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Innovative Approaches to Enhance Dissolution Rate of a Hydrophobic Drug Glimepiride

Ismail Shehada MB[1], Usman S[1*], Akram M[2] and Usman A[3]

[1]*Department of Pharmaceutics, RAK College of Pharmaceutical Sciences, UAE*

[2]*Department of Pharmaceutics, University of Karachi, Pakistan*

[3]*Sindh Medical University, Pakistan*

Address for Correspondence
Usman S, Department of Pharmaceutics, College of Pharmaceutical Sciences, RAKMHSU, Ras Al Khaimah, UAE, Postal code: 11172, Cell: +971 558902559, Fax: +971 72269997; E-mail: shahnaz.usman@rakmhsu.ac.ae; shahnazgauhar@gmail.com

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Abstract

Objective: In the present study an effort was made to design and develop an immediate release tablet of glimepiride (as a model drug) by using the combination of two approaches i.e. conventional and innovative to enhance the dissolution rate of hydrophobic drugs.

Method: In the proposed study, USP analytical method was validated for the determination of glimepiride in its formulations. The calibration curve was linear over the concentration range of 2.5-12.5 µg/ml with a regression analysis (r^2 = 0.9999). For getting an idea about the release of drug from its dosage form, innovator brands were picked and estimated for pharmaceutical parameters. On the basis of this information, 10 experimental batches of tablets were prepared. The optimized batch was prepared by using 2:1 ratios of tween 80 and PVP K30 by slurry technique. Pre-compression and post-compression parameters were evaluated to confirm the validity of the design and development of processes. The optimized batch was subjected to stability studies for 03 months at 40±2 °C & % RH: 75±5%.

Results: The selected excipients and their proportions were found compatible with drug as well as with each other. The enhancement of dissolution indicated that the combination of Tween 80 and PVP K-30 in the slurry method made the faster release of the drug possible. The release rate of drug from optimized batch was estimated by a validated HPLC analytical method and compared with innovator results.

Conclusion: It was concluded that the proposed slurry technique is a simple and easy to adopt method and could be useful for the improvement of drug release from the tablets. The results indicated that the releases of drug from formulated tablets were same as that of innovator.

Introduction

Solubility is the major limiting factor for the absorption of hydrophobic drugs. In this regard the drug needs to be solubilized first in the solution to be available for absorption site. Drug release and dissolution are considered as the rate limiting steps in order for the drug to be absorbed from the Gastrointestinal Tract (GIT). Glimepiride is the drug which has low solubility and high permeability and falls in class II drug. In such classes the only limitation is how to permit the partitioning of the drug across epithelial cell membrane. Because the drugs have a high permeability, the absorption will be very fast once the drug is solubilized.

Glimepiride is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM) [1, 2]. It is 1-(p-(2-(3-ethyle-4-methyl-2-oxo-3- pyrroline-1-carboxamido) ethyl) phenyl) sulfonyl)-3-(trans-4-methylcyclohexyl) urea which belongs to third generation of hypoglycemic sulfonylurea. Literature reviews reveal that glimepiride shows more potential benefits such as lower dose, rapid onset of action, longer duration of action and lower insulin C-peptide level, as compared to other available sulfonylureas [3,4].

The main challenge in formulating the drug dosage form is to increase the dissolution rate of drug with a simple, safe, and cost-effective formulation design. A number of techniques are available in the literature to overcome dissolution problem such as Inclusion complexes [5], Solid dispersions [6], Co-solvent [7], Self-nanoemulsifying system [8], Nanocrystal [9], Micelles Formation [10], and Hydrotropic but at the same time it is difficult to adopt such techniques in routine process because of their complexity [11,12].

In the present investigation, efforts were made to improve the dissolution of glimepiride tablets by using the combination of two approaches i.e. conventional and innovative, as it is a bioavailability controlling step. Tablets were prepared by using the wet granulation for making granules but before that the slurry of API and surfactant was prepared. In literatures, different approaches are reported but no such technique is described on the preparation and evaluation of glimepiride. Therefore, it is totally a new and easy approach to improve release of drug from its dosage form.

The primary aim of the present study is to enhance and improve the dissolution rate of hydrophobic drug (Glimepiride as model drug) by employing an innovative technique of making slurry of polysorbate 80 and PVP K-30 with API. Pre-compression and post-compression parameters were evaluated to confirm the validity of the design and development of processes. To evaluate the dissolution profile and efficacy of newly formulated tablets of glimepiride, the formulations were compared with innovator brand tablets. The study was also focused on the accuracy of the formulation and it was estimated by accelerated stability studies of the tablets.

Materials and Methods

Materials

Glimepiride reference powder (purity 99.61%) was obtained as a gift sample from Julphar, Ras Al Khaimah, UAE. Lactose monohydrate

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(VWR International, Germany), Microcrystalline cellulose (Fluka - Biochemika, Germany), Polyvinyl Pyrrolidone K-30 (PanReac - AppliChem, Italy), Cross Povidone (Basf Chemicals; Gift sample from Julphar), Tween 80 (Carl Roth, Germany), Sodium Starch Glycolate (Gift sample from Julphar), Mg stearate (Sigma Aldrich, Germany) and all other chemicals and solvents such as methanol, acetonitrile & Phosphate Buffer, used were of analytical reagent grade.

