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FORMULATION DEVELOPMENT AND *IN VITRO – IN VIVO* CHARACTERIZATION OF ORAL FAST DISINTEGRATING FILMS OF A DRUG MEANT FOR CHRONIC DISEASE

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ABSTRACT

The objective of the work was to design oral FDFs of a drug meant for management of chronic disease like type-2 diabetes mellitus which affects mostly elderly population. Glimepiride was the drug of choice because of its low dose. Since in vitro dissolution rate is the rate limiting step in drug absorption for class II drugs, in the present work, it was also proposed to make a complex of the drug with hydroxypropyl betacyclodextrin (HPBCD) to improve the physicochemical-pharmacokinetic characters of the drug. Various batches of FDFs were developed by the solvent casting method using water soluble polymers HPMC-E5 and Maltodextrin as film formers; Glycerol and PEG-600 as plasticizers; Sodium starch glycollate as super disintegrating/channeling agent; Sodium lauryl sulphate, polaxamer 407 and Tween-80 as surfactants; aspartame as a sweetener and brilliant blue as coloring agent. The drug was complexed with HPBCD by kneading method in the ratio of 1:1 and was incorporated in the film in the place of plain drug. Poloxamer containing films gave better physico-chemical characters than the other tested surfactants and addition of HPBCD complexed drug further improved the characters of the films. The formulation containing drug-HPBCD complex and polaxamer 407 as the surfactant gave lowest disintegration time, more uniform and faster dissolution profile, had better taste, highter C_{max} and lower t_{max} values during in vivo studies. It can therefore be concluded that the drug in its most soluble form gives better physicochemical and pharmacokinetic characters which results in better management of the disease as patient compliance improves.

INTRODUCTION: Fast disintegrating oral films are solid dosage forms, which disperse or dissolve within one minute, when placed in the mouth without drinking or chewing [1]. Fast disintegrating films (FDFs) are gaining interest rapidly in the pharmaceutical industry due to their many advantages the most important being improved patient compliance especially in pediatric and geriatric population [2] because of their ease of administration. Today, FDFs are a proven and accepted technology for the systemic delivery of APIs for over the counter medications and are in the early to mid development stages for prescription drugs [3]. Literature survey indicates that till now these films were used for delivery of drugs meant for acute diseases.

Therefore, the objective of the present work was to design FDFs of a drug meant for management of chronic disease like type-2 diabetes mellitus which affects mostly elderly population. Glimepiride was the drug of choice because of its low dose. It acts as an insulin secretagogue [4]. Glimepiride is a medium-to-long acting sulfonylurea. It is sometimes classified as the first third-generation sulfonylurea [5], and sometimes classified as second-generation [6]. It lowers blood sugar by stimulating the release of insulin by pancreatic beta cells and by inducing increased activity of intracellular insulin receptors.

Glimepiride has low, pH-dependent solubility. In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37^{o}C (0.004 mg/mL). In media of pH >7, the solubility of the drug substance is slightly increased (pH 7.8, 0.02 mg/mL)[7]. This poor solubility may cause poor dissolution and unpredictable bioavailability [8]. Since *in vitro* dissolution rate is the rate limiting step in drug absorption for class II drugs like glimepiride [9, 10], in the present work, it was also proposed to make a complex of the drug with hydroxypropyl betacyclodextrin (HPβCD) to overcome the above said problem [11] and thus to better the quality of the dosage form to improve patient compliance.

Cyclodextrins are able to form inclusion complexes with poorly water soluble drugs and have been shown to improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability without affecting their intrinsic lipophilicity or pharmacological properties. Out of the three parent cyclodextrins, β-cyclodextrin appears most useful as a pharmaceutical complexing agent because of its complexing ability, low cost and other properties [12, 13]. The ability of cyclodextrins to form inclusion complexes is enhanced by substitution on the hydroxyl group [14].

