Original Article

# Preparation and Optimization of Glimepiride Multiparticulate System Using Novel Liquid Layering Technique

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## ABSTRACT

**Background and the purpose of the study**: Multiparticulates by liquid layering process has advantages of producing homogenous small drug loaded units, high reliability and the possibility of applying the successive layers of drug entities using the same equipment. The aim of this study was to develop pellet formulations that could be used to improve the dissolution and bioavailability of a poorly water-soluble model drug, glimepiride. In solution/suspension layering, drug particles are dissolved in the binding liquid and particularly coated with the aim of providing a desired drug release profile.

**Method**: Multiparticulate formulation by liquid layering technology was prepared by conventional pan coating process. Selection of the suitable carrier, and pan speed were critical variables that were found to affect the dissolution of drug. Carrier loaded pellets were prepared by using mannitol, microcrystalline cellulose and starch as carriers, and pan was rotated at different speed such as 20.30.40.50.60 rpm. The prepared drug loaded pellets were evaluated by HPLC method. In vitro dissolution studies were carried out to study the effect of nature of carrier, and pan speed on drug release.

**Results**: Mannitol was found to be the effective carrier of active ingredient. Its characteristics of high solubility, low hygroscopicity and extreme inertness help in improving stability and dissolution of finished formulation. The results showed that drug release of glimepiride was found to increase with pellets having mannitol as carrier and at a pan speed of 40rpm. The compatibility between drug and polymers in the drug loaded pellets was confirmed by HPLC studies. It may be concluded that $F_6$ is an ideal formulation for once a day administration.

**Keywords**: Multiparticulate, Liquid layering, Bioavailability.

## INTRODUCTION

Multiparticulate drug delivery systems are the most accepted and extensively used dosage forms as they offer numerous advantage over unit dosage forms like improved bioavailability because of increased surface area, reduced inter subject variation, more even and predictable distribution and transportation and reduced risk of dose dumping. Pelletization is one of the most promising technique for the Multiparticulate drug delivery systems[1] .

The layering process is particularly suitable for production of small drug loaded units, multiples of which are placed into capsules for patient delivery[2]. The layering process comprises the deposition of successive layers of drug entities from solution on nuclei which may be crystals or granules of the same material or inert starter seeds[3]. In solution/suspension layering, drug particles are dissolved in the binding liquid. They are particularly coated with the aim of providing a desired drug release profile[4].

Fig1:Principle of solution/suspension layering process with different steps is illustrated in figure.

Glimepiride belongs to a 'second – generation" sulfonylurea used in treatment of type 2 diabetes mellitus. It exhibits poor aqueous solubility hence needs enhancement in dissolution and bioavailability.

## MATERIALS AND METHODS

### Preparation of carrier loaded pellets

Powder layering technique was employed to prepare starter seeds. 50g of core sugar (#30/44) was loaded into the coating pan and was allowed to rotate. The mixture of carrier and talc in 3:1 proportion was used to prepare the drug free pellets. The binder and carrier mixture were alternatively added with thorough mixing. PVP K-30 (15%W/W) in isopropyl alcohol was used as binder. Loading process was continued until the required size attained. Then, they were dried in hot air oven at 40ºC for 1hr.

### Formulation of drug coated pellets

50g of carrier pellets were charged into R & D coater. Temperature was set to $60^0$C and the pan was allowed to rotate at a speed of 30 rpm. Drug and binder (PVP K-30) were dissolved in ethyl alcohol. The solution was sprayed onto the pellets which are maintained at 60°C. Pressure was adjusted to 0.1MPa and spray rate was maintained at 3ml/min using peristaltic pump. The coating process was continued till all the solution was deposited on the sugar spheres. They were dried in hot air oven at $60^0$C for about 2h.

### Optimization of formulation variables

### Influence of nature of carrier

The three carriers employed were mannitol, microcrystalline cellulose and starch. The carriers were previously passed through #200 and mixed with talc in 3:1 proportion. The mixture was used to prepare carrier loaded pellets as per the above procedure. Then they were coated with drug using ethyl alcohol and the process conditions were set to 30rpm, 60º C, 0.1 M Pa maintaining flow rate at 3ml/min. The composition of the pellets prepared with different carriers is given in Table 1.