Estimation of glimepiride

In order to achieve the consistent, reliable and accurate data for the quality analysis of API alone and in its dosage form, analytical method play a key role. In the present study, the USP reported HPLC analytical method was first validated as per ICH (International Conference Harmonization) guideline [13] in accordance with facilities and feasibility of equipment and then used to estimate glimepiride as raw material as well as in newly formulated tablets (USP-37) [14].

Mobile phase preparation

Accurately weighed 0.5 g of monobasic sodium phosphate was taken and dissolved in 500ml of double distill water. The solution was mixed thoroughly, and the pH was adjusted to 2.4 with 10 % phosphoric acid. Acetonitrile with phosphate buffer was added in the ratio of 1:1, mixed and filtered through 0.45 µm millipore filter paper.

Preparation of diluent: Acetonitrile and water in a ratio of 9:1

Preparation of Standard stock solution: Accurately weighed 10mg of glimepiride reference powder was taken and diluted with 100 ml of diluent and sonicated for 5 minutes. The final concentration of the standard stock solution was 0.1 mg/ml (100 µg/ml).

Construction of calibration curve for the estimation of Glimepiride

A series of dilution were prepared in the diluent mixture according to the study design. From the stock solution, 0.25, 0.5, 0.75, 1.00, and 1.25 ml were pipetted out into a 10 ml volumetric flask separately and was made up to 10ml with the diluent. The concentration of these solutions was 2.5, 5, 7.5, 10, and 12.5 µg/ml respectively. Absorbance of the solutions were measured at λ = 228 nm**.**

System suitability test was carried out by six (6) replicates of sample solution (10 µg/ml) to check the repeatability, peaks symmetry, theoretical plates of the column, retention time and reproducibility of the chromatographic system.

Linearity of the method was evaluated in the range of 2.5-12.5 µg/ml. Limit of Detection (LOD) and Limit of Quantification (LOQ) was estimated by ICH guideline [15]. It gave the idea that the lowest concentration of analyte in a sample was determined with acceptable precision and accuracy.

Selection of excipients and their evaluation

For the design and development of any new formulation it is important to work on the intrinsic properties of API and the excipient. In present study, pre-formulation studies for different excipients were carried out to investigate the influence of their inherent properties on the pharmaceutical construction. The data obtained from studies provided the information regarding the interpretation of interactions among the excipients as well as with API.

Drug-excipient compatibility studies using FTIR

FTIR spectroscopy (Agilent Technologies, Cary 630 FTIR) was performed for the pure active drug and each excipient separately and also for the blended mixture of drug and excipients. This study was done to identify the presences of characteristics peaks for each functional group in the compounds for each ingredient separately as well as for interactions in the blended mixture of powders.

Differential Scanning Calorimetry (DSC) studies

Glimepiride and the excipient mixture, after preparing the granules by wet granulation and slurry method, were subjected to differential scanning calorimetric analysis to know about any interaction between the drug and excipients. The calorimeter (Model-Shimadzu -DSC 60+) was operated at a scanning rate of 10 °C per minute and heated between 25 to 400 °C.

Particle size and size distribution

The particles size and shapes affect the dissolution rate of the drug and their bioavailability. The study was done to calculate the Mean Particle Size (MPS) and Polydispersity Index (PDI) by using Malvern Zeta sizer Nano ZS (Malvern Instruments). The samples were measured for MPS and PDI at a fixed angle of 90° at a temperature of 25 °C and average zeta potential (mV) was measured at 25 °C.

Scanning electron microscopy

The shape and surface feature of the glimepiride blended mixtures were investigated by employing SEM (Hitachi, Model SU 1510) and was observed under reduced pressure employing an acceleration voltage of 15 kV.

X-ray Diffraction

patterns of drug blends were performed to confirm the nature (crystalline or amorphous) of drug. Diffractograms were captured using a step width of 2θ between 2° and 40° at a rate of 2° min^{-1} at ambient temperature.

Experimental design

The objective of the study was to maximize the release rate of drug from tablets by using some innovative approaches. In the present study, slurry method was used to improve the dissolution rate of the glimepiride which was taken as a model drug.

The preliminary information regarding the characteristics of excipients and their proportion and range was obtained from USP and BP [16]. The tablet of glimepiride was initially prepared by using wet granulation method. The trial batch of tablet was prepared as per innovator, Amaryl, 2 mg (Glim-A) tablet and dissolution test was performed according to USP.

Preparation of tablets by wet granulation

All the ingredients such as glimepiride, PVP K -30, Lactose monohydrate, microcrystalline cellulose and sodium starch glycolate were weighed carefully and dry mixed to get homogenous mixture of powder. The powder was granulated with water and passed through mesh # 40. The wet mass was dried at 35 °C and was passed again through mesh # 30. The remaining amount of sodium starch glycolate and Mg stearate were added and were compressed on 9.25 mm

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Oblong shape plain punches at a theoretical weight of 170 mg±7.5%.