MATERIALS AND METHODS

Materials: Glimepiride, Glipizide and HPβCD were obtained as gift samples from Matrix Labs, Hyderabad. HPMC-E5, Maltodextrin, Sodium Starch Glycolate, Poloxamer 407, Sodium Lauryl Sulphate (SLS) and Tween-80 were procured from S.D. fine chemicals limited, Mumbai-25, India. HPLC grade Acetonitrile was purchased from Merk Co, USA, and Formic acid, Ammonium acetate, Ethyl acetate, Diethyl ether from Sigma-Aldrich Co, USA. All other agents used were of analytical grade**.**

Methods:

Preformulation Studies:

1. **Drug-polymers-excipients interaction studies by thermal analysis:** To rule out any possible interaction between the selected drug glimepiride and the polymers-excipients under study, thermal analysis was carried out by Differential Scanning Calorimetery (DSC) (Mettler Toledo, DSC822e, Greifensee, Switzerland). Physical mixture of the drug with the solid components of the film in the same ratio as that of the formulation was prepared. After powder sieving, the mixture was analysed by DSC along with pure glimepiride, HPβCD and drug- HPβCD complex. The instrument was calibrated using indium standards. Accurately weighed samples were hermetically sealed in flat bottomed aluminum pans. The scanning was carried out at a temperature ranging from 50^{0}C to 300^{o}C at a rate of 10^{0}C/min under an atmosphere of nitrogen.

2. **Preparation of glimepiride- HPβCD complex by kneading method [14]:** Small volume of 50% ethanolic solution was added to HPβCD in a mortar while triturating to get slurry like consistency. Then slowly accurately weighed quantity of the drug was incorporated into the slurry and trituration was further continued for one hour. The slurry was then air dried at 25^{0}C for 24 hours, pulverized and passed through sieve No. 80 and stored in desiccator over fused calcium chloride.

Formulation Studies

1. **Design and preparation of glimepiride FDFs:** An aqueous solution of hydroxypropyl methylcellulose (HPMC-E5) was prepared by soaking HPMC in fixed quantity of distilled water overnight. To this, weighed quantities of maltodextrin and sodium starch glycolate were added and stirred to form homogenous mixture. An aqueous dispersion of drug/drug–HPβCD complex, surfactant, PEG-600, glycerol, aspartame and coloring agent was

prepared separately and then added to the above polymeric mixture. This mixture was stirred continuously to form homogenous suspension using magnetic stirrer. The thick viscous suspension was degassed and was poured on to the petri-dish having surface area of 63.585cm^2 and was dried at 50°C in hot air oven. The films were carefully removed from petridishes, checked for imperfections and cut into strips of dimensions of 2×2.5cm^2 and stored in air tight containers for further studies. Formulations F3 to F7 contained 2mg dose of Glimepiride in 2×2.5cm^2 films.

Characterization of the Developed FDFs

1. **Morphological properties:** Properties such as homogeneity, color, transparency and surface texture of the films were evaluated by visual inspection**.**

2. **Thickness measurements:** The thickness of each film was measured at five different locations (centre and four corners) using digital vernier caliper micrometer (Shanghai, China). Data was represented as a mean ± SD of five replicate determinations.

3. **Film mass:** The mass of the films was determined by analytical balance. This study was performed on 5 films of each formulation.

4. **Folding endurance:** The folding endurance is related to the flexibility of the film and hence represents its physical stability during manufacturing, package and use. It was measured manually by firmly folding a film repeatedly through the middle. The number of folds on the same crease required to crack in the film was noted as the value of folding endurance**.**

5. **Drug content determination:** One square centimeter samples representing five different regions (center and four corners) within the film were cut, and dissolved in an appropriate amount of the methanol and the solution was filtered through 0.45 µm membrane filter and glimepiride was assayed by the UV spectrophotometer (UV-1800, Shimadzu, Japan) at 231nm after suitable dilutions with phosphate buffer of pH 7.8 [15].

6. **Determination of percentage moisture absorption (PMA:** Films were cut into 2 × 2.5 cm (5 cm^2) strips. The moisture uptake by the films (n = 3) was determined by exposing them to an environment of 75% relative humidity (RH) at room temperature for 1 week. The uptake of moisture by the films was measured and calculated as percent increase in weight over initial weight of the specimen.

PMA = final weight – initial weight ×100/ Initial weight

7. **Determination of percentage moisture loss (PML):** Films were cut into 2 × 2.5 cm (5 cm^2) strips. The percentage moisture loss was determined by keeping the films (n = 3) in a desiccator containing calcium chloride. The films were weighed periodically to constant weight. The percentage moisture loss was calculated as percent decrease in weight over initial weight of the specimen.

PML = initial weight – final weight × 100/ Final weight

8. ***In vitro* disintegration time:** The film size required for dose delivery (2 × 2.5 cm) was placed in a glass petri dish containing 10 ml of distilled water. The time required for the film to break was noted as in vitro disintegration time[2]. Six replicates were done for each formulation.

