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Fabrication and Evaluation of Fast Disintegrating Tablets of Allopurinol Using Natural and Synthetic Superdisintegrants

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ABSTRACT:

The foremost intention of current work is to fabricate the fast disintegrating tablets of Allopurinol, employing assorted superdisintegrants *viz*, natural superdisintegrants and synthetic superdisintegrants in divergent ratios. Allopurinol, a very weak acidic drug, which is poorly soluble in water, is active for the treatment of both major hyperuricemia of gout and minor hyperuricemia related to haematological complaints of anti-neoplastic therapy. Allopurinol when given orally as conventional tablets generally displays short gastric residence time, resulting in poor bioavailability and incomplete absorption of drug; so the purpose of this work is to provide a novel way to improve the dissolution and bioavailability of the model drug. Additionally, this work also focuses on the comparative study of natural and synthetic superdisintegrants in the dissolution behavior of the formulated fast disintegrating tablet of Allopurinol. Nine formulations (F1-F9) were developed using direct compression technique. All the formulations were evaluated as prescribed by the pharmacopoeial monograph for tablets. The foremost formulation F9 containing 15% croscarmellose sodium showed a drug release of 101.875% at the end of 12 minutes with a disintegrating time of 13.31±0.59 sec. In the midst of the superdisintegrants, synthetic superdisintegrants can be successfully directed for the development of fast disintegrating tablets of Allopurinol.

Keywords: Allopurinol: Natural Superdisintegrants; Synthetic Superdisintegrants; Direct Compression Technique; Croscarmellose Sodium.

1. Introduction:

Among the various conventional dosage forms such as tablets, capsules, syrups, ointments, injectables, suppositories, etc. possessing distinct mechanism of drug delivery, the one which favors the oral route of administration are most widely exploited.[1] Solid dosage forms are even most referred among other dosages forms on account of ease of administration, accurate dosing, self-medication, pain evasion and high patient compliance.[2] Most of the orally administered drugs are intended to be kept in mouth and swallowed. These drugs undergo 'pre-systemic' or 'first pass metabolism' as it pass through the gut wall and liver, that contains several inactivating enzymes which indicates that only fraction of the administered drug actually reaches the systemic circulation.[3]

United States Food and Drug Administration (FDA) defined fast dissolving tablet (FDT) as, "a solid dosage form containing medical or active ingredient which disintegrate rapidly usually within a matter of seconds when placed under tongue." These types of dosage form dissolve or disintegrate in the oral cavity without need of water. Generally, fast dissolving tablet disintegrates in less than a minute.[4] These sort of dosage form are suitable for patients like geriatric, bedridden, mentally disabled, and for active patients who are busy and travelling, who may not have access to water. The approach to fast disintegrating tablets is the solution for swallowing difficulty problem without compromising its efficacy. This helps to attain an instant higher concentration of drug for immediate release. Some drugs are absorbed from the pharynx and esophagus as the saliva passes down into the stomach, in such cases the bioavailability is increased and the pre-gastric absorption enhance the bioavailability along with the improvement in clinical performance through a reduction of unwanted effects are some of the highlighted advantages of this delivery system.[5, 6] The use of superdisintegrants have gain popularity in past decades. The drugs which are sparingly soluble in aqueous media, the dissolution of such drugs is delayed due to poor wettability and slow liquid penetration which in turn increase disintegration time and delayed drug release. The use of superdisintegrants can overcome such obstacles and hence improve the release rate of drugs having problem in solubility.[7]

Gout is a metabolic disorder where hyperuricemia forefront acute and chronic inflammatory response due to the formation of monosodium urate crystals in the tissues, particularly in the joints and kidneys.[8] Allopurinol, the oldest xanthine oxidase inhibitors, an enzyme in the purine catabolism pathway that converts hypoxanthine to xanthine to uric acid. It has been used for more than 50 years in the treatment of gout and allied hyperuricemia condition (kidney stone and tumor lysis syndrome). Despite the 1st line drug, Allopurinol has the problem of insolubility in aqueous and acidic solutions[9], hence in the proposed study an attempt will be made to formulate the fast disintegrating tablets of allopurinol by direct compression technique using

various classes of superdisintegrants and will also be focused to evaluate the *in-vitro* release mechanism and the influence of superdisintegrants level on the release rate.