Preparation of tablets by innovative approach (Slurry method)

Calculated amount of purified water was taken and polysorbate 80 and PVP K-30 were added and mixed to dissolve. Glimepiride was added into the same solution and mixed again with the help of homogenizer (IKA; MODEL: T 25 D, Germany) to produce uniform slurry. Lactose monohydrate, microcrystalline cellulose pH 102 and half amount of sodium starch glycollate were added and mixed well. The mixture of powder was granulated with slurry till homogenous wet mass was produced then passed through sieve # 40 mesh, dried at 45 °C and the remaining amount of sodium starch glycolate and magnesium stearate was added. Finally, the blended powder was compressed by Compression machine (Single Punch, D Type Tooling; Dwell time 0.75 second; Faisalabad) on 9.25 mm oblong shape plain punches at a theoretical weight of 170 mg±7.5%.

Formulation optimization

Initially the prototype formulation was prepared by using the same ingredients as that of Glim-A. The dissolution rate of the tablets was calculated and based on the results; the series of formulations were designed with same ingredients as mentioned in (Table 1). In the proposed study, the higher and lower concentration of polyvinyl pyrrolidone K-30, Polysorbate 80 and crospovidone were used separately and in combinations in order to optimize the release pattern of drug from formulation.

After the satisfactory results of Batch # G-9 (Table 1), where the dissolution was almost 90% in 15 minutes, the prototype formulation G-9 with Polysorbate 80 and PVP K-30 was selected for further optimization. In order to improve the formulation, the changes were made in the composition of sodium starch glycolate and lactose. Finally, the following compositions were selected for the optimized Batch (G-10) with dissolution rate of more than 90% in 15 minutes (Table 1).

Quality evaluation of formulated tablets

The innovator brand tablets and formulated tablets were subjected to recommended pharmacopeial tests for their quality attributes.

Weight variation

It is one of the most important parameters related to the weight uniformity and is supposed to indicate the content uniformity of each tablet. If there is any variation in the weight, it means there is variation in amount of API in tablet.

Hardness and thickness

The ability of a tablet to withstand at specific pressure before breaking influences the disintegration and friability of tablets. Similarly, the thickness and diameter/length have a great impact on the packaging behavior of tablets dosage form.

Friability test

Friability test of tablets is one of the imperative parameters that assess the handling of drugs during transportation from manufacturer to distributer and then their delivery to the patients. Friability for all formulated tablets were performed by using the procedure defined in USP and BP [17,18].

Wetting time

The wetting test measures the ability of a tablet to allow liquid to wet and penetrate between the compact particles of powder which deals with the disintegration aptitude of tablets. In the present study 0.1% (w/v) Methyl blue solution was used. The tablet was carefully kept on the surface of the dye solution until it's wetted completely, the time was recorded [19,20].

Disintegration test

The mechanical breaks of tablet into small granulated particles help to calculate the disintegration time of a tablet. This parameter provides an in-vitro simulation for drug disintegration and dispersion after intake and gives an idea about how it will perform in the dissolution test. All the tablets were evaluated for their disintegration time as per USP [21].

Drug content assay of Glimepiride tablet

The content assay of all the tablets were carried out by using the validated HPLC method for quantitative analysis of drug.

***In vitro* drug release studies**

It is an important process that provides the in-vitro simulation for bioavailability studies. Especially in dosage form design and development, it works as a fundamental quality control parameter for the evaluation and assessment of drug release from their solid dosage forms.

Standard preparation

Accurately weighed 10mg of glimepiride reference standard powder was taken and carefully diluted with 100ml of diluent (9:1) and sonicated for 5 minutes. 1.5 ml of this solution was diluted with 50ml of dissolution medium. The final concentration was 3 µg/ml.

Sample preparation

One tablet was introduced into each of six individual vessels containing 900 ml of phosphate buffer (pH 7.8). 5ml from each vessel was withdrawn after time intervals of 5, 10, 15, 20, 30 & 45 minutes and filtered before injecting into HPLC. The samples were analyzed at λmax = 228 nm.

Stability studies

After the pharmaceutical evaluation of all formulated batches the optimized batch (G-10) was kept for stability for three months (0, 1, 2 & 3 months) under accelerated conditions i.e 40±2 °C; 75 ± 5% R.H, as per ICH guidelines and retained under the three condition of packaging [22,23]: 1) Alu/Alu blistering 2) Amber container 3) without container.

Stress testing of optimized batch

The stress testing was performed on prepared tablets (G-10) under the 4 different conditions for 24-hours i.e acidic (0.1N HCl), alkaline (0.1N NaOH) & Ultraviolet degradation and Hydrogen peroxides (6%).

Results and Discussions

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Table 1: Design and development of prototype formulations.

Materials	Formulation Code (mg/tablet)									
	Normal Wet Method				Slurry Method					
	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10
Glimepiride API	2	2	2	2	2	2	2	2	2	**2**
Lactose monohydrate	129.6	128.6	129.6	128.6	129.6	128.6	127.6	124.6	127.6	**136**
Microcrystalline cellulose	20	20	20	20	20	20	20	20	20	**20**
Polyvinyl Pyrrolidone K-30	1	2	0	0	0	0	0	2	1	**1**
Crospovidone	0	0	0	0	0	0	0	5	0	**0**
Tween 80	0	0	1	2	1	2	3	0	2	**2**
Sodium Starch	16	16	16	16	16	16	16	16	16	**8**
Mg stearate	1	1	1	1	1	1	1	1	1	**1**
Total Weight	**170**	**170**	**170**	**170**	**170**	**170**	**170**	**170**	**170**	**170**

API: Active Pharmaceutical Ingredients
G1-G10 = code for 10 formulation

Table 2: Specification of dissolution test.

