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RESEARCH ARTICLE

STUDY ON DISSOLUTION IMPROVEMENT OF ALLOPURINOL BY CO-GRINDING AND FUSION METHOD USING SOLID DISPERSION TECHNIQUE

Fayjunessa Runa[1], Md. Raihan Sarkar[2] Razia Sultana[3], Khurshid Jahan[4] and *Zubair Khalid Labu[5]

[1,2,3,4,5] World University of Bangladesh(WUB). Department of Pharmacy. Dhaka. Bangladesh.

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ABSTRACT

Allopurinol is a commonly used drug in the treatment of chronic gout or hyperuricaemia associated with treatment of diuretic conditions. One of the major problems with the drug is that it is practically insoluble in water, which results in poor bioavailability after oral administration. In the present study, solid dispersions of allopurinol (allo) were prepared by co-grinding method and melting methods to increase its water solubility. Hydrophilic carriers such as polyvinylpyrrolidone, polyethylene glycol 6000 were used in the ratio of 1:1, 1:2 and 1:4 (drug to carrier ratio). The aqueous solubility of allopurinol was favored by the presence of both polymers. These new formulations were characterized in the liquid state by phase solubility studies and in the solid state by UV spectroscopy. Solid state characterizations indicated that allopurinol was present as an amorphous material and entrapped in polymer matrix. In contrast to the very slow dissolution rate of pure allopurinol, the dispersion of the drug in the polymers considerably enhanced the dissolution rate. Solid dispersion prepared with Kollicoat IR showed highest improvement in wettability and dissolution rate of allopurinol. Therefore, the present study showed that kollicoat IR has a significant solubilizing effect on allopurinol

KEYWORDS: Allopurinol, polyethylene glycol 6000, solid dispersions, closed melting method, dissolution enhancement.

INTRODUCTION:

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. Solid dispersion is a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting, solvent or melting solvent method. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Moreover, certain combinations can be encountered, i.e. in the same sample; some molecules are present in clusters while some are molecularly dispersed.One of the major problems with the drug is that it is practically insoluble in water, which results in poor bioavailability after oral administration in the present study, solid dispersion of allopurinol were prepared by co grinding & fusion methods to increase its water solubility. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. This article focuses on the former, in particular, the use of solid dispersion technologies to improve the dissolution characteristics of poorly water-soluble drugs and in turn their oral bioavailability. Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s) and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs. Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption in vivo will be concurrently accelerated with an increase in the rate of drug dissolution.The

*Corresponding author: Zubair Khalid labu | Email: zubairlabu@yahoo.com

enhancement of oral bioavailability of such poorly water soluble drugs remains one of the most challenging aspects of drug development. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solublization by co solvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid and excess drug precipitates as fine colloidal particles or oily globules of submicron

MATERIALS AND METHOD:

Drug: Allopurinol

Excipients: PEG 6000 Polymers, KollidonVA64, HPMC, Kollicoat, PVP, Mannitol.

Equipments: Dissolution test apparatus, UV-VIS Spectrophotometer, Electronic balance. Thermostatic water bath, Laboratory oven.

PREPARATION OF SOLID DISPERSION BY CO -GRINDING METHODS:

The co-grinding mixtures of Allopurinol were prepared using PEG 6000 at ratio of 1:3, 1:5, PVP K30, 1:1, 1:2, 1:4, HPMC,1:3, 1:5 Mannitol, 1:1, 1:2, Kollicoat, Kollidon in 1:3, 1:5, 1:7.The dried mass was stored in a vial. (Formulation of Allopurinol solid dispersion with different polymer)- 100 mg of allopurinol was taken in the vial. Then different types of polymer were added .The formulations were withdrawn from vials, crushed in mortar and pestle.

