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Formulation and Evaluation of Immediate Release Tablets of Allopurinol



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**Rajiv Kumar^{1,2}, Parminder Nain*², Jaspreet Kaur²,
Vipin Saini² and Varinder Soni¹**

¹*Department of Pharmaceutical Sciences, Khalsa
College of Pharmacy, Amritsar (Punjab), India.*

²*MM College of Pharmacy, Maharishi Markandeshwar
University, Mullana-Ambala (Haryana), India.*

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ABSTRACT

The aim of the present study is to develop and evaluate the immediate release tablet of Allopurinol by direct compression method. The superdisintegrant crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG) were used for immediate release of drug from tablet. The prepared tablets were evaluated for all pre-compression parameters and post-compression parameters. The drug-excipients interaction was investigated by FTIR. All formulation showed compliances with Pharmacopoeial standards. The study reveals that formulations prepared by direct compression F9 exhibit highest dissolution using crospovidone showed faster drug release 99.65% over the period of 12min while disintegration time of the tablet was showed 30sec comparison to other formulations of Allopurinol.



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1. INTRODUCTION

An immediate release dosage form allows a manufacturer to extend market exclusivity while offering patients a convenient dosage form or dosage regimen. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features such as special coatings and other techniques,^{1,2} immediate releases and fast dispersing drug delivery system may offer a solution to these problems. Recently, immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities.^{3,4}

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong to an appreciable extent, the rate of drug release and/or absorption. This term excludes formulations which are adapted to provide for “modified”, “controlled”, “sustained”, “prolonged”, “extended” or “delayed” release of drug^{5,6}.

Allopurinol is an inhibitor of the enzyme commonly known as xanthine oxidase. Allopurinol is an analogue of hypoxanthine. It is effective for the treatment of both primary hyperuricemia of gout and secondary hyperuricemia related to hematological disorders or anti-neoplastic therapy^{7,8}. Allopurinol is rapidly absorbed from the upper gastrointestinal tract and it has a plasma half-life of about 1 to 2 hours. It is relatively insoluble in water and freely soluble in alkaline aqueous solutions^{9,10}. It is very weak acid with a dissociation constant (pka) of 9.4 and is therefore essentially unionized at all physiological pH values¹¹. Its lipid solubility is quite low as is indicated by its octanol: water partition coefficient of 0.28¹². Allopurinol is a polar compound with strong intermolecular hydrogen bonding and limited solubility in both polar and non polar media^{13,14}.

2. MATERIALS AND METHODS

2.1 Materials

Allopurinol powder was kindly provided by Jackson Pharmaceutical (Amritsar, Punjab); All other excipients and materials used during the experiment are LR grade or the best possible pharma grades available were used as supplied by the manufacturer.

2.2 Methods

2.2.1 Study of physicochemical interaction of Allopurinol with tablet excipients

Excipients were integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage forms depends on the selection of excipients which are added to facilitate administration of the drug and protect it from degradation.

Fourier Transforms Infrared Spectroscopy (FTIR)

In the preparation of tablet formulations, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Allopurinol and selected polymers. The pure drug, drug-polymers combinations and formulations were subjected to FT-IR studies. Potassium bromide, pure drug and the polymers were heated to 105⁰C for one hour to remove the moisture content if present in a hot air oven. Then in presence of IR lamp, potassium bromide was mixed with drug and /or polymer in 1:1 ratio. Grinding in smooth mortar can effect mixing. The mixtures were then placed in the sample holder of the instrument and the spectra were taken. The spectra were run from 4000 cm⁻¹ to 1000 cm⁻¹ wave number. FT-IR spectrum of Allopurinol was compared with FT-IR spectrum of Allopurinol with polymer. The pure drug and the drug with excipients were scanned separately. Disappearance of Allopurinol peaks or shifting of peak in any of the spectra was studied.

2.2.2 Manufacture of Allopurinol tablets

Direct compression technique

Allopurinol tablets were manufactured for nine batches F1 to F9 using different ratios of superdisintegrants mentioned in the (Table No. 1) keeping the total weight (200mg) of the tablet constant in all the formulations. Allopurinol tablets were prepared by direct compression technique as per the formula given in the Table 1. The superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate were used in different proportions.

All the ingredients were passed through sieve #40 and were subjected to drying to remove moisture content at 40 to 45⁰C. Weighed amount of drug and excipients except magnesium stearate and talc were mixed properly by geometric addition method for 20 minutes manually. Talc and magnesium stearate were then passed through sieve #80, mixed and blended well with the initial mixture. The mixed blend of drug and the excipients were compressed on Karnavati 10 station rotary punching machine using 2mm diameter round concave punch (force used: 58.5 kN).

