

A STUDY ON EFFECT OF PEG 6000 ON DISSOLUTION ENHANCEMENT OF A MODEL DRUG PIROXICAM BY USING SOLID DISPERSION TECHNIQUES

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ABSTRACT

Clonazepam was used as a model medication for these objectives in order to examine the impact of polymers on the release mechanism of poorly soluble medicines from solid dispersions. Using polyethylene glycol 6000 (PEG-6000), Kollicoat IR, Kollidon VA 64, and Poloxomer in varying drug-to-carrier ratios (1:2, 1:4, 1:6, 1:8, 1:10), five distinct forms of solid dispersions were created. Solid dispersions were made using the solvent evaporation technique. In each dissolution basket for the pure drug and solid dispersions, 1000 cc of distilled water was used as the dissolving medium in an in-vitro dissolution investigation with a temperature of 37° C and a paddle technique at 100 rpm. The dissolution rate of pure Clonazepam was found to be very sluggish, but the dissolution rate of the solid dispersion was significantly increased. The medication's amorphous and crystalline fractions were presumably caused by its wettability and dispersibility. PEG-6000, Poloxomer, and Kollidon VA 64 (1:10 ratio) showed the greatest improvement in clonazepam's wettability and dissolving rate.

When compared to pure clonazepam, solid dispersions including polymer (1:10 ratio) made by solvent technique shown a significant improvement in the release profile.

Key words: Kollidon VA 64, PEG 6000, solid dispersions, Kollicoat IR, and clonazepam..

I. INTRODUCTION

The mechanisms for the enhancement of the dissolution rate of solid dispersions have been proposed by several investigators. Molecular dispersion of drug in polymeric carriers may lead to particle size reduction and surface area enhancement, which results improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process and improvement of drug solubility and wettability due to surrounding hydrophilic carriers¹. Most of the recently introduced drugs suffer from poor solubility as they are developed by combinatorial chemistry and high throughput screening techniques. Solid dispersions are useful for solving the solubility and bioavailability problem of such drugs². By definition solid dispersions are formulations of finely crystalline or amorphous drug dispersed in an inert matrix³. Reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. The methods used to prepare solid dispersions include the melting method, the solvent method, and the solvent wetting method^{4, 5}. Among various approaches employed to improve the dissolution of poorly soluble drugs, solid dispersion has been proven successful. Fast or immediate drug dissolution from solid dispersions has been observed due to increased wettability, improved dispersibility of drug particles, and existence of the drug in amorphous form with improved solubility and absence of aggregation of drug

Polymeric carriers are the most successful for solid dispersions, because they are able to originate amorphous solid dispersions. They are divided into fully synthetic polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural productbased polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivatives, like cyclodextrins. Amorphous solid dispersions can be classified according to the molecular interaction of drug and carriers in solid solutions, solid suspensions or a mixture of both. In amorphous solid solutions, drug and carrier are totally miscible and soluble, originating a homogeneous molecular interaction between them. In these systems, the drug and carrier interaction energy is extremely high, resulting in a really true solution 8.

In the present experiment Clonazepam belongs to a class of anticonvulsants that enhances gamma-aminobutyric acid (GABA) receptor responses. Anticonvulsants used for several types of seizures, including myotonic or atonic seizures, photosensitive epilepsy, and absence seizures. Clonazepam exerts its action by binding to the benzodiazepine site of the GABA receptors, which causes an enhancement of the electric effect of GABA binding on neurons resulting in an increased influx of chloride ions into the neurons. This results in an inhibition of synaptic transmission across the central nervous system 9, 10. Clonazepam is a light yellow crystalline powder which is practically odorless. It is freely very soluble in methanol, ethanol, and acetone, and practically insoluble in water (at 25°C < 0.1 mg/ml). It is generally considered that compounds with very low aqueous solubility will show dissolution rate-limited absorption and, hence, poor absorption,

distribution, and target organ delivery 11. Improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy.