Table 1: Formulation of Allo solid dispersion by changing the amounts of Kollicoat with PEG 6000

Formulation	F1(1:3)	F2(1:5)
Allopurinol	100mg	100mg
PEG 6000	500 mg/300mg	500 mg
Kollicoat IR 2cps	300mg	500mg

Table 2: Formulation of Allo solid dispersion by changing the amounts of Kollicoat

Formulation	F1(1:3)	F2(1:5)	F3(1:7)
Allopurinol	100 mg	100 mg	100 mg
Kollicoat	300 mg	500 mg	700 mg

Table 3: Formulation of Allopurinol solid dispersion by changing the amounts of Kollidon

Formulation	F1(1:3)	F2(1:5)	F3(1:7)
Allopurinol	100 mg	100 mg	100 mg
Kollidon VA64	300mg	500mg	700mg

Table 4: Formulation of Allo solid dispersion by changing the amounts of HPMC

Formulation	F1(1:3)	F2 (1:5)
Allopurinol	100 mg	100 mg
HPMC	300mg	500mg

Table 5: Formulation of Allopurinol solid dispersion by changing the amounts of Mannitol

Formulation	F1(1:1)	F2(1:2)
Allopurinol	100 mg	100 mg
Mannitol	100mg	200mg

PREPARATION OF STANDARD CURVE OF ALLOPURINOL IN DISTILL WATER:

To prepare a standard curve for Allopurinol, 0.02g Allopurinol of was accurately weighted & dissolved in 100 ml of Ethanol to produce a solution 0.2 mg/ml. Then 900ml distilled water was added. Then 1, 2, 3, 4, 5, 6, 7, 8, 9 & 10 ml of this solution was taken in 10ml volumetric flask & 9, 8, 7, 6, 5, 4, 3, 2, 1 & 0 ml distilled water was added respectively to them for the purpose of serial dilution. This serial dilution was carried out to get different Allopurinol concentration. These were then analyzed by UV spectrophotometer at 260 nm and absorbance was noted. Then the absorbance values were plotted against drug concentration and standard curve of was produced.

Table 6: Absorbance values of the standard solution of Allopurinol for standard curve using distil water

Concentration	Absorbance
0	0
1	0.101
2	0.190
3	0.264
4	0.360
5	0.451
6	0.575
7	0.647
8	0.738
9	0.827
10	0.925

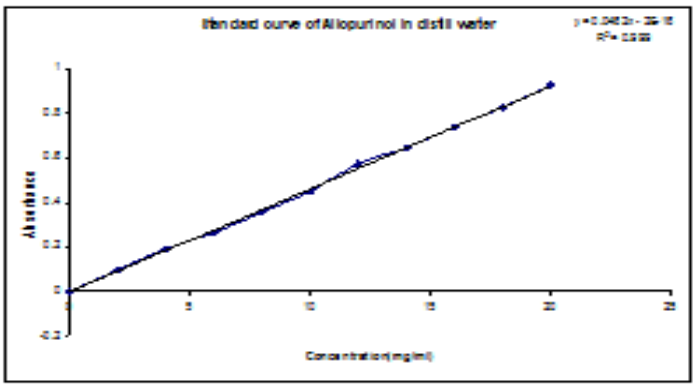

Figure 1: Standard curve of Allopurinol in distilled water In-vitro dissolution study of allopurinol from solid dispersion:

In-vitro dissolution study was performed in a basket type Dissolution Apparatus (Dissolution Test Apparatus, Intelli series, INDIA). A fixed amount of solid dispersion containing 100mg equivalent Allopurinol from each batch was calculated for dissolution purpose. Distill water was used as dissolution media. 900 ml of distill water was used as dissolution medium in each dissolution basket at a temperature of 37° c and a paddle speed of 75 rpm. The fixed amount of solid dispersion from each batch was weighed and transferred in each dissolution basket. The dissolution was carried out for 1 hour and 5 ml sample was withdrawn at predetermined intervals of 10, 20, 30, 40, 50 & 60 minutes. Each and every time 5 ml dissolution sample was compensated by another fresh 5 ml distil water/ distilled. Dissolution sample were withdrawn with the help of disposable syringe filter and were kept in a test tube. The dissolution samples were then analyzed spectrophotometrically in a UV-VIS spectrophotometer (UV-1600, South Korea). The dissolution study for each batch was performed in duplicate.

POLYMER ALLO INTERACTION STUDY USING UV-VIS SPECTROPHOTOMETER FOR PURE ALLO:

First 100 mg Allopurinol was taken for dissolution purpose. Distill water was used as dissolution media. 900 ml of distill water was used as dissolution medium in each dissolution basket at a temperature of 37° c and a basket speed of 75 rpm. The dissolution was carried out for 1 hour and 5 ml sample was withdrawn at predetermined intervals of 10,20,30,40,50& 60 minutes. Each and every time 5 ml dissolution sample was compensated by another fresh 5 ml distill water. Dissolution sample were withdrawn with the help of disposable syringe filter and were kept in a test tube. Then the samples were analyzed spectrophotometrically in a UV-VIS spectrophotometer (UV-1600, South Korea) at the wavelength 260nm.

