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Formulation and Evaluation of Oral Dispersible Tablet of Poorly Water-Soluble Drug 'Glimepiride' by Using Solubility Enhancement Technique

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Abstract:
The present study is regarding Glimepiride (GMP) is poorly water-soluble drug. According to the BCS, Glimepiride undergoes Class II - High Permeability and Low Solubility. The objective of the research project is to enhance the solubility of Glimepiride by using solubility enhancement techniques. The endeavor is to improve its solubility by using super disintegrating agent to enhance the ability of disintegration of Oro dispersible tablet. To enhance of solubility of GMP, our select the method i.e. solid dispersion technique because Solid dispersion is an effective way of improving the dissolution rate of poorly water-soluble drugs and hence its bioavailability. The polymers used were PEG 4000 and PEG 6000 for prepared solid dispersions in different ratio by two method i.e. Fusion and solvent evaporation method. The solvent evaporation method is better result of drug for enhancement of solubility. Oral dispersible tablet of Glimepiride was prepared by direct compression method. ODTs of glimepiride by using different super disintegrants such as sodium starch glycolate, cross povidone and croscarmellose sodium. Further, post evaluation parameters like Shape and Color of Tablets, Thickness, hardness, friability, weight variation, Uniformity of Drug Content, In vitro Dissolution Rate Studies and In-vitro disintegration time were also evaluated and the results were discussed.

KEYWORDS: Orodispersible tablet, glimepiride, solid dispersion, solvent evaporation method, direct compression Method and super disintegrating agents

1. Introduction

Oro dispersible tablets have been placed in the mouth where they disperse fast before being swallowed and they are uncoated tablets. When the disintegration tests are carried out up to the test for tablet disintegration, Oro dispersible tablets dissolve in 180 seconds. The terms Oro dispersible tablets, quick-dissolving tablets, mouth-dissolving tablets, fast-dissolving

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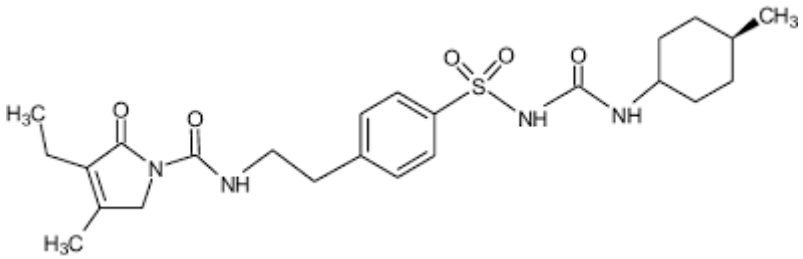
tablets, rapid-dissolving tablets and porous tablets are also used to describe oral disintegrating tablets.[1]

Disintegrating agents are substances that are commonly added to tablet formulations in order to facilitate the dissolution or release of the active components when the tablet is placed in a fluid environment by dissolving the compacted mass into its constituent particles. Recently, new materials known as super disintegrants have been discovered to improve disintegration processes.[2]

Diabetes mellitus is a condition in which an individual has elevated blood sugar levels due to insufficient insulin production by the body or improper response of body cells to the insulin that is produced. The hormone insulin, which the pancreas produces, allows body cells to absorb glucose and convert it into energy. glucose builds up in the blood and can cause problems with the blood vessels, nerves, and other tissues if the body cells are unable to absorb it. Four primary kinds of diabetes mellitus are recognized. They are, Type -I, Type –II, Gestational diabetes, and other types of diabetes.[3]

Glimepiride is one derivatives of sulfonyl urea used in the treatment of Type II. According to the BCS, Glimepiride undergoes Class II - High Permeability and Low Solubility. It is anti-diabetic drug. It is practically insoluble in water, soluble in dimethyl formamide, slightly soluble in methanol, sparingly soluble in methylene chloride. It is weak stimulating the release of insulin from pancrease, which help to lower blood sugar level. Half-life is Approximately 5 hours following single dose. It is completely (100%) absorbed after oral administration. Over 99.5% bound to plasma protein. [4]



Structure of Glimepiride

Glimepiride is an insulin secretagogue and like other sulfonylureas, is only effective in patients with residual pancreatic beta-cell activity. It stimulating release of insulin from the beta cell of the pancreas and increasing sensitivity peripheral tissue to insulin. It works to binding to specific receptor on the beta cell of pancreas which triggers that lead to release of insulin. It also helps to reduce the production of glucose by the liver, which further contributed to its glucose lowering effects. Saliva is mostly secreted in the mouth cavity by parotid, submandibular (submaxillary), sublingual, and other smaller glands. It plays a significant part in the decomposition of FDTs. Saliva is mainly composed of water (99.5% w/v) and the remaining 0.5 % w/v is constituted by dissolved compounds.[4,5]

Advantage of Oro dispersible Tablets

- Increased stability suitable for continuous, regulated, offers patients and prescribers increased compliance and convenience.