### Influence of pan speed

Pan was loaded with selected starter seeds and the drug was coated onto them using alcohol at different pan speeds such as 20,30,40,50 and 60rpm. The composition of pellets formulated is given in Table 2.

### Preparation of standard plot of glimepride

Stock solution of 50 mg of the drug in 50 ml of methanol was prepared and further diluted with pH 7.8 phosphate buffer to obtain concentrations of 0, 2, 4, 6,8 &10 µg/ml and

analyzed spectrophotometrically at 228 nm against suitable blank. The results were plotted to obtain calibration equation and correlation coefficient (0.998).

### *In vitro* drug release studies

*In vitro* drug release studies for various formulations was performed in dissolution rate testing apparatus maintained at 37±0.5$^{O}$C employing USP apparatus type II. The paddle speed was set to 75rpm. Pellets equivalent to 2mg of drug were weighed and kept in the dissolution bowel containing 900mL of dissolution media ($P^{H}$ 7.8 phosphate buffer). 5mL of sample was periodically withdrawn and the dissolution medium was replaced with the same volume of medium. The collected samples were filtered, suitably diluted and analyzed at 228nm using UV-Visible spectrophotometer. The content of drug was calculated using the equation generated from Standard curve.

### High performance liquid chromatography (HPLC) spectral analysis

HPLC is a basic and reliable analytical tool for Preformulation study because of the high-resolution capacity, accuracy, and reproducibility of the equipment[5]. A reversed-phase method for the determination of Glimepiride in layered pellets formulations has been reported that also was used in the analysis of drug–excipients compatibility[6].

The system consisted of Waters Automated 2669 with a PDA detector. The software used in the system was Enpower version 2.0. In this method mobile phase, Acetonitrile : 0.03M di potassium hydrogen phosphate buffer (50:50) at a pH of 7.8, and a 250 X 4.6 mm Inertsil ODS 3V column having a 5µm packing as a stationary phase were used. Flow rate was 1.0 ml/min and the temperature of the column was ambient. 100 mg of Glimepiride in diluents as mobile phase was dissolved and the volume was made up to 100ml in the volumetric flask with the same. From the stock (1000µg/ml) further dilutions is made to get 100 µg/ml with the diluent, and used as testing solutio, were injected for the identification analysis. The chromatogram obtained was shown in the Figure 5.

## RESULTS & DISCUSSION

The *in vitro* drug release study for prepared pellets was carried out and the drug release was studied. Higher values of R indicate higher correlation coefficient for the best fit drug release model. The drug release from different batches $F_1$ to $F_8$ are shown in the figures 2 and 3 respectively. Best batches selected on the basis of their in vitro release were further evaluated and compared with in vitro release of pure drug[7].

The drug layered pellets ($F_3$) prepared by using mannitol as carrier, revealed an improved drug solubility. Hence mannitol was selected as effective carrier for preparing drug layered pellets. These mannitol starter seed were loaded in pan coater and the drug was coated on to these pellets, while the pan rotates at different speeds as mentioned in the table 4.

Increase in pan speed decreases the size of layered pellets, hence the in vitro profile of glimepiride pellets coated at speed of 40 rpm ($F_6$) showed good drug release profile[8].

In vitro dissolution studies were studied for pure drug and optimizes drug layered glimepiride pellets. The amount of drug release for optimized formulation was 99.88% within 10 min. It is due to the reason that mannitol is water soluble and it created pores in the pellets thus increasing the accessible surface area to the dissolution medium[9]. Which in turn leads to increased release of drug. Hence, formulation $F_6$ was considered as the best formulation.

The retention time of Glimepiride pure API and Glimepiride layered pellets were found to be 7.035 and 7.176

respectively. The blank chromatogram indicated no visible peaks at λ 228 nm. Thus indicating authenticity of Glimepiride in pellets[10].

## CONCLUSION

This study reports formulation and dissolution performance of mannitol based multi-unit pellets of poorly soluble drug that was obtained by novel drug layering technique. From the results it can be concluded that mannitol pellets coated with drug at pan speed of 40 rpm, can be used to formulate an effective multiple sub units with minimum time required for cumulative drug release. Glimepiride pellets prepared from drug layered process provide a feasible approach for development of a rapidly acting oral formulation for poorly water – soluble drug, with significant enhancement in the aqueous solubility and dissolution profile. However further study has to be carried out for optimizing other formulation and process variables.