Dissolution Conditions (USP)	Specification
Type of apparatus	USP II (paddle method) (Labindia-D5 8000: Shimadzu)
Dissolution medium	900ml, Phosphate Buffer (pH 7.8)
Speed	75rpm
Temperature	37±0.5 °C
Wavelength (λmax)	228 nm
Sampling Time (mint)	5, 10, 15, 20, 30 & 45 minutes

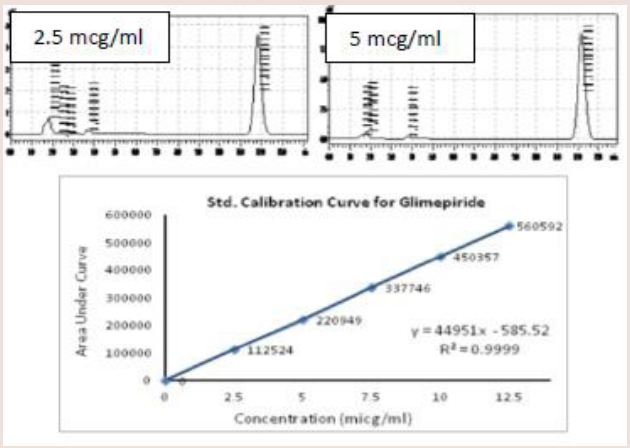

Figure 1: Calibration Curve (Linearity).

In 2015, Kline & Co-workers conducted a market survey and they found that the large number of drugs belonged to BCS class II (poor solubility, high permeability) [24]. The drugs of this class had poor bioavailability due to their limited solubility. Thus, they required improvement in solubility to enhance the effectiveness of the compounds. The pharmaceutical researchers are continuously working to overcome this problem and try to develop a set of bioavailability enhancement methods and technologies. Few of these methods give a better understanding, whereas some others require a specialized expertise and manufacturing capabilities.

In the present study we have made an attempt to develop a simple and easy method to improve the dissolution rate of a formulated glimepiride tablet. Moreover, it was made sure that the hardness of the tablets is pertained to appropriate limit in order to control the shipping and handling.

Analytical methods validation for the estimation of Glimepiride [25]

In the present study the analytical method used for the determination of glimepiride was taken from USP-38 [26]. The reason for opting this method was to make sure that the release of drug from newly formulated tablets must be same as that of innovator tablets, as the USP method is actually established by the innovator. Before the estimation of glimepiride, it is necessary to validate the method as per the feasibility to make sure that the estimation is accurate and reproducible. The main objective of method validation is to demonstrate the reliability of a particular equipment and analytical method for the quantitative determination of an analyte(s) concentration in a specific sample.

Construction of calibration curve

The calibration curve of glimepiride was linear in the concentration range of 2.5 to 12.5 µg/ml, with a regression analysis (R^2) of 0.9999, 0.9998 and 0.9995 with different time intervals (Figure 1). The curve was plotted by area under the curve *vs* concentration of glimepiride at λ = 228 nm. Six consecutive injections of 10 µg/ml were used to

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Table 3: System suitability of chromatographic system.

Injection Number	Retention Time (min)	Peak area of glimepiride	Tailing Factor	Tangent
1	18.046	633094	1.11	6681.36
2	18.046	633583	1.077	6823.03
3	18.052	631881	1.088	6819.23
4	18.062	629544	1.067	6819.03
5	18.083	631188	1.103	6819.57
6	18.071	631087	1.111	6845.34
Mean	**18.06**	**631729.5**	**1.093**	**6801.26**
%CV	**0.0825**	**0.2327**	**1.674**	**0.8764**

%CV = Percentage Coefficient of Variation.

Table 4: Pre-formulation studies of active and excipients.

Material	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hauser's Ratio	Angle of Repose (θ)
Glimepiride API	0.355	0.193	45.6	1.83	38.9°
Lactose monohydrate	0.574	0.75	33.91	1.31	43.96°
Microcrystalline cellulose	0.31	0.395	27.42	1.27	24.19°
Polyvinyl Pyrrolidone K-30	0.714	0.8	12.05	1.12	14.32°
Sodium Starch Glycolate	0.692	0.9	30.06	1.3	28.2°
Mg stearate	0.233	0.312	39.87	1.29	27.91°

***Angle of Repose Range =** 16 - 31 (Good to Excellent)
***Flow Characters:** 1. Compressibility index = ≤22 (Passable to Fair)
2. Hausner's Ratio = ≤1.28 (Passable to Good)

Table 5: Flow properties of the powder blends (based on mean±SD; N = 3).