9. ***In-vitro* dissolution studies [15]:** The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus I. The dissolution studies were carried out at a temperature of 37 ± 0.5°C with stirring speed of the basket at 75 rpm in 500mL of freshly prepared phosphate buffer of pH 7.8. A film size of 1 × 1 cm was used and 5mL aliquots of dissolution media were collected at predetermined time intervals of 2, 4, 6, 8, 10, 12, 14, 16 & 20 minutes and replaced with equal volumes of the fresh dissolution medium. The collected samples were filtered through 0.45 µm membrane filter and after suitable dilutions with phosphate buffer of pH 7.8, the concentration of the dissolved glimepiride was determined by UV spectrophotometer and the amount of drug released was determined from the calibration curve. The studies were carried out six times and

mean values plotted verses time with standard error of mean, indicating the reproducibility of the results.

10. **Taste of the Formulations:** The most promising FDFs were tasted by 10 human volunteers in the age group of 22 to 50 years.

11. ***In-vivo* Studies:**

Determination of Glimepiride in Rabbit's Plasma by Reverse-Phase LC/MS/MS[16-18]

A. **Sample Preparation:** Calibration curves were prepared by adding various amounts (2, 5, 10, 20, 50, 100, 200, 400, 1000, 2000 and 5000 ng) of glimepiride to aliquots of (1 mL) drug free plasma, and a fixed amount (1 µg/mL) of the internal standard glipizide. The drug and the internal standard were extracted from plasma by liquid-liquid extraction using a mixture of ethyl acetate-diethyl ether in 1:1 (v/v) ratio as the organic solvent. The samples were vortexed for 4 minutes followed by centrifugation for 4 minutes at 3200 rpm. The supernatant organic solvent was collected and evaporated. The residue obtained was reconstituted with the mobile phase of acetonitrile-5mM: ammonium acetate (60:40, pH 3.0 adjusted using formic acid) and an aliquot of which was analyzed by reverse phase LC/MS/MS[17]. The method was validated for accuracy.

B. **Chromatographic Conditions:** Agilent 1100 HPLC system was used. Chromatography was performed on X-terra, C18 (4.6mm i.d. × 50mm) analytical column (Waters, Milford, MA, USA) operated at 40^0C. The flow rate of mobile phase was 600µL/min, the temperature of the auto sampler was 4^0C and the run time was 2.0 minutes.

C. **Mass Spectrometric conditions and Data Collection:** The API-4000 triple-quadrupole mass spectrometer (Applied Biosystems/MDS SCIEX, Foster City, CA/Concord, Ontario, Canada) was equipped with an electro spray source, which operated in the positive ion mode. The optimized parameters were, curtain gas - gas 1 and gas 2 (nitrogen) at 40, 40 and 60 units respectively; dwell time was 200ms; source temperature was 500^oC; ion spray voltage was 5500V. Unit mass resolution was set in both mass-resolving quadrupole Q1 and Q3. Data was collected and processed using MDS Sciex Analyst 1.4.2 data collection and integration software on a Dell compatible computer.

D. ***In vivo* Study Design:** The study was conducted in accordance with the principles of Laboratory Animal Care and was approved by the Institutional Animal Ethics Committee (Ref. No: P1/VCP/IAEC/ 2012/3/PVL/AE3/Rabbits/M8F8; Date: 13/04/ 2012). Modified procedure of the method followed by *Doaa Ahmed El-Setouhy et al [2].,* was followed. 12 Albino New Zealand rabbits (weight 1.5 to 1.75 kg) of either sex were selected for this study. The rabbits were fasted overnight before administration of the dosage form, but had a free access to water. The rabbits were randomly divided into 3 groups each of four rabbits. The 1st group was control group whereas group 2 and 3 received the formulations containing plain drug and drug-HPβCD complex respectively. 0.35cm^2 films containing animal dose of the drug were carefully placed on the tongue of the animal through wooden gag.