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- ODTs are thought to be the ideal dose form for rapid medication delivery.[6,1]
- Improved quiet consistence.
- Rapid onsets of action should increase bioavailability.
- Comfort of taking and precise dosing when contrasted with fluid.[1,7]

Disadvantage of Orodispersible Tablets

- The tablets typically don't have enough mechanical strength. Therefore, careful handling is necessary.
- If the tablets are not made properly, they may leave a bad taste and/or grittiness in the mouth.
- They need specific packaging because they cannot be packaged in regular strips or bottles.
- Bitter medications must be taste-masked using a variety of methods, which extends production time and costs.[1,6,7]

2. MATERIALS AND METHODS

2.1 Drug and chemicals used

Glimepiride was received as a gift sample from Auro Laboratories Limited Mumbai (Maharashtra) and other excipients such as peg 4000, PEG 6000, talc, sodium starch glycolate, Croscarmellose Sodium, Cross povidone, lactose, magnesium stearate were obtained from the Modern Laboratories, Indore,Loba Chemie Pvt. Ltd. Mumbai.

2.2 Method

2.2.1 Evaluation parameters of preformulation [8,10]

A) Standardization of Glimepiride by UV–Vis spectrophotometer:

Accurately weighed 20 mg of glimepiride was dissolved in 20 ml of dimethylformamide was taken in 50 ml capacity of volumetric flask. Then flask Shaked & volume makeup to 50ml with dimethylformamide to obtain the stock solution 4000µg /ml. Then 0.5 ml of stock solution was taken and diluted with 10 ml of dimethylformamide to obtain concentration 20µg /ml. The spectrum of this solution was recorded in 200-400 nm range using U.V. spectrophotometers. After the complete scan λmax of glimepiride was 228 nm and shown fig.1.[8]

Preparation of standard stock solution

1ml was taken and diluted up to 10 ml. from this solution 0.5, 1.0, 1.5, 2.0 and 2.5ml solutions were transferred to 10ml volumetric flasks and make up the volume up to methanol gives standard drug solution of 5, 10, 15, 20 and 25µg/ ml concentration

Preparation of calibration curve in dimethylformamide :

20 mg of glimepiride was weighed and transferred to 50ml of volumetric flask and volume make up with dimethylformamide to achieve the resulting 400 µg/ ml (stock solution). After that dilution make from stock solution with dimethylformamide in concentration range 5,10,15,20,25,30 µg/ ml. The UV spectrum of glimepiride is shown in fig. 2

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Table 1: Calibration Curve of glimepiride in dimethylformamide

S. No	Conc.(mg/ml)	Absorbance
1	5 µg/ml	0.080
2	10 µg/ml	0.175
3	15 µg/ml	0.254
4	20 µg/ml	0.341
5	25 µg/ml	0.425
6	30 µg/ml	0.507

B) Melting point

Melting point is one of the parameters to just the purity of drug. If there should arise in occurrence of unadulterated chemicals, melting point are sharp and constant. Since the drug contains the blended chemicals, they are depicted with certain scope of melting point.

Procedure for determine melting point

A little quantity of powder was placed into a small capillary tube. The thermometer and capillary tube placed in melting point apparatus and read the temperature at which power began to liquefy and note down temperature. The melting point of Glimepiride was found 213 °C.

C) Determination of pH

Determine the pH of a drug is important because it helps us understand how acidic or basic of drug. pH can affect how a drug is absorbed, distributed and metabolized in our bodies. The pH of drug is measured using pH meter.

Procedure for determine pH

Firstly, the electrode dipped in KCL solution for 24 hours. After these hours, electrode rinse with distilled water and set room temperature(25º). After that calibrated pH meter using standard buffer solution pH 7, pH 4 and pH 9.2. Then making drug solution (10mg drug in 10ml methanol) and note down pH reading when the pH reading is stable. The pH of Glimepiride was found 6.3

D) Bulk density: It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder in to a measuring cylinder and the volume was reported in table 8.