Table No. 1- Formulation of Immediate release Allopurinol Tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Allopurinol	100	100	100	100	100	100	100	100	100
Crospovidine (CP)							10	20	30
Croscarmellose sodium (CCS)				10	20	30			
Sodium starch glycolate (SSG)	10	20	30						
MCC	30	25	20	30	25	20	30	25	20
Mannitol	30	25	20	30	25	20	30	25	20
Aspartane	15	15	15	15	15	15	15	15	15
Magnesium stearate	8	8	8	8	8	8	8	8	8
Talc	7	7	7	7	7	7	7	7	7
Total weight	200	200	200	200	200	200	200	200	200

2.2.3 Quality control study of the prepared tablets

The prepared tablets from each formulation were subjected to the tablets quality control tests as drug content, weight uniformity, tablets thickness, disintegration time, hardness and friability.

Weight variation test of tablet

20 tablets for weight variation as per USP weight variation test. Calculate the average weight and comparing the individual tablet weights to average weight. Standard deviation from mean weight was also calculated^{15, 16}.

Friability testing

Friability was determined by weighing 10 tablets and placing them in a Roche type friabilator and rotating it at 25rpm for 4min. After that, tablets were weighed for their final weight and % friability was calculated^{15, 16}.

% Friability was calculated by:

$$\% \text{ Friability} = \left[\frac{\text{Weight}_{\text{initial}} - \text{Weight}_{\text{final}}}{\text{Weight}_{\text{initial}}} \right] \times 100$$

Hardness testing

Monsanto hardness tester used to measure the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. 3 tablets were used and force was measured in kg/cm²^{15, 16}.

Other physical parameters

Four tablets of each formulation were examined for their diameter, thickness and height of tablets by using micrometer gauge^{15, 16}.

Drug content

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 100mg of Allopurinol was transferred to 100ml volumetric flask and dissolve with 20ml of methanol. The mixture was shaken for 10 minutes by hand. The volume was made up with 0.1N HCl and filtered through Whatmann filter paper No. 41. Transferred 10ml of the filtrate into a

100ml volumetric flask and made up the volume to mark with 0.1N HCl. The respective absorbance of diluted samples was determined at 250nm against 0.1N HCl as blank 17.

***In vitro* disintegration time**

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration. The results are shown in table 2. This was determined as per I.P for all the formulations. All the formulations show disintegration time less than 60 seconds. Crospovidone has high water uptake and swelling pressure which leads to faster disintegration. Sodium starch glycolate shows disintegration time in between and Croscarmellose sodium shows more disintegration time.

***In vitro* dissolution study**

Drug release was assessed using a USP type II dissolution apparatus at 75rpm in 900mL 0.1N HCl maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ (Abd-Elazeem, 2001). Sample of 5ml was withdrawn at regular intervals and replaced with the same volume of prewarmed ($37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No. 1, Whatman, Maidstone, UK) and drug content in each sample was analyzed after suitable dilution, the amount of Allopurinol dissolved was determined spectrophotometrically at 250nm. Plain Allopurinol tablets were used as a control.

3. RESULTS

Drug- excipients compatibility studies:

To study the compatibility of the drug with various polymers, IR spectra of drug and formulation component were carried out. The FTIR spectra of drug and all excipients were shown in figure 1. No major differences in the I.R. patterns of pure drug and excipients were observed. Therefore, the FTIR studies ruled out the possibilities of any drug excipients interaction during the preparation of tablets.