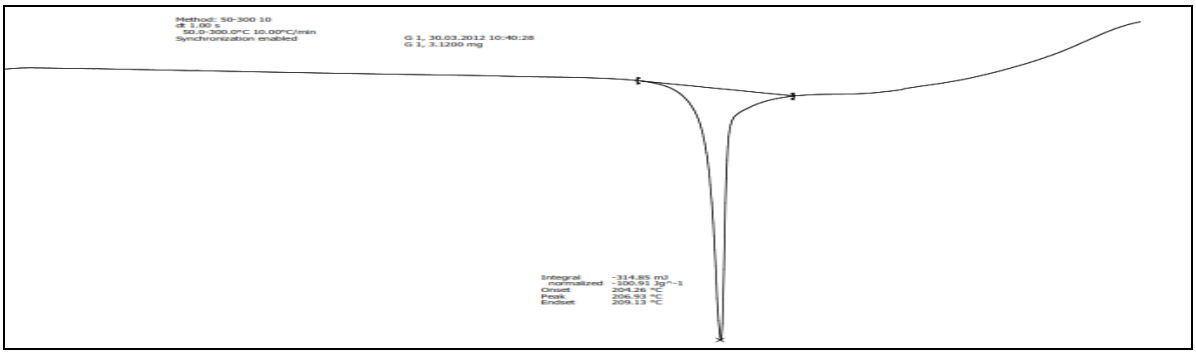
A few ml of water was administered at the end of about 1 minute to ensure that the animal's mouth is completely cleared off of any dissolved portions of the film. Blood samples for pharmacokinetic analysis were obtained immediately before drug administration and at 0.15, 0.30, 1, 2, 3, 4, 8, 12 and 24 h after dosing. Blood vessels were dilated by applying warm water before withdrawing the blood. Blood samples from marginal ear vein were collected in heparinized tubes using 22 gauge needles and were centrifuged for 10 minutes at 3,000 rpm at room temperature. Separated plasma was aspirated and transferred into plastic tubes and was stored at -20°C until assayed.

Statistical Analysis: The pharmacokinetic parameters of the tested formulations were compared by unpaired two-tailed t-test using GraphPad Prism® software (Version 4). A difference below the probability level of 0.05 was considered statistically significant.

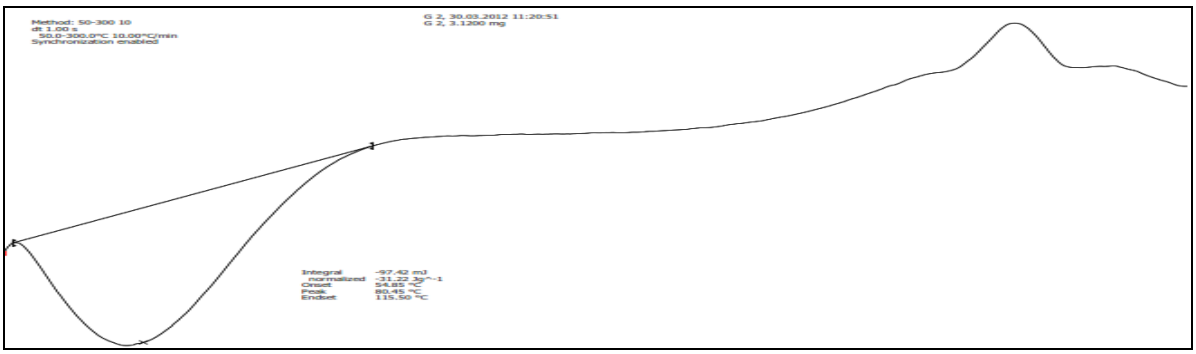
RESULTS AND DISCUSSION:

Preformulation Studies:

A. **Drug-Polymers-Excipients interaction studies by Thermal Analysis:** Thermogram of the physical mixture of the drug with the polymers-excipients obtained was compared with the thermogram of the pure drug and HPβCD as indicated in **Figure 1**.



A



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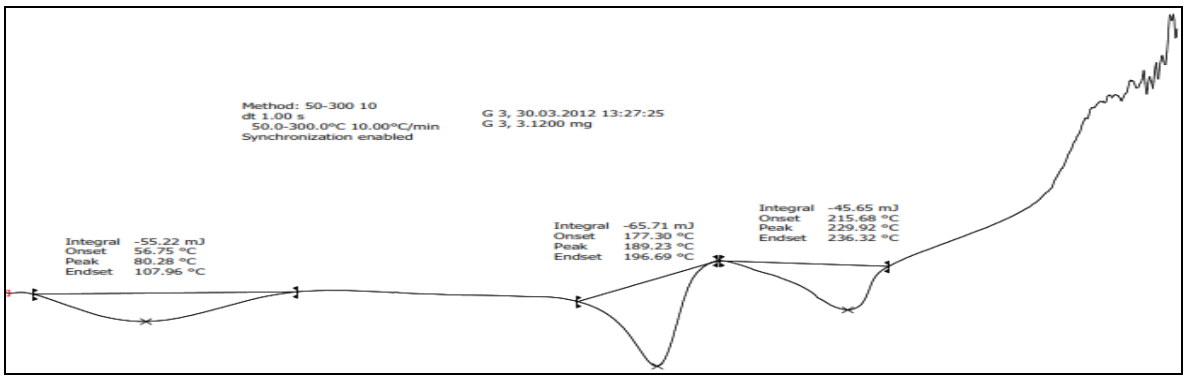