Bulk density = Weight of powder / Bulk volume

E) Tapped density: It is the ratio of total mass of powder of the tapped volume of powder. In this method powder is filled in measuring cylinder. After that it is mechanically tap 100 times on device and the tapping was continued until no further change in volume was reported in table 8.

Tapped Density = Weight of powder / Tapped volume

F) Compressibility Index: It can help us understanding how the powder will behave during processing and 8storage. Powders with compressibility values lesser than about 20% has been

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found to exhibit good flow properties. Tapped (TD) and Apparent Bulk density (BD) measurements can be used to estimate the compressibility of a material and result was reported in table 8.

Carr's Index (%) = [(TD-BD) x100] / TD

G) Hausner's Ratio: It is the ratio of bulk volume to tapped volume or tapped density to bulk density and result was reported in table 8.

Hausner Ratio = tapped bulk density / bulk density

H) Angle of repose: The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using equation and result was reported in table 8.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

θ= Angle of repose, h = height of the powder cone, r = radius of the powder cone

2.2.2 Preparation of solid dispersion

Preparation of solid dispersion using PEG 4000 and PEG 6000 solid dispersion were used to prepare at weight ratio of 1:3,1:7 and 1:10 using two different preparation methods such as fusion methods and solvent evaporation.

S. No.	Solid Dispersion Complexes	
	Drug: PEG 4000	Drug: PEG 6000
1.	1:1	1:1
2.	1:5	1:5
3.	1:10	1:10

Table 2: Preparation of solid dispersion complexes

Method of preparation of solid dispersion by solvent evaporation method

In the solvent evaporation method, drug was dissolved in 25ml of methanol, while PEG 4000 and PEG 6000 were dissolved in 50ml of distilled water. The two solutions were mixed together and stirred for 1hr (magnetic stirrer, Electric India) methanol was evaporated off by heating at 40ºC under constant stirring, Water was then removed under reduced pressure using rotary evaporator. The mixture was placed overnight for 24hr in an oven at 40ºC to remove the residue solvent. The inclusion complex was ground using pestle and mortar. After sieving through a #65 mesh sieve, the inclusion complex was kept in a closed container. [8]

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Method of preparation of solid dispersion by fusion method

Solid dispersion of drug: PEG 4000 and PEG 6000 in weight ratio of 1:1,1:5 and 1:10 were prepared by fusion method. Solid dispersion was prepared by melting the accurate weighted amount of career (PEG 4000, PEG 6000) in a water bath at the temperature of 60ºC and the drug dispersed in the molten solution. Weight amount of drug was taken in petri dish and required amount of career (PEG 4000 and PEG 6000) were added to prepare drug formulation. The preparation was transferred to the refrigerator for just 5 minutes to solidify. The solid dispersion prepared were pulverized and sifted (40#) sieve and stored in a desiccator. [11]

Selection of solid dispersion

Preparation of solid dispersion was performed by methods, i.e., Fusion method and solvent evaporation method. By these 2 methods, solvent evaporation shows a better result. Solubility was performed by adding a cross amount of solid dispersion in 50 ml of distilled water. The flask was vortex mixed for 3 minutes and agited at 120 rounds per minutes in a water bath maintained at 30ºC for 72 hours. Samples of 3 ml were withdrawn and filtered through a 0.45µm nylon membrane filter. Filtrate (0.1ml) was diluted appropriately and measured spectrophotometrically (Lab India 3000+) at 228 nm. Each measurement was repeated three times.

2.2.3 Formulation development of Oro dispersible tablet of glimepiride

Orodispersible tablets of glimepiride were be prepared by direct compression method. The drug with solid dispersion and mannitol as diluents, sodium starch glycolate, cross povidone and croscarmellose sodium as super disintegrants and aspartame as sweetener was screened through 40 # and properly mixed together. Talc as flow promoter and magnesium stearate as lubricant, lactose as a binder was screened through 80 # and blended with initial mixture. Powder thus obtained was compressed into tablets on single punch rotary tablet compression machine. [5,8,9]