Formula Code	Bulk Density (g/cc)	Tapped Density (g/cc)	Flow Properties*		
			Carr's Index %	Hausner's Ratio	Angle of Repose* θ
G1	0.48	0.59	19.23	1.24	28.58
G2	0.5	0.63	20	1.25	27.38
G3	0.47	0.6	22.22	1.28	31.93
G4	0.44	0.51	13.79	1.16	30.84
G5	0.48	0.58	16.98	1.2	31.58
G6	0.47	0.55	17.39	1.17	26.47
G7	0.48	0.55	14.58	1.15	25.5
G8	0.43	0.5	15.62	1.16	16.5
G9	0.46	0.53	15.22	1.15	23.76
G10	0.46	0.54	17.39	1.17	21.23

***Angle of Repose Range =** 16 – 31 (Good to Excellent)
***Flow Characters:** 1. Compressibility index = ≤22 (Passable to Fair)
2. Hausner's Ratio = ≤1.28 (Passable to Good)

verify the resolution and reproducibility of the chromatographic system (System suitability) as recommended by the ICH guideline for analytical method validation [15] (Table 2 and 3).

The % CVs of the retention times and peak areas of glimepiride for the six injections was 0.0825 and 0.2327 respectively. The Mean theoretical plate count, based on USP tangent calculations, was 6801.26 (Table 3). The Limit of Detection (LOD) and Limit of Quantitation (LOQ) were estimated as 0.0625 µg/ml and 0.125 µg/ml respectively (Table 3).

Pre-formulation studies

Before the development of any dosage form, it is necessary to determine the physical and chemical properties of drug powder. This type of information might be needed as the formulation progresses. In pre-formulation studies the physiochemical properties of the pure drug alone and with the excipients were investigated (Table 4 and 5). The main reason to conduct pre-formulation studies is to determine the core characteristics of excipients which will be used in the formulation and development of an enhanced dissolution rate of glimepiride tablet.

The studies quantified that glimepiride had a very poor compressibility and very bad flow properties which were mainly due to its hygroscopic nature (Table 4). Other excipients also had variation in their flow properties and for this reason different techniques are used to prepare granules for tablets compression. In the present study, tablets were prepared by wet granulation as well as an innovative technique (slurry method) was introduced for tablets erection to improve drug release rate from dosage form (Table 1).

After the study of flow properties (Table 5), it was observed that the bulk and tapped densities for blended powders varied from 0.43-0.50 g/ml and 0.51-0.63 g/ml respectively. Carr's index values were in the range of 13.79 to 22.22%, which indicated that, the use of different ratios of PVP K-30, crospovidone and Tween 80 have made their effect on the flow of the powder blends. The angle of repose for excipients were 14.32° - 43.96° which indicated the two extreme ends whereas the ten (10) formulations were found in the range of 16.50 to 31.93, which indicated an excellent to good blend flow property (aid not needed) according to the USP [27] (Table 4 and 5).

The values also indicated that when changes were made in

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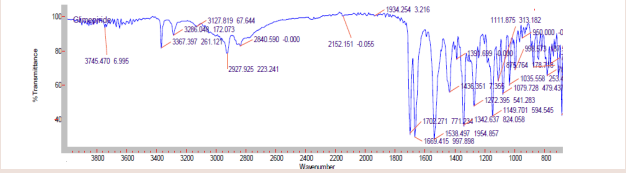

Figure 2: Fourier-transform infrared (FTIR) spectrum of glimepiride pure drug.

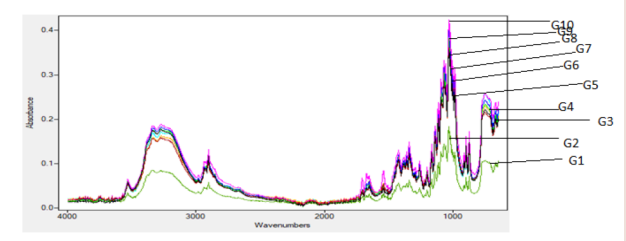

Figure 3: Comparative FTIR Spectrums of blended mixture of powders.
G1: blend of API with PVP K-30 (1 mg) with other excipients; G2: with PVP K-30 (2 mg); G3: with Tween 80 (1 mg); G4: with Tween 80 (2 mg); G5: with Tween 80 (1 mg, slurry); G6: with Tween 80 (2 mg, slurry); G7: Tween 80 (3 mg, slurry); G8: Tween 80 + Crospovidone (slurry); G9: Tween 80 + PVP K-30 (slurry); G10: Tween 80 + PVP K-30 (slurry) in the ratio of 2:1

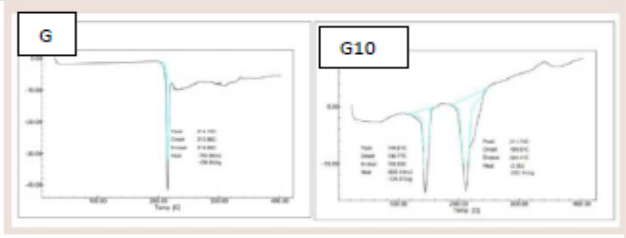

Figure 4: Differential Scanning Calorimetry (DSC) plots of drug.
G: DSC of Glimepiride Reference drug; G10: Blended dispersion of Glimepiride with Tween 80, PVP K-30 & sodium starch glycolate, prepared by slurry method.