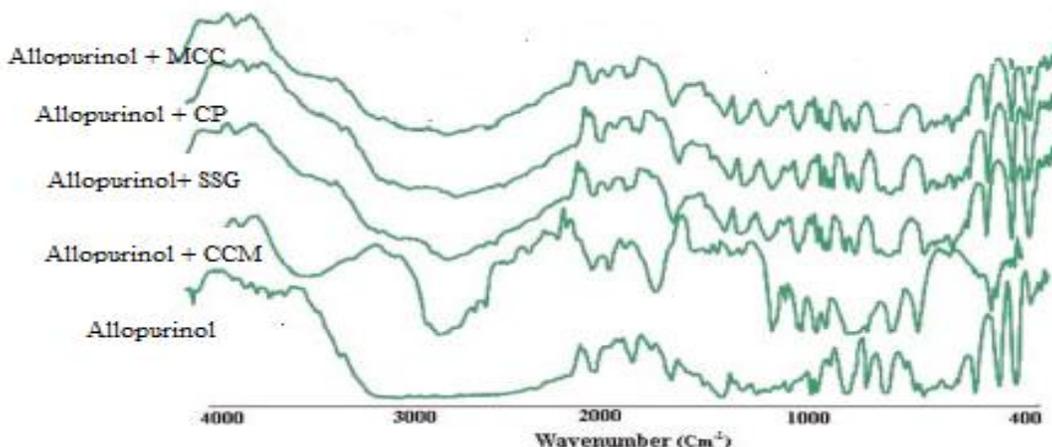


Figure 1. FTIR spectrum of Allopurinol with tablet excipients

Table No. 2- Result of In process quality control test

Formulation Code	Weight variation (mg) ±SD (n=20)	Hardness (kg/cm ²) ±SD (n=3)	Thickness (mm) ±SD (n=3)	Friability (%) (n=6)	Drug Content Uniformity (%) ± SD (n=3)	In-vitro Disintegration Time (sec)
F1	198±0.14	3.0±0.10	3.38±0.09	0.56	98.31±0.68	40±1.01
F2	200±0.47	3.6±0.15	3.37±0.20	0.72	99.65±1.40	39±1.00
F3	201±1.14	4.0±0.21	3.43±0.21	0.52	99.50±1.31	35±1.01
F4	199±0.61	4.0±0.21	3.29±0.12	0.52	97.68±0.95	60±1.28
F5	198±0.42	3.5±0.05	3.27±0.17	0.47	98.41±1.33	52±2.51
F6	200±1.42	3.0±0.18	3.40±0.10	0.42	99.91±1.81	34±1.55
F7	198±0.60	3.0±0.14	3.27±0.13	0.67	98.65±0.57	16±1.00
F8	201±0.50	3.0±0.10	3.30±0.25	0.49	99.05±1.16	20±1.70
F9	202±0.43	3.5±0.10	3.25±0.20	0.73	98.56±1.42	28±1.01

The lower standard deviation values indicated that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness. Friability was in between 0.42% to 0.73%. Results revealed that the tablets possess good mechanical strength.

The weight of all the tablets was found to be uniform. The drug content of the tablets was found

between 97.68% and 99.91% of Allopurinol. The results indicated that in all the formulations the drug content was uniform.

***In vitro* dissolution studies**

All the nine formulations were subjected for the *In vitro* dissolution studies using tablet dissolution tester (USP) TDT-08L, Electro lab. Solution having pH 6.8 was used as dissolution medium. The samples were withdrawn at different time intervals, filter and analyzed at 250nm. Cumulative % drug release was calculated on the basis of mean amount of Allopurinol present in the respective tablet. The results obtained in the *In-vitro* drug release for all formulations F1 to F9 are tabulated in Table 3.

Table No. 3- Result of *In vitro* dissolution study of immediate release of Allopurinol

Formulation code	After 3 min % Release	After 6 min % Release	After 9 min % Release	After 12 min % Release	After 15 min % Release
F1	27.95	40.43	58.32	67.01	72.36
F2	27.31	50.90	63.08	71.95	85.82
F3	30.52	51.53	63.13	71.50	90.72
F4	44.21	53.46	65.90	73.94	88.15
F5	40.73	60.77	75.47	83.17	95.99
F6	30.15	45.84	65.01	87.21	99.17
F7	31.63	50.65	62.33	69.30	79.75
F8	34.51	49.92	66.03	88.12	99.28
F9	48.68	65.43	82.44	99.65	-

Every value is an average of triplicate.