FOR ALLOPURINOL AND DIFFERENT POLYMER:

A fixed amount of solid dispersion containing 100mg equivalent Allopurinol from each batch was calculated for dissolution purpose. Distilled water was used as dissolution media. 900 ml of distilled water was used as dissolution medium in each dissolution basket at a temperature of 37° c and a basket speed of 75 rpm. The fixed amount of solid dispersion from each batch was weighed and transferred in each dissolution basket. Absorbance value was determined using UV-spectrophotometer wavelength 260 nm.

This procedure was performed six times for six polymers (HPMC, kollicoat IR, PEG 6000, Mannitol, PVP and kollidon VA64).

FUSION METHOD:

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Solid dispersions were prepared by melting the carriers at 55 to 60°C in PEG 6000 on water bath, dispersing the drug onto molten carrier and cooling immediately on ice bath with continuous stirring to dry mass. The dried mass was stored until further use.

RESULT AND DISCUSSION:

Allopurinol is one of the most commonly used anti-gout drugs. It is practically insoluble in water. The present study was aimed to observe release pattern of drug from the solid dispersion by using different Excipients such as Polyethylene Glycol 6000 (PEG 6000) and different polymer such as HPMC, PVP, Mannitol, Kollidon VA64, Kollicoat IR. The efficacy of these excipients on drug release was also evaluated with different solvent such as ethanol and water in terms of in vitro drug dissolution. The variables affecting drug dissolution were dispersion property, hydrophilic polymer loading and physicochemical property of the drug molecule. Secondary curve was obtained from the dissolution rate of the different formulation.

Table 7: The efficiency of excipient in enhancing the dissolution rate of Allopurinol and PVP.

Formulation	Drug excipient ratio	% of release
Allopurinol and PVP	1:1	48.10
	1:2	48.22
	1:4	55.91

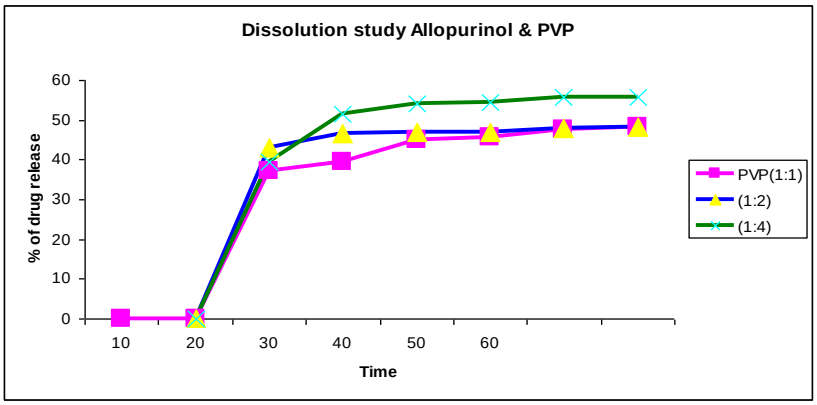

Figure 2: In vitro release of Allo from physical mixture of Allo and PVP

From this data, it can be clearly seen that PVP gave rapid and very high rates of dissolution. This difference in dissolution rate is more obvious from 60 minutes. The formulation with the drug excipient ratio 1:4 has shown greater dissolution study. Their aqueous solubility resulting in increased wet ability of the micron zed dug particles and increase in the effective surface area of the drug.

