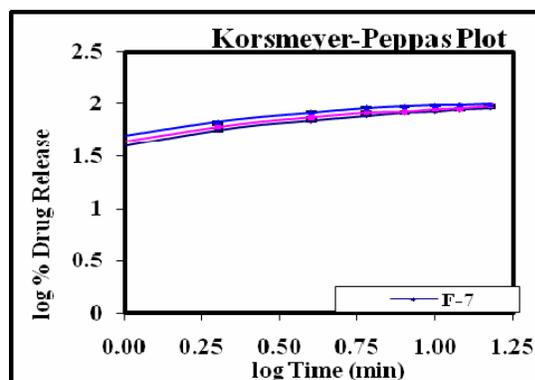


Figure 13. Korsmeyer-Peppas release model of allopurinol FDTs of Group C formulations containing crospovidone (F-7, F-8 and F-9).

CONCLUSIONS

The use of superdisintegrants for preparation of FDTs is highly effective and commercially feasible. These superdisintegrants accelerate disintegration of tablets by their ability to absorb a large amount of water when exposed to an aqueous environment. This disintegration is reported to have an effect on dissolution characteristics as well. According to the studies, the release was found in the following order of superdisintegrants: crospovidone (Group C) > croscarmellose sodium (Group A) > sodium starch glycolate (Group B). In this research work, overall results suggest that FDTs containing Crospovidone 4.17% (F-9) shows best results in terms of percent drug release, compressibility index, wetting time, *in vitro* dispersion and *in vitro* disintegration time. So, the proposed formulation F-9 may be used for the development of allopurinol fast dissolving tablet, for quick onset of action without need of water for swallowing or administration and also to meet the patient's demand for the treatment of gout. However, further investigation is required to establish *in vivo* - *in vitro* correlation to reveal the accurate pattern of drug release in *in vivo* environment as well *in vivo* efficiency of these allopurinol fast dissolving tablets.

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