Several attempts have been reported in literature using solid dispersion technique to increase the dissolution characteristics where Hydroxy Propyl methyl cellulose (HPMC), polyvinylpyrrolidone (PVP), polyethylene glycol, sodium carboxymethyl cellulose, sodium starch glycolate, pregelatinized starch were used as solubilizing agents 12-14.

In this study, solid dispersions were formulated with three water soluble polymers by solvent evaporation technique. Micronized poloxamer 407, Kollicoat IR and Kollidon VA 64 were utilized for this purpose. Poloxamers are nonionic polyoxyethylene-polyoxypropylene copolymers used primarily as emulsifiers, solubilizing agents, wetting agents and have been reported for enhancing the solubility and bioavailability of sparingly soluble drugs in solid dosage forms 15-17. Solid dispersions were prepared with poloxamer by melting method for rofecoxib and ibuprofen¹⁸. Reduced crystalline structure and improved wettability 19, 20 were mentioned as the mechanism by which poloxamer can enhance dissolution from solid dispersions. Solid dispersions formulations of gliclazide can be successfully used to design a solid dosage form of the drug, which would have significant advantages over the current marketed tablets²¹.

The objective of the present study was to improve the solubility of Clonazepam by using three different types of water soluble polymers. The formulations were characterized by in vitro dissolution study to compare the effects of polymers on the preparation of solid dispersion and dissolution enhancement.

II. MATERIALS AND METHODS

Materials: Clonazepam was a gift sample from Rangs Pharmaceuticals Ltd., Dhaka,

Bangladesh. Poloxamer 407 (Lutrol 127), Kollicoat IR and Kollidon VA 64 was gifted by BASF, PEG 6000 (Loba Chemie, India), reagent grade methanol (Merck, Germany) were purchased from the market.

Preparation of solid dispersions

Solid dispersion with different polymer showed in the table 1-3. 50 mg of clonazepam was taken in the vial and 4ml acetone was added in each. The drug was completely dissolved in the solvent. Then different types of polymer were added in the solution and sonicated it for 1 min. All solutions were dried by hot air. When the solutions were evaporated completely, they were stored in a dessicator. The formulations were withdrawn from vials, crushed by mortar and pestle, passed through 36 micron sieves. Finally lactose was added in the formulation. Then formulations were transferred in vials and stored in a dessicator. A slightly different approach was warranted for solid dispersions containing poloxamer as it is low melting substance (melting temp. 52-57°C) and melting method was most suitable for this polymer 18, 19 . The drug was dispersed with methanol in a glass flask and heated in a water bath at 50°C. Poloxamer was added to the dispersion and it was melted at that temperature. The solvent was evaporated during constant mixing and the resulting solid mass was dried at 40°C in hot air oven. The dried samples were crushed by mortar and pestle followed by sieving through 30 mesh screen. The ratio between drug and polymer for all formulations was kept at 1:2, 1:4, 1:6, 1:8 and 1:10.

Table 1. Formulation of clonazepam solid dispersion by changing the amounts of Kollicoat IR with PEG 6000

Formulation of solid dispersion						
Component	F1	F2	F3	F4	F5	F6
	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)
Clonazepam	50	50	50	50	50	50
PEG 6000	100	100	100	100	100	100
Kollicoat IR	500	400	300	200	100	0
Lactose (g)	3	3	3	3	3	3

Table 2. Formulation of clonazepam solid dispersion by changing amounts of Kollidon VA 64 with PEG 600

Formulation of solid dispersion						
Component	F1	F2	F3	F4	F5	F6
	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)
Clonazepam	50	50	50	50	50	50
PEG 6000	100	100	100	100	100	100
Kollidon VA 64	500	400	300	200	100	0
Lactose (g)	3	3	3	3	3	3

Table 3. Formulation of clonazepam solid dispersion by changing the amounts of Poloxamer 407 with PEG 6000