Table 8:

Formulation	Drug excipient ratio	% of release
Allopurinol and HPMC	1:3	31.22
	1:5	31.68

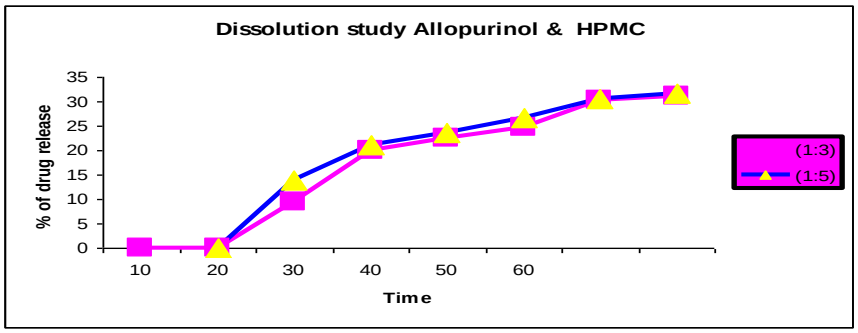

Figure 3: In vitro release of Allo from physical mixture of Allo and HPMC

From this data, it can be clearly seen that HPMC has prominent effect on the dissolution rate.

Table 9:

Formulation	Drug excipient ratio	% of release
Allopurinol and Kollicoat	1:3	60.61
	1:5	64.40
	1:7	70

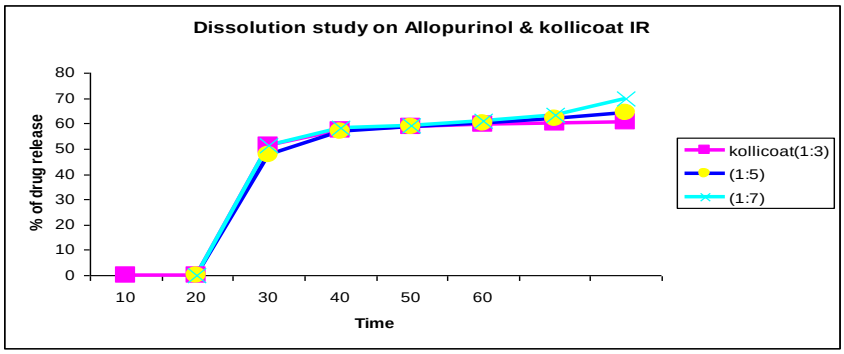

Figure 4: Allopurinol and kollicoat drug release curve

From the curve in case of F1 the % release 47.41% and F2 51.20%, F3 51.54% respectively when time 10min. In case of F1 60.61%, F2 64.40%, F3 70.03% release when the time was 60min. We can see that, with increasing drug- carrier ratio, amount of % release is increasing. The formulation with the drug excipient ratio 1:7 has shown greater dissolution study.

Table 10:

Formulation	Drug excipient ratio	% of release
Allopurinol and Kollidon	1:3	55.33
	1:5	56.83
	1:7	59.81

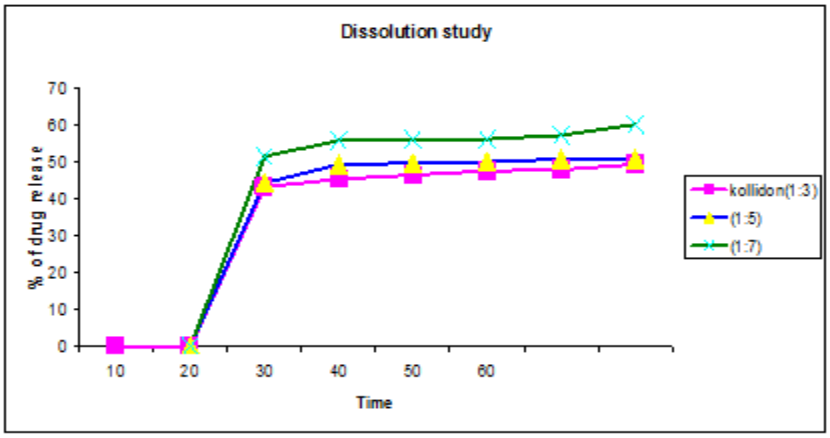

Figure 5: Allopurinol and kollidon drug release curve

From the curve in case of F1 the % release 47.99% and F2 43.62%, F3 51.32%when time 10min. In case of F1 56.83%, F2 56.60%, F3 59.81% release when the time was 60min. so it is clear that the amount of % drug release is gradually increasing with the increasing drug carrier. The formulation with the drug excipient ratio 1:7 has shown greater dissolution study.