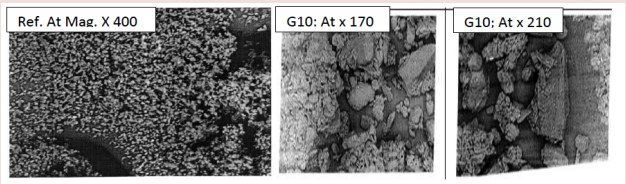

Figure 5: Scanning Electron Microscopy of glimepiride.
Ref: glimepiride at 400X; G10: Formulation blend of Glimepiride with Tween 80, PVP K-30 & sodium starch glycolate at 170X & 210X.

ingredient such as in place of polyvinyl pyrrolidone K-30, Tween 80 was used, the angle of repose also changed from 27.38 (G2) to 30.84 (G4) (Table 5). Similarly, when the polyvinyl pyrrolidone K-30 and crospovidone were used in combination with Tween 80, angle of repose of G8, G9 and G10 were moved from good to excellent range (Table 5).

Drug-Excipient Compatibility Studies using FTIR

Sometimes interactions can happen between the pure active drug and the additive excipients. In order to estimate the level of this interaction, FTIR studies were performed for the active drug, excipients and for blended powder mixtures of 10 batches respectively (Figure 2 and 3). Figure 2, glimepiride pure active drug shows the bond vibrations at 3367 cm^{-1} (N-H stretch), 1707 cm^{-1} (C=O) and 1346 cm^{-1} (S=O). After mixing the pure active drug with other excipients, there were no major shifting in the peaks and all the functional groups were clearly observed (Figure 3). From this data it was concluded that there were no interactions between the glimepiride functional peaks and the excipients in the formulations mixtures, indicating that all of the ingredients used in the formulations were compatible chemically

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Table 6: Particle size analysis of formulations blends.

Sample code	z-ave (nm)	PI	ZP±zeta deviation
G2	2556	0.824	-39.9±4.42
G4	3342	1	-40.1±6.62
G6	6796	1	-46.4±5.52
G8	5039	1	-36.2±8.30
G9	6096	1	-39.3±7.88
G10	6398	1	-37.2±5.11

ZP = zeta potential
z-ave = zeta-average
PI = Polydispersity index

Table 7: Comparison of *in-vitro* drug release from formulated tablets.

Formulation Code	% Release of Drug in different Time Interval (minutes)					
	5	10	15	20	30	45
Glim-A (Innovator)	**54.9**	**93.3**	**94.9**	**95.6**	**94.3**	**94.9**
G1	18.54	53.52	69.4	85.87	91.57	97.52
G2	49.75	64.18	75.3	80.11	87.52	90
G3	29.76	60.66	80.64	87.73	94.24	96.59
G4	38.69	62.55	81.53	86.34	90.89	97.44
G5	36.93	62.93	78.13	86.92	91.89	98.98
G6	47.4	64.56	82.52	87.07	95.34	101.96
G7	44.92	68.41	76.52	79.57	84.52	94.4
G8	50.49	68.2	78.87	88.63	95.09	99.77
G9	54.609	69.878	80.527	83.628	89.885	91.89
G10	65.29	83.2	91.53	97.86	99.917	102.328
Mean	**43.64**	**65.81**	**79.5**	**86.37**	**92.09**	**97.09**
% CV	**13.26**	**7.69**	**5.69**	**5.09**	**4.35**	**4.04**

Table 8: Evaluation of pharmaceutical parameters of formulated batches with innovator tablets.

Formulation Code	Weight Variation	Hardness	Friability(%w/w)	Wetting Time (Sec)	Disintegration Time (Sec)	Drug Content (%)
Glim-A (Innovator)	170.2±1.43	3.98±0.106	0.2	90.00±0.92	77.50±0.11	102.3±0.75
G1	165.65±2.06	3.025±0.082	0.35	59.00±0.55	15.0±1.03	97.3±1.95
G2	168.5±1.81	3.275±0.311	0.3	48.00±1.35	41.8±1.33	100.01±1.01
G3	169.15±1.48	2.575±0.096	0.22	51.00±1.98	36.8±2.55	96.78±1.34
G4	169±1.77	2.275±0.055	0.31	55.00±2.45	45.0±2.11	98.33±1.21
G5	169.95±1.75	3.0±0.070	0.2	46.00±2.11	26.0±1.65	97.19±1.10
G6	169.45±1.76	3.625±0.108	0.16	30.00±2.33	20.8±0.98	100.37±0.79
G7	169.6±1.45	3.725±0.055	0.14	22.00±1.77	31.5±0.88	100.3±0.83
G8	169.15±1.38	3.95±0.065	0.22	31.00±0.43	35.3±0.73	97.9±0.65
G9	169.6±1.27	4.0±0.092	0.16	26.00±0.67	24.3±0.85	99.78±1.32
G10	170.45±1.04	4.35±0.104	0.11	94.00±1.55	96.8±1.22	100.34±0.66

with each other (Figure 3).

Differential Scanning Calorimetry (DSC) studies

In order to confirm the physical state, DSC was also performed to analyze the different samples. The glimepiride coarse powder exhibited a single endothermic peak with a single melting point [28]. Thermal analysis was conducted on blended dispersion of G2, G4, G6, G8, G9 & G10 of glimepiride. The second peak appeared but it was separated from drug peak. This indicated that there was no interaction between drug and excipients, but the dissolution enhancement occurred due to solubilization of drug by Tween 80, not due to the change in structure or amorphous formation (Figure 4).