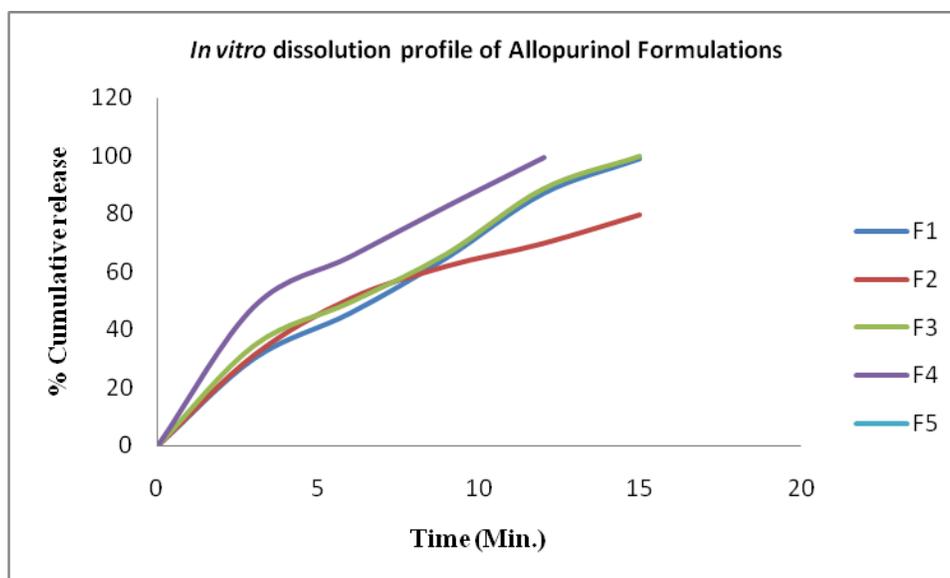


Figure 2. *In vitro* drug release of Allopurinol formulation F1-F5

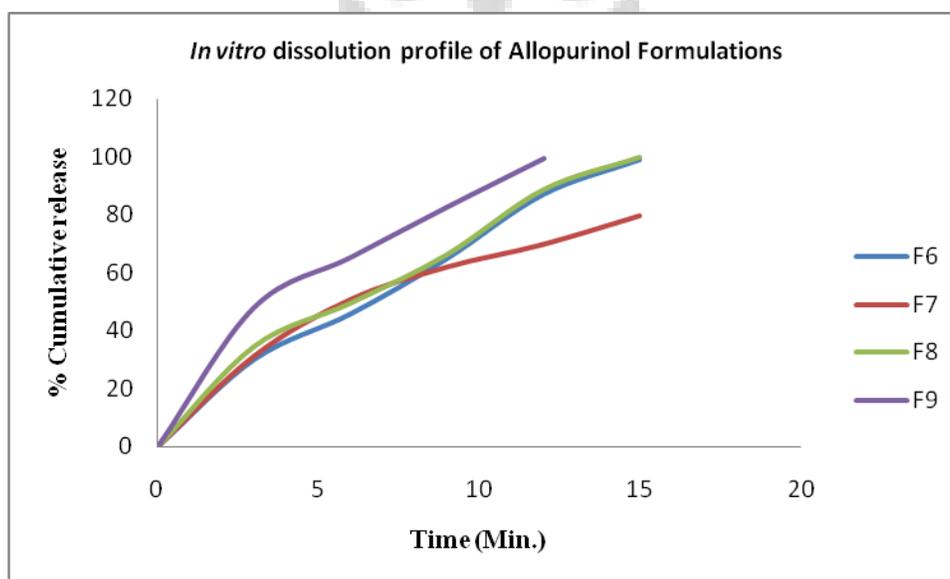


Figure 3. *In vitro* drug release of Allopurinol formulation F6-F9

The rapid dissolution was observed in formulations F1, F2 release 72.36%, 85.82% of drug respectively at the end of 15 minutes and formulation F3 releases 90.72% at the end of 15 minutes. Formulations F4, F5 and F6 which show drug release 88.15%, 95.99%, 99.17% respectively at the end of 15 min. Formulations F7, F8 release 79.75%, 85.82% respectively at the end of 15 minutes. Formulation F9 almost completely release (99.65%) at 12 minutes only. This rapid dissolution might be due to fast breakdown of particles and rapid absorption of the

drug. The drug release was completely achieved in a shorter duration of time. In all the formulations the drug release was within 15 minutes. High dissolution may occur due to faster breakdown.

Best optimized batch was F9 because of lesser disintegration time and highest percentage drug release at the end of 12 min among all the formulations.

4. CONCLUSION

Preformulation studies of Allopurinol were performed; the FT-IR analysis revealed that the superdisintegrants and excipients used were compatible with Allopurinol. Immediate release tablets of Allopurinol is to be prepared by direct compression technique using superdisintegrants, namely crospovidone, sodium starch glycolate and croscarmellose sodium.

Amongst all the formulations, formulation containing crospovidone as superdisintegrants is fulfilling all the parameters satisfactorily. It has shown excellent *in vitro* disintegration compared to other superdisintegrants. Combines multiple mechanisms to achieve disintegration at low levels without forming gel i.e. require slow dissolution, disintegration and provides rapid disintegration in direct compression tablet as well increases tablet breaking force and reduces friability; enhances the dissolution of poorly soluble drugs. Apart from all the formulations, F9 formulation showed maximum drug release (99.65%) at the end of 12 min.

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