2. Materials and Methods:

2.1 Materials:

Allopurinol was received as a gift sample from Omnica Laboratories Pvt. Ltd. Suryabinayak Municipality, Bansghari, Bhaktapur, Nepal. All other chemicals and reagents used were of analytical grade.

2.2 Method:

Fast disintegrating tablets of Allopurinol were prepared by direct compression technique. Starch was used natural superdisintegrant; Croscarmellose sodium and Sodium starch glycolate were used as synthetic superdisintegrants. The powder blends have been evaluated for bulk density, tapped density and angle of respose. Compressibility Index and Hauser's ratio were calculated from bulk and tapped density of the powder blends. After fabrication of tablets, each formulations were subjected for post compression studies.

Formulations (F1-F9) were prepared in three different combinations, each three formulation containing different ratios of different polymers. Total amount of superdisintegrants in the formulation was fixed in the tablet of total weighing 200 mg. Compositions of various tablet formulations are provided in the Table 1.

Table 1: Composition of various Allopurinol FDTs

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Allopurinol	100	100	100	100	100	100	100	100	100
Starch	-	-	-	12.5	18.75	25	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	12.5	25	37.5
Sodium starch glycolate	12.5	25	37.5	-	-	-	-	-	-
Talc	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
Magnesium stearate	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Lactose	112.5	100	87.5	112.5	106.25	100	112.5	100	87.5
Total wt. in mg	250	250	250	250	250	250	250	250	250

First of all the mixture of the drug, superdisintegrants, binder, diluents, talc were screened through #40 and mixed geometrically in mortar pestle. Finally magnesium stearate was mixed to form uniform blend. Thus tablets of 250 mg each containing 100 mg of Allopurinol were prepared by direct compression technique as per the aforementioned table.

2.2.1 Evaluation of Powder Blends: [10-15]

a. Drug-polymer interaction study:

Infrared spectrum of API and other polymer was determined on Fourier transform infrared spectrophotometer. Small quantity of sample was taken and directly put on IR platform. Then the spectra were scanned over wavelength region of 4000 to 400 cm^{-1}.

b. Bulk Density (Db) and Tapped Density (Dt):

Bulk density is defined as the ratio between bulk mass of powder and bulk volume of powder. For this, accurately weighed & sieved powder was subjected to the bulk density apparatus and initial bulk volume (Vb) was noted. Bulk density was calculated by using equation given below.

$Db = M/Vb$

Where, Db=Bulk density

M =mass of powder

Vb= bulk volume of the powder.

The tapped density is defined as an increased bulk density attained after mechanically tapping a container containing the powder sample. The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel 50 times containing the powder sample. Tapped density was calculated by using equation given below

$Dt = M / Vt$

Where, Dt =Tapped density M= mass of powder

Vt =tapped volume of the powder.

c. Hausner's ratio:

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. Hausner's ratio is indication of easiness of powder flow. It is calculated by following formula.

Hausner's ratio = Dt / Db.

where, Dt= tapped density.

Db= bulk density.

d. Compressibility index:

The compressibility index also known as Carr's Index and is defined as an indication of the compressibility of a powder. It was determined by using following equation:

Carr's Index (%) = [(Dt– Db) × 100] / Dt

where, Dt= tapped density of powder

Db= bulk density of powder

Table 2: Effects of Hausner's ratio and Compressibility index on flow properties

Hausner's ratio	Flow property	Compressibility index
1.00-1.11	Excellent	0-10
1.12-1.18	Good	11-15
1.19-1.25	Fair	16-20
1.26-1.34	Passable	21-25
1.35-1.45	Poor	26-31
1.46-1.59	Very poor	32-37

e. Angle of repose:

Angle of repose is determined by funnel method. The powder is poured through a funnel that can be raised vertically until a maximum cone height (h) is obtained. The diameter (d) of the base of pile was measured and radius(r) is calculated. Therefore, angle of repose is calculated. The frictional pressure is an unfastened powder or granules can be measured by using angle of repose.