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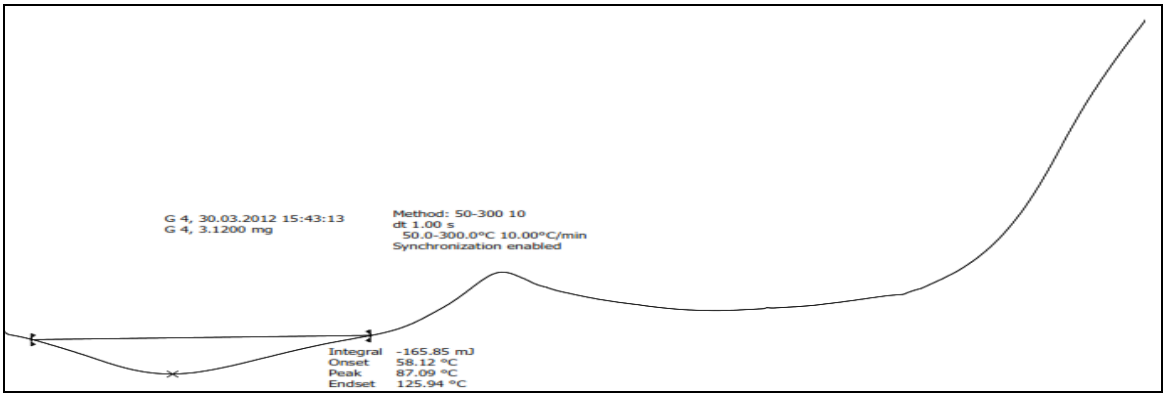

D

FIGURE 1: DSC THERMOGRAMS OF GLIMEPIRIDE (A), HPBCD (B), PHYSICAL MIXTURE OF THE DRUG WITH THE POLYMERS-EXCIPIENTS (C) AND INCLUSION COMPLEX OF DRUG WITH HPBCD (D)

Pure glimepiride exhibited an endothermic peak at 206.93^{o}C, which started to melt at 204.26^{o}C, the range of which corresponded to its melting point (205-207^{0}C). In the DSC curve of pure HPβCD, the endothermic peak corresponding to the evaporation of water appeared at 80.45°C. The characteristic feature of the drug was lost in the physical mixture of drug with the polymers-excipients with no other relevant effects, thus ruling out any interaction between the drug and all the examined components.

B. **Preparation of glimepiride-HPβCD complex and complex confirmation by DSC studies:** As per literature [14], glimepiride forms an inclusion complex with HPβCD in the molar ratio of 1:1 with a solubility constant K_c value of 42.57 M^{-1}. Such complex prepared by kneading method was found to give better dissolution rate. Therefore, in the present work, drug-HPβCD complex was prepared by using same method and ratio.

In the DSC thermogram of inclusion complex of drug with HPβCD prepared by kneading method, the characteristic feature of the drug was lost as indicated in the Figure 1. The disappearance of the thermal feature of the drug indicated that the drug had penetrated into the cyclodextrin cavity replacing the water molecules[19], and had complexed with the carrier.

Formulation Studies

A. **Design and preparation of Glimepiride FDFs:** As indicated in Table 1, various batches of glimepiride FDFs were prepared by the solvent casting method. FDFs of Glimepiride were prepared using water soluble polymers HPMC-E5 and Maltodextrin as film formers. Glycerol and PEG-600 were used as plasticizers. Sodium starch glycollate was used as super disintegrating/ channelling agent. Sodium lauryl sulphate, polaxamer 407 and Tween-80 were used as surfactants, aspartame as a sweetener and brilliant blue as coloring agent. Formulations F1 and F2 were dummy films. As film formulation F1 was thicker, formulation F2 was attempted with lower concentrations of polymers and a higher concentration of super disintegrant.