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**Table 1. Composition of Glimepiride pellets formulated using different carriers**

| Ingredient | $F_1$ | $F_2$ | $F_3$ |
|---|---|---|---|
| **Carrier in pellets** | Mannitol pellets 50g | Starch pellets 50g | MCC pellets 50g |
| **Drug** | 3.571g | 3.571g | 3.571g |
| **PVP K-30** | 3.7g | 3.7g | 3.7g |
| **Ethyl alcohol** | 100ml | 100ml | 100ml |

**Table 2. Composition of Glimepiride pellets formulated at different pan speeds**

| Ingredient | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ |
|---|---|---|---|---|---|
| **Mannitol pellets** | 50g | 50g | 50g | 50g | 50g |
| **Drug** | 3.571g | 3.571g | 3.571g | 3.571g | 3.571g |
| **PVP K-30** | 3.7g | 3.7g | 3.7g | 3.7g | 3.7g |
| **Alcohol** | 100ml | 100ml | 100ml | 100ml | 100ml |
| **RPM** | 20 | 30 | 40 | 50 | 60 |

**Table 3. Composition of Glimepiride pellets formulated at different pan speeds**

| Time (min) | Cumulative % drug released | | |
|---|---|---|---|
| | $F_1$ | $F_2$ | $F_3$ |
| 0 | 0 | 0 | 0 |
| 5 | 93.858 | 80.376 | 87.367 |
| 10 | 98.874 | 89.311 | 93.345 |
| 15 | 99.919 | 95.797 | 98.355 |
| R | 0.9955 | 0.972 | 0.9733 |
| K($min^{-1}$) | 0.4734 | 0.223 | 0.2831 |
| $T_{50}$(min) | 1.5 | 3.1 | 2.4 |
| $T_{90}$(min) | 4.9 | 10.3 | 8.1 |

**Table 4. Composition of Glimepiride pellets formulated at different pan speeds**

| Time (min) | Cumulative % drug released | | | | |
|---|---|---|---|---|---|
| | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 91.362 | 95.856 | 96.355 | 98.353 | 93.858 |
| 10 | 95.364 | 99.384 | 99.886 | 99.398 | 98.874 |
| 15 | - | - | - | - | - |
| R | 0.9346 | 0.9876 | 0.9999 | 0.9322 | 0.9883 |
| K($min^{-1}$) | 0.3437 | 0.5346 | 0.6749 | 0.5733 | 0.4706 |
| $T_{50}$(min) | 2 | 1.3 | 1 | 1.2 | 2.1 |
| $T_{90}$(min) | 6.7 | 4.3 | 3.4 | 4 | 6.7 |

**Table 5. Composition of Glimepiride pellets formulated at different pan speeds**

| Time in min | Cumulative % drug released | |
|---|---|---|
| | Pure drug | $F_6$ |
| 0 | 0 | 0 |
| 5 | 45.922 | 96.355 |
| 10 | 77.635 | 99.886 |
| 15 | - | - |
| R | 0.9936 | 0.9999 |
| K($min^{-1}$) | 0.1444 | 0.6749 |
| $T_{50}$(min) | 4.8 | 1.0 |
| $T_{90}$(min) | 15.9 | 3.4 |
| $\%DE_{10}$ | 42.37 | 73.15 |