Table 11:

Formulation	Drug excipient ratio	% of release
Allopurinol and Mannitol	1:1	51.89
	1:2	55.10

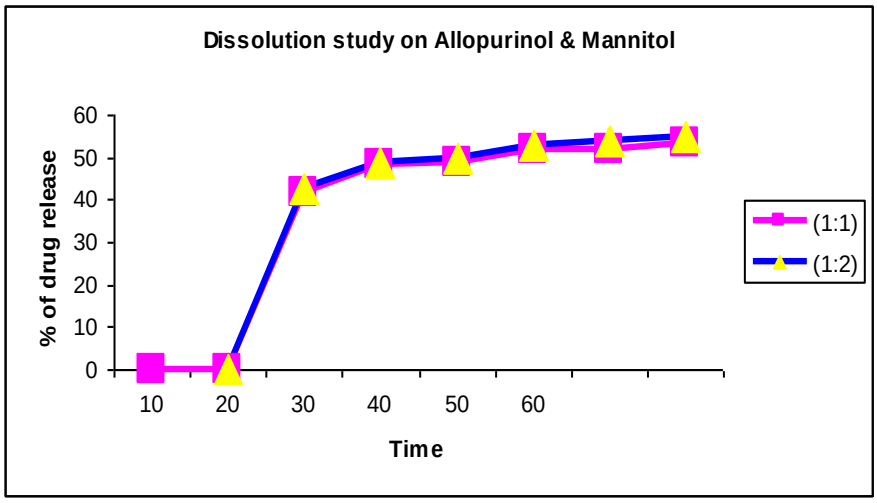

Figure 6: Allopurinol and Mannitol drug release curve

From the curve in case of F1 the % release 41.90% and F2 42.84%, when time 10min. In case of F1 53.55%, F2 55.10%, release when the time was 60min. We can see that the amount of %release increasing .The formulation with the drug excipient ratio 1:2 has shown greater dissolution study.

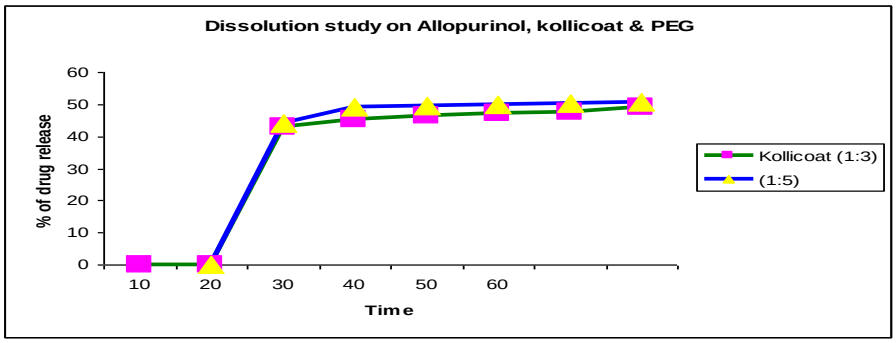

Figure 7: Allopurinol and Kollicoat IR and PEG 6000 drug release curve

From the curve in case or F1 the % release 43.053% and F2 44.316%, when time 10min. In case of F1 49.253.83%, F2 50.51%, release when the time was 60min. We can see that the amount of %release increasing .The formulation with the drug excipient ratio 1:5 has shown greater dissolution study

CONCLUSION:

Based on the current study, improvement in the dissolution of the water-insoluble drug allopurinol was achieved through solid dispersion using different carriers, the best of which was Kollicoat in a drug carrier ratio of 1:7, which may be attributed to the improved wet ability, and decreased drug crystallinity, which can be modulated by appropriate level of hydrophilic carriers. Finally, based on the above study, it was concluded that the solid dispersion technique was shown to be a successful approach for improving the dissolution rate of allopurinol. The nature and amount of the carrier used played an important role in the enhancement of the dissolution rate. The increased solubility and dissolution rate of ALLOPURINOL provided the rapid onset of action. From the above study it was concluded that the solvent evaporation, co precipitation and co-grinding are powerful techniques for the preparation of rapidly dissolving formulations of allopurinol. All processes can potentially lead to better bioavailability of allopurinol drug products. The nature and the amount of the carrier used played an important role in the enhancement of the dissolution rate. The increased in the solubility and dissolution rate of allopurinol would provide the rapid onset of action

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