As the thickness and the texture of formulation F2 was satisfactory, drug was incorporated in the same to obtain formulation F3. As formulation F3 was gritty and ununiform in texture due to the insolubility of the drug in water, formulation F4 was developed by incorporating poloxamer 407 as suspending agent. Surfactants are used as solublising or wetting or dispersing agents so that the film gets dissolved within seconds and releases active agent immediately. Poloxamer 407 is used as solubilising, wetting and dispersing agent in oral films [3].

TABLE 1: FORMULAS OF THE VARIOUS BATCHES OF THE DEVELOPED GLIMEPIRIDE FDFS

Formulation code	F1	F2	F3	F4	F5	F6	F7
Glimepiride:HPβCD	-	-	-	-	1:1	1:1	1:1
HPMC-E5 (%)	40	36	36	36	36	36	36
Maltdextrin (%)	40	36	36	36	36	36	36
Sodium starch glycollate (%)	20	27	27	27	27	27	27
PEG-600 (mL)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Glycerol (mL)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aspartame (mL) (Aqueous solution)	-	-	0.5	0.5	0.5	0.5	0.5
Polaxamer 407 (%)	-	-	-	0.03	0.03	-	-
SLS (%)	-	-	-	-	-	0.03	-
Tween 80 (%)	-	-	-	-	-	-	0.03
Brilliant blue	-	-	-	-	qs	qs	qs
Water (mL)	25	25	25	25	25	25	25

Values are in % of total solid content. qs – Quantity sufficient

As glimepiride is practically insoluble in water and has unpleasant taste, the drug was complexed with HPβCD by kneading method in the ratio of 1:1[14] and was incorporated in the film in the place of plain drug to obtain formulation F5. Formulations F6 and F7 contained SLS and Tween 80 respectively in the place of poloxamer 407 as it was proposed to evaluate the effect of various surfactants at the same concentration on the physicochemical properties of the dosage form. Formulations F3 to F7 contained aspartame and formulations F5 to F7 contained coloring agent.

Characterization of the Developed FDFs

A. **Morphological properties:** It was observed that formulations F1 and F2 were totally homogenous, absolutely transparent, colorless and both sides were smooth. Except for formulation F3, which was ununiform in texture, formulations F4 to F7 were homogenous, slightly opaque and both the sides were found to be smooth.

B. **Thickness measurements:** The thickness of the formulations F3 to F7 was found to vary between 0.12±0.02mm to 0.14±0.03mm as indicated in Table 2. A low standard deviation indicated that the method used for the formulation was reproducible and gave films of uniform thickness and hence accuracy in each film could be ensured.

C. **Film mass:**The weight of each film formulation was pre-determined and differed depending on the amounts of ingredients used for preparation of the films as indicated in **Table 2**.

TABLE 2: PHYSICOCHEMICAL CHARACTERS OF THE VARIOUS BATCHES OF THE DEVELOPED GLIMEPIRIDE FDFS

FC	Drug content* (%)	Thickness (mm)*	Film mass** (mg)	PMA**	PML**	DT*** (Sec)	Folding endurance
F1	-	0.18±0.03	-	-	-	-	-
F2	-	0.11±0.02	63± 3	15.7±0.2	4.7±0.7	19±3.6	>100
F3	104.8±0.7	0.12±0.02	68±1.73	14.1±0.1	4.0±0.4	21±2.7	>100
F4	102.8±0.5	0.13±0.03	76±1	12.0±0.3	2.8±0.1	16±2	>100
F5	***103.9±0.3***	***0.14±0.03***	***79±0.5***	***14.8±0.4***	***4.4±0.8***	***12±2.1***	***>100***
F6	105.4±0.4	0.14±0.03	80±1.15	13.0±0.6	3.5±0.2	13±2.1	>100
F7	101.1±0.5	0.13±0.03	82±1.52	12.3±0.5	2.9±0.5	13±1.2	>100

FC - Formulation code; DT - disintegration time. *Average of 5 readings; ** Average of 3 readings; ***Average of 6 readings

D. **Folding endurance:** The folding endurance of all the developed formulations F2 to F7 was found to be more than 100 as indicated in Table 2.

E. **Drug content determination:** The drug content of all the batches of the developed formulations is indicated in Table 2. The observed results of content uniformity indicated that the drug was uniformly dispersed throughout the films. The percentage drug content of the examined formulations F3 to F7 varied between 101.1±0.5% to 105.4±0.4%.