Particle size analysis of glimepiride blended powders

The z-ave and PI of the reconstituted suspensions were analyzed to determine particle size and their distribution. The results indicated that the z-ave of formulations blend increased when mixed with Tween 80 (G4), when made blend with slurry method (G6), PVP K-30 with crospovidone (G8), PVP K-30 with Tween 80 (G9) and G10 with reduce amount of sodium starch glycolate. On the other hand, there were no changes in PI that indicated that all the particles were almost under the same population and were mono dispersed. Therefore, a negative charge on ZP indicated that any of excipient of the formulation blends having -ve charge also had the surface charged with -ve. (Table 6).

The addition of stabilizers, binder or suspending agents in formulation can affect the morphology of particle in suspensions, which was already confirmed by other authors [29]. In order to characterize the morphology of glimepiride particles, SEM imaging was performed, and the micrograph of the particles showed that particles were irregular in shape and size (Figure 5).

X-ray diffraction studies were conducted to confirm the physicochemical characteristics of blended mixture of formulations. Diffractograms exhibited sharp peaks of diffraction at an angle of 2θ value of 12.656°, 16.540°, and 20.120°, with very ignorable variation

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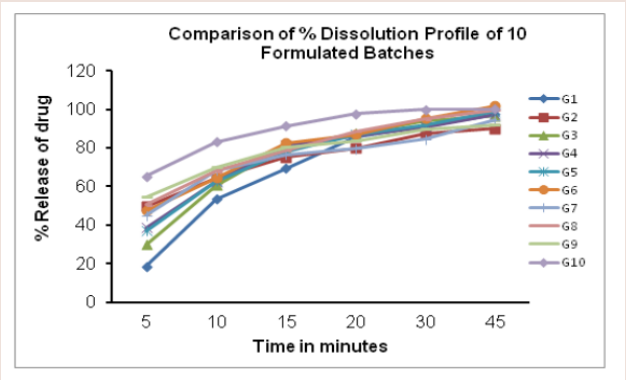

Figure 6: Graphical Presentation of % Dissolution Profile of ten Formulated Batches.
G1 & G2: Tablets prepared by wet granulation method with PVP K-30 (1 mg); G3 & G4: Tablets with Tween 80 (1 mg/tab & 2 mg/tab); G5, G6 & G7: with Tween 80 (1 mg, 2 mg, 3 mg, slurry); G8: Tablets with Tween 80 + Crospovidone (slurry); G9: Tween 80 + PVP K-30 (slurry); G10: Tween 80 + PVP K-30 (slurry) in the ratio of 2:1.

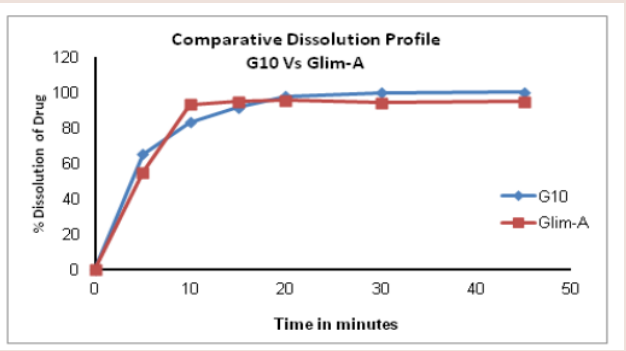

Figure 7: Cumulative Release Profile of Optimized Batch G10 & Innovator (Glim-A).
Glim-A: Innovator (Sanofi-Aventis, Germany) tablets (2mg); G10: tablets prepared by slurry method with Tween 80 + PVP K-30 in the ratio of 2:1.

Table 9: Analysis of pharmaceutical parameters of optimized prototype formulation (G10) during stability studies.

Test	Open			Blister			Amber		
Duration	**1st Month**	**2nd Month**	**3ed Month**	**1st Month**	**2nd Month**	**3ed Month**	**1st Month**	**2nd Month**	**3ed Month**
Weight Variation (mg)	174.25±0.024	172.4±0.014	173.6±0.021	178.7±0.05	178.2±0.046	178.1±0.045	172.5±0.015	174.7±0.027	174±0.023
% Drug Release (After 15 min)	86.26±0.45	98.48±0.37	100.13±0.44	85.85±0.50	94.77±0.49	92.07±0.62	90.85±0.61	97.09±0.41	94.4±0.62
Hardness (Kp)	2.75±0.313	2.50± 0.375	2.125 ±0.469	3.75 ±0.062	3.50± 0.125	3.50 ± 0.125	3.50 ±0.125	3.50±0.125	3.25± 0.188
Friability % w/w	0.33	0.11	0.37	0.22	0.19	0.21	0.36	0.34	0.41
Disintegration time (sec)	101± 0.11	89.0± 1.31	99±1.34	87±2.02	100±1.97	105± 1.27	111±0.83	67±0.92	88±1.99

Table 10: Force degradation of glimepiride in tablets (G10).