Tan (θ) = h/r

(θ) =tan-1(h/r)

Where, h is height of pile

r is radius of the base of pile

Table 3: Angle of repose and their effect in flow properties

Angle of Repose (in °)	Flow properties
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

2.2.2 Evaluation of Tablets: [16-21]

a. Hardness:

The hardness of a tablet is determined using the Monsanto hardness tester. The tester is placed across the diameter in between the spindle and the anvil. The knob is adjusted to hold the tablet in position. The reading of the pointer is adjusted to zero; the pressure is increased slowly to break the tablet. Hardness factor, the average of the several determinations was recorded.

b. Thickness

The thickness of a tablet is determined by using Vernier caliper. The tablets are placed between two arms of the Vernier caliper and measure the thickness of the tablets. Three tablets were used and average value was calculated.

c. Friability

Friability of tablets from different batches was determined using Roche friabilator. Ten tablets from each batch were randomly sampled and were weighed. The tablets were transferred to friability test apparatus which were rotated at 25 rotations per minute for 100 revolutions. After completion of revolution tablets were de-dusted and weighed again. Then % friability was calculated by using the given equation:

Friability= $[(W_1-W_2)\times100]/W_1$

Where, W_1 = weight of the tablets before test

W_2 = weight of the tablets after test

d. In vitro Disintegration Test

The disintegration time was recorded by using a digital tablet disintegration test apparatus. Tubes were placed with one tablet each in the basket assembly. The basket with the bottom surface made of a stainless steel screen (mesh no.60) was then suspended in a 1 liter beaker containing 900ml phosphate buffer pH-6.8 at temperature 37±20C. The basket was operated at 28-32 cycle per min. The time required for complete disintegration of tablet in each tube was determined using a stop watch.

e. Dissolution Test

The rate of drug release from solid dosage from can be evaluated by dissolution test. It provides knowledge of bioavailability of drug by correlating the drug dissolving pattern in gastrointestinal tract before reaching the systemic circulation. The release rate of fast dissolving tablets of Allopurinol was carried out by using USP Dissolution testing apparatus II (paddle method). *In- vitro* dissolution studies for fast dissolving tablets of Allopurinol were carried out using phosphate buffer with pH-6.8.The apparatus was set with 900ml of buffer at 37±0.5^{0}C and 50 rpm. 1ml of sample solution was withdrawn at different time intervals and the samples were diluted with prepared phosphate buffer. Absorbance of these solutions was measured at 251nm using a UV visible spectrophotometer.

f. Weight variation

10 tablets were randomly selected and weighed individually and average mass was calculated, further % weight variation was calculated as per the official procedure. IP limits for weight variation are given below:

Table 4: Weight variation

Weights	Limit
80mg or less	±10%
More than 80mg or less than 250mg	±7.5%
250mg or more	±5%

g. Assay:

Ten tablets were weighed, ground and mixed in a mortar then this powder was sieved. A quantity of 0.25 g of the powder was taken and dissolved in 10 ml of phosphate buffer pH 6.8 and diluted to 250 ml with distilled water. The sample was filtered through a Whatman filter paper (no. 4). The concentration was calculated in terms of ppm. Then, absorbance was measured using UV spectrometer.

3. Results

a. Characterization:

- Colour and Appearance:

The drug was almost white crystalline powder

- Melting point:

The melting point of allopurinol was found to be 350°C.

- Solubility:

The solubility of the given drug was observed in different solvent for the selection of appropriate solvent for analysis of formulated products. The result obtained from solubility analysis is tabulated in table:

Table 5: Solubility profile of Allopurinol

S.N	**Solvent**	**Solubility**
1	Water	Very slightly soluble
2	Ethanol(95%)	Very slightly soluble

3	Methanol	Soluble
4	Dilute solutions of alkali hydroxides	Soluble
5	Chloroform and ether	Insoluble

- FTIR Analysis:

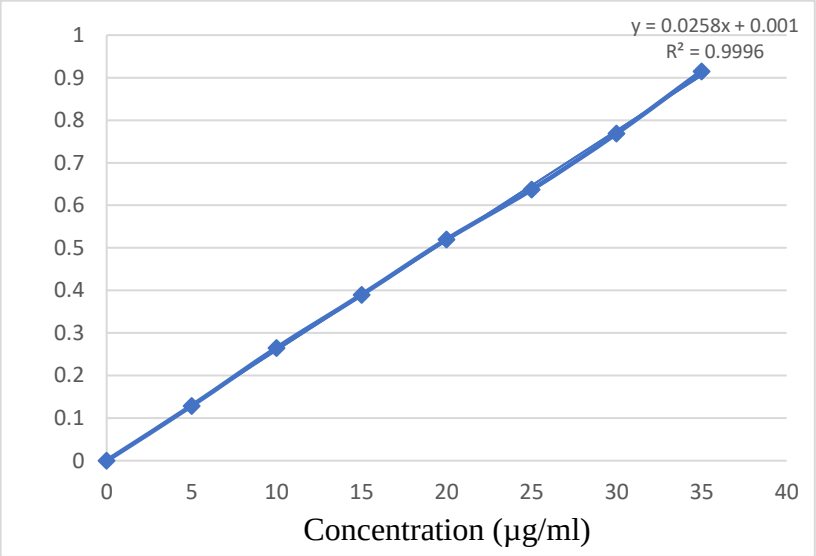
No any unusual interaction between drug and polymers was found used in formulation.

- Standard Calibration Curve of Allopurinol:

Standard calibration for absorbance versus concentration (5, 10, 15, 20, 25, 30 & 35) µg/ml of Allopurinol in phosphate buffer pH 6.8 shows linear relationship with correlation coefficient (R^2) 0.9996 & regression equation.

y= 0.0258x + 0.001

Figure 1: Standard Calibration Curve



b. Pre-compression Parameters:

Table 6: Pre-compression parameters of FDT of Allopurinol

Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's Ratio	Carr's index (%)	Angle of repose (θ)
F_1	0.54 ±0.04	0.72 ±0.05	1.46 ±0.25	30.95 ±9.42	44.07 ±2.72
F_2	0.54 ±0.01	0.85 ±0.08	1.57 ±0.17	36.29 ±6.50	42.07 ±1.4
F_3	0.51 ±0.03	0.68 ±0.07	1.24 ±0.07	19.60 ±4.22	43.63 ±2.04
F_4	0.54 ±0.051	0.71 ±0.125	1.32 ±0.22	22.85 ±12.85	37.60 ±1.29
F_5	0.52 ±0.035	0.81 ±0.04	1.55 ±0.137	35.37 ±5.54	44.07 ±2.72
F_6	0.55 ±0.04	0.75 ±0.10	1.36 ±0.20	23.63 ±12.13	38.46 ±1.19
F_7	0.51 ±0.03	0.82 ±0.009	1.60 ±0.10	37.55 ±3.96	36.78 ±2.20
F_8	0.48 ±0.03	0.75 ±0.09	1.57 ±0.36	35 ±10.5	37.99 ±2.63
F_9	0.56 ±0.05	0.67 ±0.4	1.19 ±0.05	16.39 ±3.66	41.43 ±0.60

The above table shows that bulk density ranges from 0.48±0.03 to 0.56±0.05, tapped density ranges from 0.67±0.4 to 0.85±0.08, the compressibility index value ranges from 16.39±3.66 to 37.55±3.96, Hausner's ratio ranges from 1.19±0.05 to 1.60±0.10 and the angle of repose of pre-compressed powders was found to be in the ranges from 37.60±1.29 to 44.07±2.72.

c. Post-compression Parameters:

All the tablet formulations were evaluated for various post-compression parameters such as hardness, friability, thickness, weight variation, disintegration time and *in-vitro* dissolution studies.