F. **Percentage moisture absorption and moisture loss:** Presence of moisture in films helps them from becoming dry and brittle due to plasticizing effect of water. All the FDFs lose water in dry conditions and pick moisture over 60% RH (2). Such studies give idea about the stability of the films. The PMA of the formulations F2 to F7 was found to range from 12.0±0.3 to 15.7±0.2 whereas PML was found to range from 2.8±0.1 to 4.7±0.7 as indicated in Table 2. The moisture uptake by the formulations may be attributed to the hygroscopic nature of polymer-glycerol composite film.

G. ***In vitro*** **Disintegration Time:** Table 2 gives the time in seconds in which the films of the various developed formulations disintegrated. Dummy films F2 disintegrated faster in 19±3.6 seconds compared to formulation F3 containing plain glimepiride in 21±2.7 seconds. Formulations F4 to F7 showed better disintegration time which could be due to the presence of surfactants which influences the disintegration time in the predictable manner. Being emulsifiers, they facilitate the diffusion of fluid into the film resulting in faster disintegration of the film. The disintegration time further improved if the drug is present in a more solubilised form as in the case of formuations F5 to F7 containing drug- HPβCD complex compared to the formulation F4

containing plain drug. Of all the surfactants used, poloxamer 407 containing films F5 disintegrated faster in 12±2.1 seconds than the films F6 and F7 containing SLS and Tween-80 respectively, the disintegration time of which is almost the same.

H. ***In vitro* Dissolution Studies:** The dissolution profiles of the most satisfactory formulations F5 to F7 based on the disintegration time were compared with the formulation F4 containing plain drug as indicated in Figure 2.

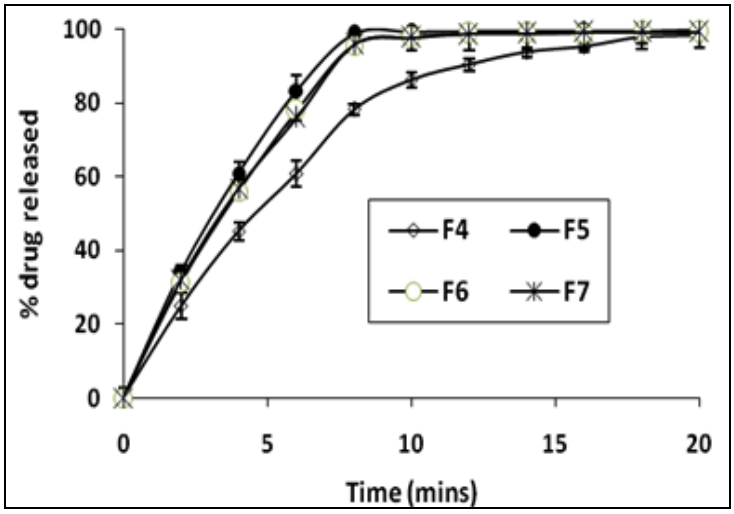

FIGURE 2: DISSOLUTION PROFILES OF THE DEVELOPED FORMULATIONS F4 TO F7

Formulations F5 to F7 containing drug- HPβCD complex released almost 100% of the drug by 8th minute whereas only 78.17%± 3.430258 of the drug was released from the formulation F4 during the same duration of time. Among the formulations F5 to F7, as the dissolution profile of formulation F5 was found to be faster, better and uniform as indicated in the Figure 2, it was chosen as the most satisfactory formation and further studies were carried out on it.

I. **Taste of the Formulations:** The taste of the formulation F5 which contained drug-HPβCD complex was accepted well by all the volunteers over the formulation F4 which contained plain drug. It was concluded that the slight bitterness of the plain drug in the formulation F4 was masked by the complexation of the drug with HPβCD[12, 13] in the formulation F5.

J. ***In Vivo* Studies:** The calibration curve was constructed in the range of 2ng/mL to 5000ng/mL in blank plasma. The linear response across the concentration range used was found to be r^2 = 0.9970. The plasma samples were assayed by reverse-phase LC/MS/MS with positive ion electro spray ionization, using multiple reaction monitoring. Glimepiride produced a protonated precursor ion ([M+H]+) at m/z 491 with a major product ion at m/z 352. Whereas, glipizide (internal standard) produced a protonated precursor ion ([M+H]+) at m/z 446, with a major product ion at 321 [17]. The assay method showed acceptable accuracy with relative error < 9% over a wide concentration range (20 to 1000ng/mL). A representative LC-MS/MS chromatogram of glimepiride (200ng/mL) in plasma is given **in Figure 3**.