Formulation of solid dispersion						
Formulation	F1	F2	F3	F4	F5	F6
	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)
Clonazepam	50	50	50	50	50	50
PEG 6000	100	100	100	100	100	100
Poloxamer 407	500	400	300	200	100	0
Lactose (g)	3	3	3	3	3	3

Preparation of standard curve of clonazepam in distilled water

10mg of Clonazepam was accurately weighted & dissolved in 100 ml of Methanol to produce a solution 0.1 mg/ml for preparation of a standard curve for Clonazepam. Then 20ml of preparation was taken and made up to 100ml with distil water. 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 distil water was added to them for the purpose of serial dilution. This serial dilution was carried out to get different Clonazepam concentration. These were then analyzed by UV spectrophotometer at 254 nm and absorbance was noted. Then the absorbance values were plotted against drug

concentration and standard curve of Clonazepam was produced.

Quantitative assay

Formulation containing clonazepam was taken in a mortar and triturated properly until fine powder was formed. 5 mg equivalent of fine powder was taken in a 10 ml volumetric flask with the help of a funnel. 5 ml methanol and 5 ml distil water was added with the powder, sonicated in a sonicator to make a clear solution and then finally was filtered. From this solution 2 ml drug solution was withdrawn and taken in a 100 ml volumetric flask. The volume of drug solution was then adjusted up to 100 ml with distil water. In the same way, 10 mg equivalent of fine powder was taken in a 25 ml volumetric flask with the help of a funnel. 10 ml methanol and 15 ml distil water was added with the powder, sonicated in a sonicator to make a clear solution and then finally was filtered. From this solution 2 ml drug solution was withdrawn and taken in a 100 ml volumetric flask. The volume of drug solution was then adjusted up to 100 ml with distil water. For reagent blank 1 ml methanol was transferred into a 100 ml volumetric flask, diluted to 100 ml with distil water. Absorbance value was determined using UV-spectrophotometer (UV-mini-1240, SHIMADZU CORP., Kyoto, Japan), at 254 nm. Solutions were also diluted if necessary. Using the absorbance value, the amount of clonazepam entrapped was determined with the help of standard curve.

In-vitro release study of Clonazepam from solid dispersion

A paddle type Dissolution Apparatus (USP Type II Dissolution Apparatus, VEEGO, INDIA) used in in-vitro dissolution study. In a fixed amount of solid dispersion containing 10 mg equivalent clonazepam from each batch was calculated for dissolution purpose. Distil water was used as dissolution media. 1000 ml of distil water was used as dissolution medium in each dissolution

basket at a temperature of 37° C and a paddle speed of 100 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 5, 10, 15, 20, 30, 40, 50 & 60 minutes. Each and every time 5 ml dissolution sample was compensated by another fresh 5 ml distil water.

Dissolution samples were withdrawn with the help of disposable syringe filter and were kept in a test tube. The dissolution samples were then analyzed spectrophotometrically by UV-VIS spectrophotometer (UV-mini-1240, SHIMADZU CORP., Kyoto, Japan) at 254 nm and absorbance was noted. The dissolution study for each batch was performed in triplicate. These were then analyzed by UV spectrophotometer

III. RESULTS AND DISCUSSION

The effects of three water soluble polymers (Kollicoat IR, Kollidon VA 64 and poloxamer 407) on the formulations of Clonazepam solid dispersions were compared. The potencies of Clonazepam in prepared solid dispersions were analyzed by UV spectrophotometer and the results were within 99-100% in all cases which indicates uniform mixing of the dispersions.