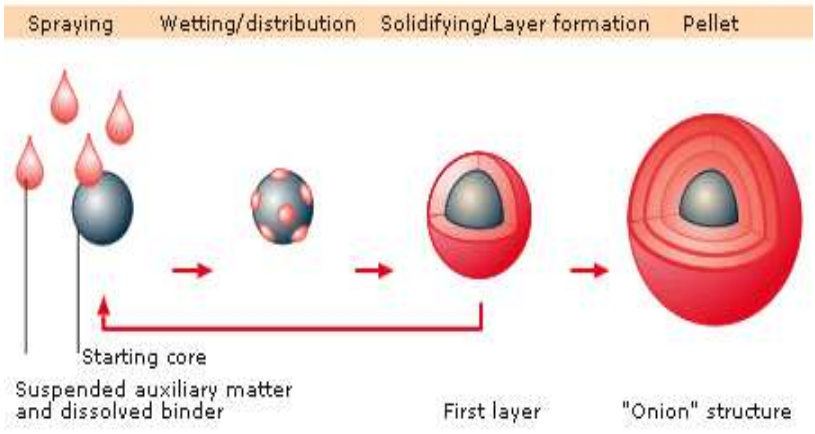


Figure.1. Principle of solution/suspension layering process with different steps

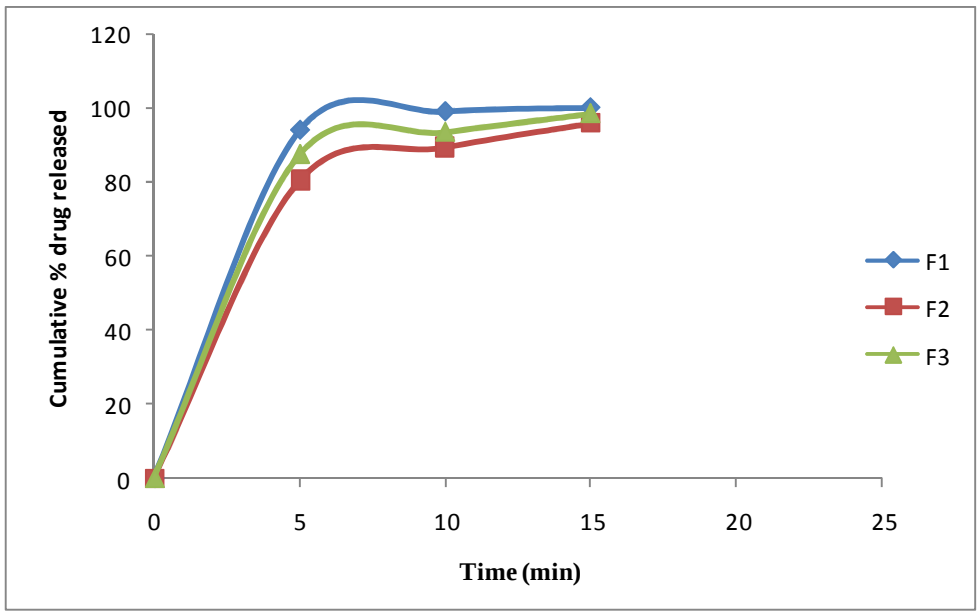


Figure.2. In vitro dissolution profiles of Glimepiride pellets formulated using different carriers

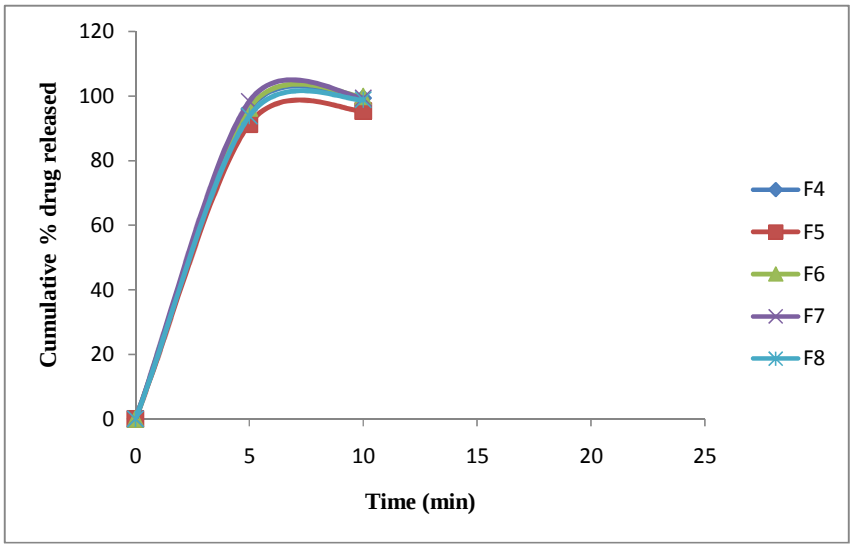


Figure.3. In vitro dissolution profiles of Glimepiride pellets formulated at different pan speeds