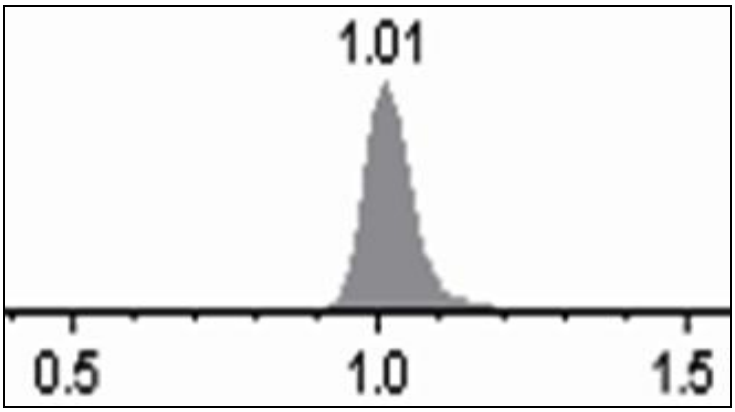

FIGURE 3: A REPRESENTATIVE LC-MS/MS CHROMATOGRAM OF GLIMEPIRIDE (200NG/ML) IN PLASMA

The pharmacokinetic parameters of the FDF formulations F4 containing plain drug was compared with the formulation F5 containing drug- HPβCD complex as indicated in the **Table 3 and Figure 4**.

TABLE 3: COMPARISON OF PHARMACOKINETIC PARAMETERS OF THE FORMULATION F4 WITH THAT OF FORMULATION F5

Pharmacokinetic parameters	Data of the group given formulation F4	Data of the group given formulation F5
AUC_{0-24} (mcg.h/mL)	1.6678 (±0.1109)	1.6910 (±0.1032)
$AUC_{0-\infty}$ (mcg.h/mL)	1.7546 (±0.1468)	1.7724 (±0.1487)
C_{max} (ng/mL)	195.05 (±7.8800)	212.14 (±9.2640)
t_{max} (h)	2.75 (±0.5)	1.75 (±0.5)
K_e (h^{-1})	0.1403 (±0.0229)	0.1510 (±0.0078)
$t_{1/2}$ (h)	5.04 (±0.7763)	4.60 (±0.2270)

Even though the AUC_{0-24} and $AUC_{0-\infty}$ values between both the formulations were found to be statistically insignificant (P = 0.7704 and P = 0.8352 respectively), there was a significant difference in the C_{max} and t_{max} values (P = 0.0307 and P = 0.03 respectively). The peak levels of the drug in plasma was significantly higher and rapid from formulation F5 than formulation F4, which could be attributed to the increase in the solubility and dissolution rate of glimepiride upon complexation with HPβCD [20].

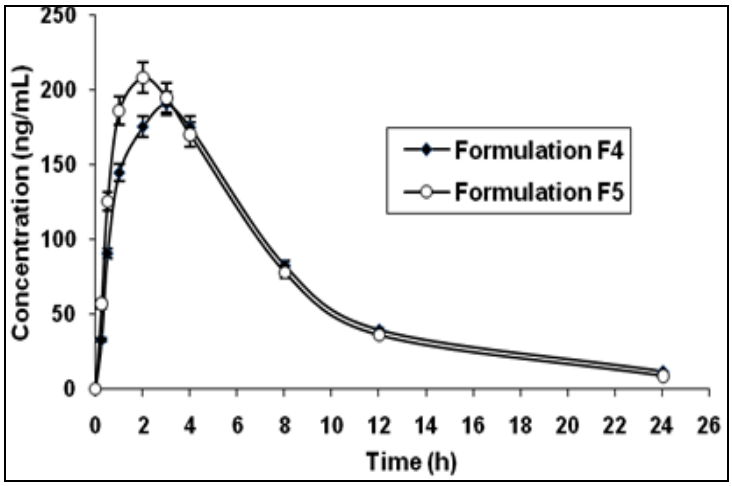

FIGURE 4: MEAN PLASMA CONCENTRATION FOLLOWING ADMINISTRATION OF FORMULATIONS F4 AND F5 TO RABBITS

CONCLUSION: It can therefore be concluded that the standardized formulation F-5, in which the drug is present in its most soluble form, improved the physico-chemical-pharmacokinetic parameter requirements of a oral FDF dosage form of glimepiride, which is suitable for improving patient compliance for better management of the disease.

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