DISSOLUTION STUDIES

The enhancement of polymers on drug release from solid dispersion was evaluated by comparing the solubility of drug present in the mixtures as well as of pure drug. The in vitro dissolution testing was performed for 45 minutes to ascertain the effect of formulations on immediate drug release enhancement. Theoretically the solid dispersions improve drug dissolution by decreasing particle size, formation of amorphous forms and improve wettability². The better dissolution rate of solid dispersion may be due to an improved wettability of drug particles, a significant reduction in particle size during formation of

solid dispersion and dissolution due to increase in the surface area of drug, proper dispersion and increase in the amorphicity of drug by adsorption on the surface of adsorbent. High rate of dissolution of soluble polymer component of solid dispersion along with more insoluble but finely mixed drug into dissolution medium is the factor for fast dissolution of drug. Compacting poorly water-soluble drug particles with different hydrophilic polymers like HPMC, Kollicoat IR, PVP and Chitosan particles resulted in a granular powder having enhanced drug solubility and dissolution properties. Drug dissolution rates were comparably high for compacted granules then their physical mixture and drug alone, suggesting that compaction processes with hydrophilic polymers improve the drug dissolution rate. The mechanism is believed to be a microenvironment polymer effect facilitated by keeping the polymers and drug particles in close proximity during drug dissolution 22 .

Comparison of % release of Drug from Formulation of Kollicoat IR

From the curve it is observed that increasing of Kollicoat IR when other polymer were fixed, the drug release was increased significantly. In the case of pure drug, release was decreased than drug with combination of other polymers. When Kollicoat IR was increased, drug release from solid dispersion was increased significantly due to wetting ability and convert crystalline to amorphous. The formulation containing increased Kollicoat IR increased drug release.

The formulation containing 1:10 drug-polymer, the drug release was highest due to wetting ability (Fig. 1). At high concentration, Kollicoat IR provides wetting of drug and improves dissolution. The increase in dissolution rate of drug in the presences of carriers could be attributed to an increasingly effective solubilization process. Because of the formation of amorphous phases, the dissolution rate is very

high since the drug simply dissolved along with the polymer. Therefore, the high aqueous solubility and low viscosity of Kollicoat IR enhances the dissolution process 23, 24 .

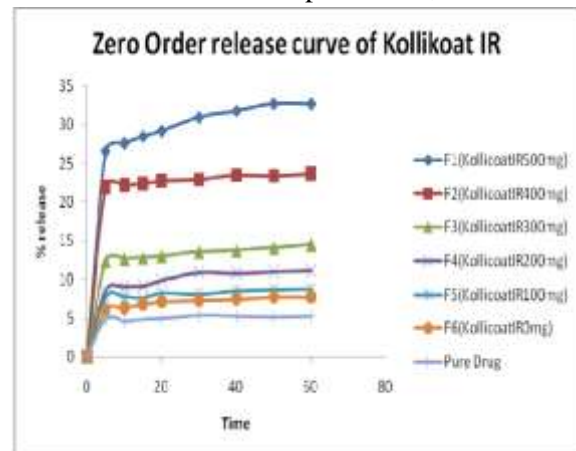


FIG. 1. Drug release from Kollicoat IR formulations

Comparison of % release of Drug from Formulation of Kollidon VA 64

From the curve (Fig. 2) it is observed that increasing of Kollidon VA 64 when other polymer were fixed, the drug release was increased significantly. In the case of pure drug, release was decreased than drug with the combination of other polymer. When Kollidon VA 64 was increased drug release from solid dispersion was increased significantly due to wetting ability and convert crystalline to amorphous. The formulation containing increased Kollidon VA 64 increased drug release. Similar studies were conducted, formulations of Biphenyl dimethyl dicarboxylate in Kollidon VA 64 solid dispersions remarkably improved the dissolution rate of the drug 25 .

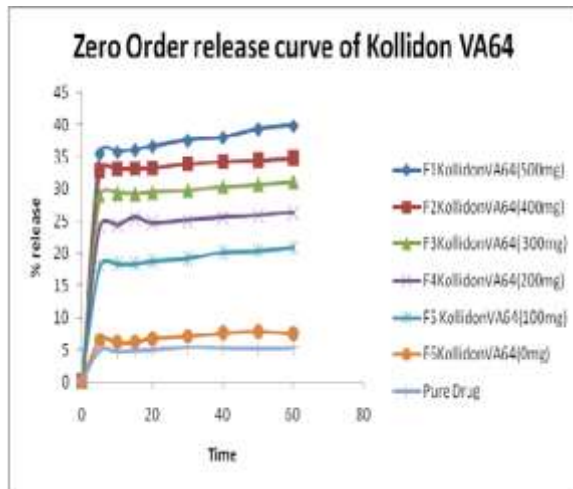


FIG. 2. Drug release from kollidon formulations
 Comparison of % release of Drug from
 Formulation of Poloxamer407