Formulation Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Glimepiride Solid Dispersion (Equivalent to 40mg)	240	240	240	240	240	240	240	240	240
Sodium Starch Glycolate	6	12	18	-	-	-	-	-	-
Cross povidone	-	-	-	6	12	18			
Croscarmellose Sodium	-	-	-	-	-	-	6	12	18
Talc	5	5	5	5	5	5	5	5	5
Mg. Stearate	5	5	5	5	5	5	5	5	5
Lactose	34	28	22	34	28	22	34	28	22
Aspartame	5	5	5	5	5	5	5	5	5

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Mannitol	5	5	5	5	5	5	5	5	5
Total wt.	300	300	300	300	300	300	300	300	300

Table No 3: Formulation of Oro dispersible tablet

2.2.4 Evaluation of post compression method [8,9,1,12,13]

A) Shape and Color of Tablets: Uncoated tablets were examined under a lens for the shape of the tablet and color was observed by keeping the tablets in light.

B) Thickness Test: Thickness can be measured using a simple procedure. Five tablets were taken and their thickness was measured using Vernier calipers. The thickness was measured by placing tablet between two arms of the Vernier calipers and result was reported in table 8.

C) Weight Variation Test

For uniformity of tablet weight, 20 tablets were being taken randomly from each tablet formulation and weighed individually using an electronic digital balance and mean of tablet weights was calculated. The average weight of all tablets and percentage deviation from the mean for each tablet was determined and result was reported in table 8.

Table 4: % Deviation in Weight Variation

S. No.	Average weight of a tablet	% deviation
1.	130 mg or less	10
2.	More than 130 mg and less than 324 mg	7.5
3.	324 mg or more	5

D) Friability Test

Friability was determined using Roche friability. Pre-weighed 20 tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed, and percentage weight loss (friability) was calculated by

$$\% \text{ Friability} = W_0 - W / W_0 \times 100$$

$W_\circ$ = initial weight of 20 tablets

W = weight of 20 tablets after 100 revolutions

E) Uniformity of Drug Content:

10 tablets were weighed and powdered. An amount of drug equivalent to 10 mg of drug dissolved in 10 ml phosphate buffer (pH 6.8) sonicate it for 20 min. till the entire drug reached out from complex, then the solution was filtered through Whatman filter paper. From this Solution take 1 ml and diluted up to 100 ml with phosphate buffer (pH 6.8) and the drug content was determined UV- Visible spectrophotometer at 228nm and result was reported in table 8.

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F) In vitro disintegration time:

Disintegration test was performed using a USP disintegration apparatus, with 900 ml distilled water at 37±2°C. Time required for complete disintegration of six tablets was recorded and result was reported in table 8.

G) In vitro % drug release:

In vitro release studies of glimepiride were performed according to USP II Paddle apparatus. Paddle speed was maintained at 50rpm and 900mL of 6.8pH of phosphate buffer was used as the dissolution medium. Samples (10ml) were collected at predetermined time intervals and replaced with equal volume of fresh medium, filtered through a 0.45µm filter and analyzed with a UV-Visible spectrophotometer at λ=228nm. Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug release.

Result and Discussion

In the present investigation poorly, water-soluble drug is one of the most important parameters of oral formulations successfully developed glimepiride was using solvent evaporation method drug: PEG 6000 in (1:5 w/w). The precompression and post compression parameters studies are reported in table 5. The UV spectra of pure drug was reported in figure 2. In table 4 shows that the formulation F7 that orodispersible tablets of glimepiride shows 79.98% drug release within 15 min. Thus, it can be concluded that in vitro release of drugs is a direct function of its solubility in the dissolution medium when the regression coefficient values of were compared, it was observed that 'r^2' values of higuchi rel ease kinetics was maximum i.e. 0.999 hence indicating drug release from formulations was found to follow Higuchi release kinetics.

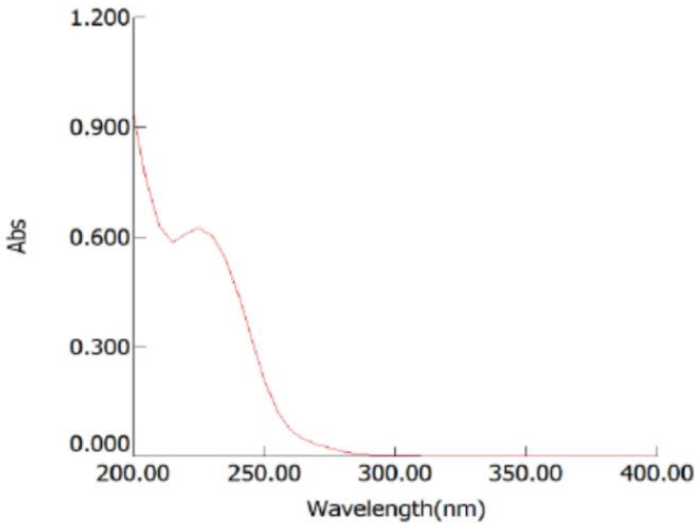

Figure 1: UV spectrum of pure drug (glimepiride)