Table 7: Post Compression parameters of FDT of Allopurinol

Code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight Variation (mg)	Disintegration time (sec)
F_1	2.33 ±0.288	2.5 ±0.005	0.46 ±0.16	250.88 ±1.37	33 ±9.61
F_2	2.5 ±0.5	3.67 ±0.057	0.44 ±0.081	248.33 ±2.516	25.87 ±3.68
F_3	2.16 ±0.288	3.67 ±0.15	0.43 ±0.15	250 ±1	20 ±1
F_4	2.13 ±0.15	3.43 ±0.264	0.6 ±0.11	249.33 ±1.52	24.33 ±2.51
F_5	2.33 ±0.28	3.5 ±0.1	0.74 ±0.08	249.66 ±2.081	35 ±3
F_6	2.33 ±0.28	3.76 ±0.11	0.42 ±0.087	250.46 ±1.650	27.33 ±2.51
F_7	2.33 ±0	3.63 ±0.05	0.74 ±0.072	249.6 ±1.345	14 ±4.35
F_8	2.5 ±0.5	3.7 ±0.01	0.16 ±0.072	250.5 ±1.553	13.50 ±0.74
F_9	2.75 ±0.25	2.36 ±0.005	0.33 ±0.031	250.5 ±1.159	13.31 ±0.59

Tablet hardness of all batches was found to be in range of 2.13±0.15 to 2.75±0.25 kg/cm2, thickness between 2.36±0.005-3.76±0.11 mm, friability between 0.16 ±0.072 % to 0.74 ±0.08 %, tablet weight in the range of 248.33±2.516 to 250.88±1.37mg and disintegration time was found to be in the range of 13.31±0.59 - 35±3sec.

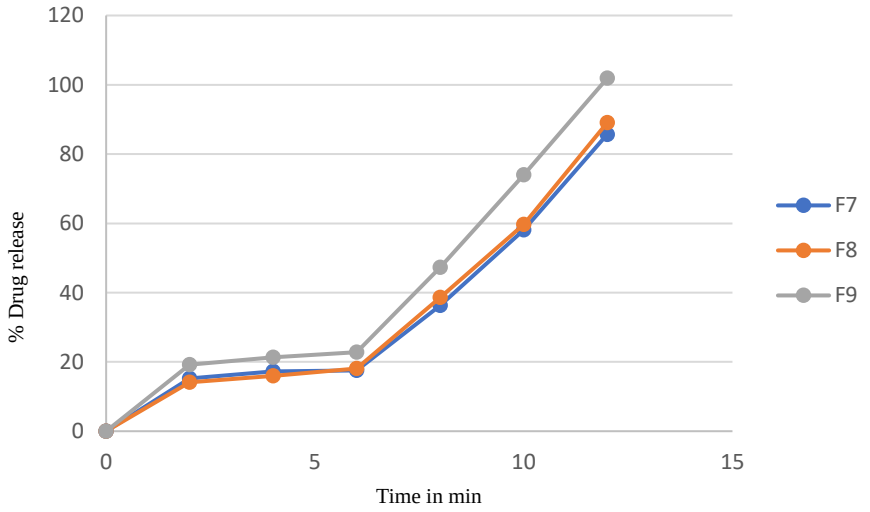


Figure 2: Dissolution Profiles of Formulation F1-F9

As depicted in the figure above when the dissolution profile is plotted in a graph taking % drug release in the y-axis and time in minute in x-axis, various graph lines will be observed for various formulations. Among all the formulations, F9 showed an inclined graph as compared to others, to be exact it showed a drug release of 101.875% at the end of 12 minutes.

4. Discussion and Conclusion:

An attempt was made to formulate the fast disintegrating tablets of Allopurinol implementing direct compression technique with various ratios of different superdisintegrants. Pre-compression and post-compression parameters were evaluated as prescribed by the pharmacopoeias. FTIR analysis showed that there were no interaction between drug and polymers. Pre and post- compression studies showed that all the formulations were within the pharmacopoeial limits. The formulated tablets showed compliance with various physic-chemical parameters, hardness, friability, etc.

5. Summary:

Fast disintegrating tablets of Allopurinol were successfully prepared by direct compression technique using various concentrations of superdisintegrants. Starch as natural superdisintegrant and sodium starch glycolate and croscarmellose sodium as synthetic superdisintegrants were used to ensure rapid disintegration time varying concentrations. According to the studies, the release order was found in the following order of superdisintegrants: CCS > SSG > Starch. In this research work, overall results suggest that FDTs containing 15% CCS showed disintegration time of 13.31±0.59sec, 0.33±0.031 % friability with % drug release of 101.87 % at the end of 12 min which satisfied all the tablet evaluation parameters for fast disintegrating tablets. From all the experimental data, it can be summarized that F_9 was the optimized formulation.

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