Time	0.1 M HCL	0.1 N NaOH	H_2O_2 (6%)	UV Light
Zero Time	98.02%	97.10%	89.26%	100%
1 hr	94.74%	94.12%	85.05%	**After 6hrs**
24 hrs	91.82%	98.71%	83.12%	105.33%

between different blends of powder, which indicated the presence of crystalline structure.

Development & optimization of glimepiride tablets

After analyzing the pre-formulation parameters of glimepiride powder mixture, immediate releasing tablets were prepared. The main goal of this study was to improve the dissolution of poorly soluble drugs (glimepiride), 10 different batches were designed by using different excipients like PVP K-30, Crospovidone and Tween 80 with different concentrations (Table 1). The basic concept of excipients selection was based on actual components of innovator tablets (Glim-A; 2 mg).

First two batches of tablets (G1 & G2) were prepared by wet granulation method by using Glim-A information followed by dissolution. The results of these tablets were not satisfactory (69.40% and 75.30% in 15 min) in comparison to innovator product (94.9% in 15 min). G3 & G4 were constructed with Tween 80 by using 1 mg/tab and 2 mg/tab instead of PVP K-30 (Table 1). The assortment of Tween 80 was due to its well-known functions as wetting agent, the

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main reason for its selection was that Tween is a nonionic surfactant and has remarkable properties as emulsifier. Therefore it is considered for not only improving the wetting of the drug but also enhances the solubility. But the results obtained were not as per the desired target (Table 7 and Figure 6).

The innovative technique slurry method were used to design G5, G6 & G7 by using 1, 2 & 3 mg/tab Tween 80 separately (Table 1). Dissolution test were performed and it was found 78.13%, 82.52% & 76.52% respectively. (Table 7 and Figure 6).

All the above mentioned design of formulations indicated that the Tween 80 (2 mg/tab) gave the best release of drug as compared to others. So, the formulation containing 2 mg/tab amount of Tween 80 was selected as model for further modification in the formulations. The first amendment was made with Crospovidone and Tween (G8) (Table 1). Tablets were prepared by slurry method. The Crospovidone works as super disintegrants so it was supposed that the dissolution would significantly increase. But practically there were no notable change i.e. 78.87% drug released in 15 minutes (Table 7). G9 was designed with PVP K-30 & Tween 80 (Table 1). The wet mass of granules was prepared by slurry method with calculated amount of water (34 µl/tab). The granules were compressed on 9.25 mm oblong shape plain punches at a theoretical weight of 170 mg±7.5%. The quality control parameters were analyzed to calculate the release of drug. It was found 80.53% in 15 min (Table 7).

Prototype optimized batch (G10) was prepared by using the same concentration of Tween 80 and PVP K-30 as that of G9 with the reduction in the amount of sodium starch glycolate i.e. from 16 mg/tab to 8 mg/tab and addition in the amount of lactose monohydrate that was 136 mg/tab (Table 1). The tablets were prepared by the same slurry method with slight increase in the quantity of water (54.4 µl/tab).The dissolution test revealed marked increase in release of the drug i.e. 91.53 % in 15 minutes (Table 7). G10 was taken as the Check Point Batch (CPB). For further verification and conformation of drug release from the tablets, comparatively a larger batch was prepared. The data was collected and compared with innovator tablets for the release of drug repetitively (Figure7).

Pharmaceutical evaluation of formulated tablets

The pharmaceutical evaluation of tablets was carried out to keep the check on the quality, consistency, uniformity and efficacy of the tablets in the same batch of formulation as well as between the batches (Table 8). After quality analysis the tablets (G10) was kept for stability studies.

Stability Studies [30]

The optimized prototype formulation (G10) was subjected to stability studies for 03 months. The tablets were kept under three conditions such as Alu/Alu blister, amber and an opened container along with refrigerator for comparison with standard condition. The tablets were evaluated at accelerated stability conditions (40±2 °C and 75±5% RH). No significant variation was observed that evidenced the stability of formulation in terms of both, drug content and dissolution profile i.e 86.26±0.45 - 100.13±0.44 in open container; 85.85±0.50 - 94.77±0.49 in blister packing and 90.85±0.61- 97.09±0.41 in amber container respectively after 15 min of drug dissolution (Table 9). Based on the results, it was concluded that the newly formulated glimepiride tablets were stable after 3 months of storage at accelerated stability conditions indicating good compatibility with the excipients that were used in the formulation (Table 9).

Stress Testing of Drug

In the present study the degradations of glimepiride in tablet dosage form (Formulation G10) were also done under different stress conditions as per the ICH guideline [31]. The results of the study indicated that the glimepiride underwent the slight degradation in 0.1N HCl whereas there were no changes observed in 0.1N NaOH, H_2O_2 (6%) and UV light (Table 10).

Conclusion

The concept, on which this study was based, was to develop an oral dosage form with higher release rate in-vitro as compared to the previous formulations made to attain the maximum bioavailability possible. The model drug taken was glimepiride, an antidiabetic agent BCS class II drugs with low solubility and high permeability. To achieve our goal, a novel approach was designed for the enhancement of dissolution rate. The strategy adopted was to develop slurry of API with Tween 80, to reduce the surface tension between active and Tween and to improve the solubility. It was concluded that the present exploration indicates that it is not only a simple and easy technique and could be used for large scale production but also has a good capacity to improve the flow properties of material.

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