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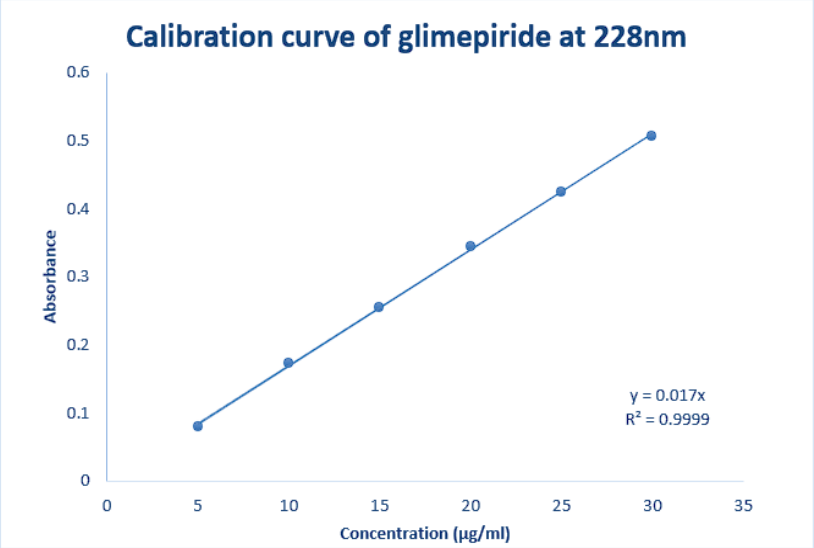

Figure 2: Calibration Curve of glimepiride in dimethylformamide

Time (min)	Square root of time	Log time	Cumulative % drug release	Log cumulative % drug release	Cumulative % drug remaining	Log cumulative % drug remaining
1	1	0	26.65	1.426	73.35	1.865
5	2.23607	0.6989	48.85	1.689	51.15	1.709
10	3.16228	1	69.98	1.845	30.02	1.477
15	3.87298	1.1761	79.98	1.903	20.02	1.301

Table 5: *In Vitro* % drug release for Optimized batch F7

Batch	Zero order release kinetic	First order release kinetic	Higuchi release kinetic	Korsmeyer peppas release kinetic
	r^2			
F7	0.999	0.958	0.995	0.995

Table 6: Regression analysis data

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Optimized Formula:

Ingredients (F7)	Each tablet quantity (mg)
Glimepiride (Equivalent to 40mg solid dispersion)	240
Croscarmellose Sodium	6
Talc	5
Mg. Stearate	5
Lactose	34
Aspartame	5
Mannitol	5
Total wt.	300

Table 7: Optimized formula of Glimepiride Orodispersible Tablets

Evaluation of precompression and post compression parameters for Optimized batch F7:

Evaluation Parameters	Batch F7
Bulk Density(gm/cm^3)	0.534
Tapped Density(gm/cm^3)	0.638
Carr's Index (%)	22.011
Hausner's Ratio	1.312
Angle of Repose(º)	25.4
Thickness(mm)	2.1±0.2
Hardness(kg/cm^2)	2.9±0.12
Friability (%)	0.72±0.11
Weight variation	301±6
Disintegrating Time (sec)	50±1
Drug Content (%)	99.85±0.32

Table 8: Evaluation of precompression and post compression parameters for Optimized batch F7 glimepiride Orodispersible Tablets

CONCLUSION:

Orodispersible tablets of Glimepiride was successfully prepared. The dissolution rate of Glimepiride was increased by solid dispersions prepared by direct compression method by using super disintegrants. It can be concluded that developed poorly water-soluble drug for orodispersible tablets prove to be were beneficial. The formulation batch of F7 was the optimized formula showed satisfactory results with various evaluation of precompression parameters like disintegration time and *in vitro* % drug release. Thus, it was concluded that in vitro release of drugs is a direct function of its solubility in the dissolution medium and orodispersible tablets of glimepiride can be successfully prepared.

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