From the curve (Fig. 3) it is observed that increasing of Poloxamer when other polymer were fixed, the drug release was increased significantly. In the case of pure drug, release was decreased than drug with the combination of other polymer. When poloxamer is increased drug release from solid dispersion was increased significantly due to wetting ability and convert amorphous to crystalline. The formulation containing increased poloxamer increased drug release. Poloxamer 407 can act as gelling agent at high concentration and it can affect drug dissolution from solid dispersions. Drug release was very rapid compared to other polymers ratios.

But similar to HPMC, higher amount of poloxamer facilitated drug release. When the poloxamer concentration was decreased the drug release was also decreased.

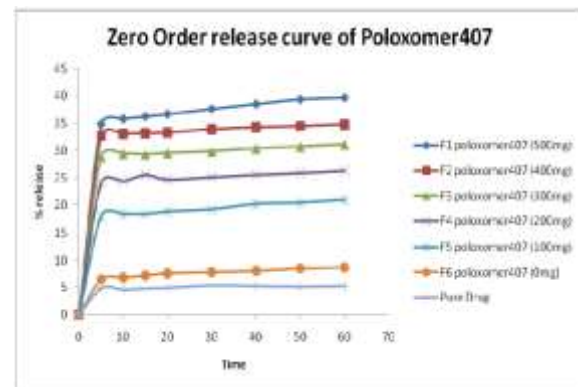


FIG. 3. Drug release from plooxemer formulations

Although dissolution rate for poorly water-soluble drug can be enhanced by converting the drug into its amorphous form 26 but it can be thermodynamically unstable, and under certain levels of heat and humidity, could recrystallize into a more stable, poorly water-soluble form 27. Clonazepam could be crystallized out of the formulations from poloxamer containing solid dispersions after contact with aqueous media. Poloxomers rapidly dissolved away from the solid dispersions and amorphous clonazepam reverted back to its crystalline state.

It was reported that molecular dispersion is one of the important roles of drug release from the polymer-drug system. The present work shows that the dissolution rate of Clonazepam from solid dispersions with PEG 6000 and poloxamer was improved compared to the pure drug. Further, solid dispersions performed better than the corresponding physical mixtures. Various studies have shown that freely water soluble carriers inhibit crystallization of drugs in solid dispersions resulting in amorphous form of the drug in the solid dispersions 28, 29. Crystallization inhibition is attributed to two effects: interactions, such as hydrogen bonding between the drug and the polymer and the entrapment of the drug molecules in the polymer matrix during solvent evaporation or a combination of both. The present study confirmed the advantage of improved aqueous

solubility of Clonazepam in its solid dispersions form, which can be formulated as tablets with better dissolution characteristics.

IV. CONCLUSION

Drug solubility was improved by solid dispersions made from polymers using the solvent evaporation technique. Solid dispersion has been shown to be a helpful method for increasing the solubility of medications that are weakly soluble, such as clonazepam. Increased drug release from produced solid dispersions was seen in all situations when the polymeric component of the dispersions was increased. When compared to the Kollicoat IR dispersion or pure medication, the dispersion including Poloxamer and Kollidon VA 64 demonstrated an adequate dissolution. The results of the research showed that the ideal concentrations of hydrophilic carriers and hydrophilic porous adsorbants guarantee the quick and thorough dissolution of clonazepam from solid dispersions for use in oral medication formulations. Based on experimental results, it is determined that the drug-polymer ratio and polymer type play a crucial role in the formation of solid dispersions.

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