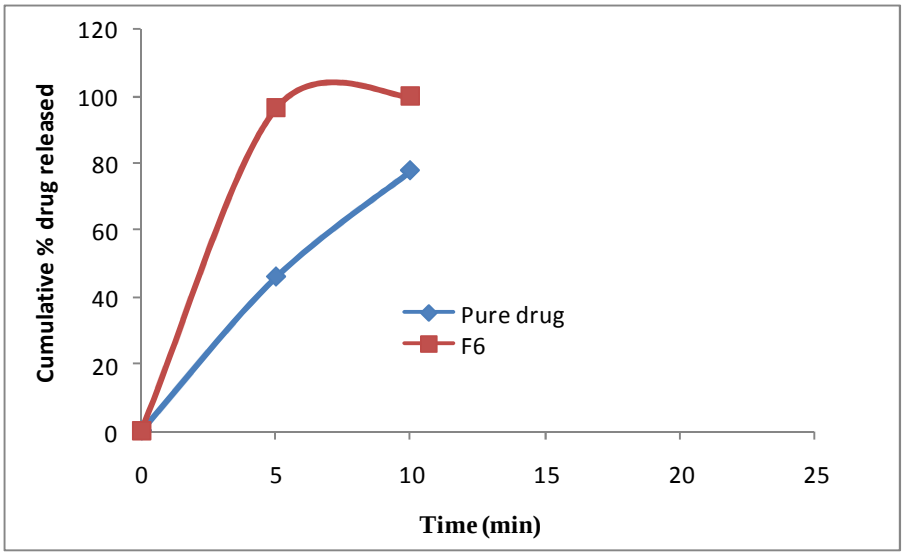


Figure.4. In vitro dissolution profiles of optimized Glimepiride pellets formulation and pure drug

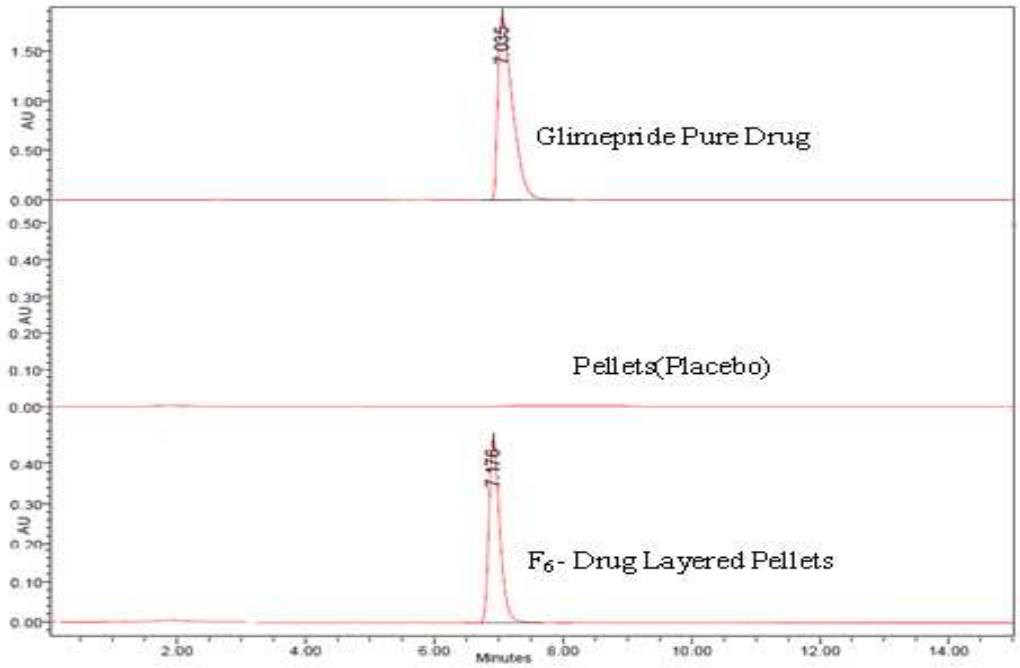


Figure.5. RP-HPLC chromatogram of Glimepride Pure Drug, Pellets and F6- Drug layered pellets