

EFFECTIVE FORMULATION OF GLIMEPIRIDE LOADED ORAL THIN FILMS FOR RAPID DRUG AVAILABILITY

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ABSTRACT

Objective: Patient convenience and compliance-oriented research has resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance. Fast dissolving films (FDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips, but now regarded as the most advanced form of oral route of drug Administration. Problems such as poor solubility and wettability of drugs has resolved to higher extent. This project was aimed to formulate Fast Dissolving Oral Thin films of Glimepiride GOTFs, glimepiride is a new oral sulfonylurea hypoglycemic agent for the treatment of non-insulin dependent (type II) diabetes mellitus. It is classified under class II according to biopharmaceutical classification system with low solubility and high permeability. **Method:** GOFTs were prepared by using solvent casting method and Hydroxy Methyl Propyl Cellulose (HPMC) as a polymer. **Results:** GOTFs 0.1mm in thickness were prepared which were appropriate in appearance as well as fulfilled all criterions of Oral Thin Films Formulations. The disintegration time for GOFTs was 3 seconds and oral films. The pH of films was 6.2, Tensile strength was 7 N/mm² and percent elongation was 19%. **Conclusion:** From the results of this study it can be concluded that prepared optimized fast dissolving Oral Films of glimepiride are the better option to treat diabetes.

Keywords: Fast Dissolving Oral Films (FDF), Glimepiride, Solvent casting method, HPMC.

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INTRODUCTION

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and ease of administration lead to high level of patient compliance. The oral route is problematic because of the swallowing difficulty for pediatric and geriatric patients who are afraid of choking. Patient convenience and compliance-oriented research has resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self-administration even without water or chewing. Fast dissolving drug delivery systems were first invented in the late 1970s as to overcome swallowing difficulties associated with tablets and capsules for pediatric and geriatric patients.

Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which

includes adhesive tablets, gels, ointments, patches, and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films. It is interesting to note that the permeability of buccal mucosa is approximately 4-4,000 times greater than that of the skin, but less than that of the intestine. Hence, the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration [1, 2].

Where OTFs can be defined as, "Oral Fast Dissolving Films are most advance form of solid dosage form due to its flexibility. It improves efficacy of Active Pharmaceutical Ingredient (API) dissolving in short duration oral cavity after contact with less amount of saliva as compared to dissolving tablets" [2]. Advantages of oral dissolving film (ODF) over fast dissolving tablet (FDT) are: Accessibility of larger surface area that leads to quickly disintegrate and dissolution in the oral cavity within seconds ODF is flexible so they are not as fragile and need not any kind of special package for protection during

transportation and storage as compared to FDT. No need of water has led to better satisfactoriness amongst the dysphasic patients and there is no fear of choking as compared to FDT. The large surface area available in the film dosage form allows rapid wetting by saliva then quickly disintegrates and dissolve and absorbed directly and can enter the systemic circulation without undergoing first pass hepatic metabolism and increase the bioavailability. Thin Films can be consumed at any place and any time as per convenience of the individual. Most importantly the avoidance of the first pass effect cause reduction in the dose which can lead to reduction in side effects associated with the molecule. Patients suffering from dysphagia, repeated emesis, hypertension, heart attack, asthma, motion sickness, paralysis and mental disorders prefer this dosage form as they are not capable to swallow large quantities of water [3, 4].

Diabetes mellitus, an endocrine disorder affecting glucose metabolism, has been crippling mankind for the past two centuries. It is a condition in which a person has a high blood sugar level, either because the body doesn't produce enough insulin, or because body cells don't properly respond to the insulin that is produced. Insulin is a hormone produced in the pancreas which enables body cells to absorb glucose, to turn into energy. If the body cells do not absorb the glucose, the glucose accumulates in the blood, leading to vascular, nerve, and other complications. Glimepiride, 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]sulfonyl]-3-(trans-4-methylcyclohexyl) urea, is a new oral sulfonylurea hypoglycemic agent for the treatment of non-insulin dependent (type II) diabetes mellitus [5]. It stimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites. The molecular formula of glimepiride is $C_{24}H_{34}N_4O_5S$ and the substance is characterized by a molecular weight of 490.6. Glimepiride is an orally active hypoglycemic substance belonging to the sulphonylurea group. It acts at ATP sensitive potassium channels (KATP) on pancreatic β -cells to promote insulin release, reducing potassium conductance and causing depolarization of the membrane. Glimepiride after oral administration lowers blood glucose 3.5 times more potently than Glibenclamide. Glimepiride is classified under class II according to biopharmaceutical classification system. The drug shows low, pH dependent solubility. In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37 °C (<0.004 mg/mL). In media with pH >7, the solubility of drug is slightly increased to 0.02 mg/mL. This poor solubility may

cause poor dissolution and unpredicted bioavailability. The very poor aqueous solubility and wettability of glimepiride give rise to difficulties in the design of pharmaceutical formulations and led to variable oral bioavailability, so it is beneficial to prepare it into a new dosage form [6].

To manufacture fast dissolving oral films, following methods are generally employed - Solvent casting, Hot melt extrusion, Semisolid casting, Rolling and Solid dispersion extrusion. Solvent casting method is used for preparation of Glimepiride loaded Oral Thin Films (GOTFs) as solvent casting is feasible, preferable and undoubtedly widely used method mainly due to the straightforward manufacturing process and low cost of processing.

The objective of the project is to formulate orally dissolving films containing glimepiride for improving onset of action, lowering the dosing, and enhancing the efficacy and safety profile thereof. Oral films also improve the dosing accuracy relative to other administration forms. Rapid absorption by the liver after oral administration, extensive first pass metabolism in the liver, very poor aqueous solubility and wettability of Glimepiride give rise to difficulties in the design of pharmaceutical formulations and led to variable oral bioavailability, [7] rendering it strong candidate for administration in the form of oral films.

The polymer used in this formulation is Hydroxypropyl methylcellulose (HPMC) which belongs to the group of cellulose ethers. HPMC is hydrophilic (water soluble), a biodegradable, and biocompatible polymer having a wide range of applications in drug delivery, dyes and paints, cosmetics, adhesives, coatings, agriculture, and textiles. HPMC is also soluble in polar organic solvents, making it possible to use both aqueous and non-aqueous solvents. It has unique solubility properties with solubility in both hot and cold organic solvents. HPMC possesses increased organo-solubility and thermo-plasticity compared to other methyl cellulose counterparts. It forms gel upon heating with gelation temperature of 75–90 °C [8].

Novelty of Project

Diabetes without a proper treatment can cause many complications, e.g. hypoglycemia, diabetic ketoacidosis, nonketotic hyperosmolar coma, cardiovascular disease, chronic renal failure, and retinal damage. Adequate treatment of diabetes is thus important, as well as lifestyle factors such as smoking cessation and healthy diet regimen. Glimepiride is the first III generation sulphonyl urea it is a very potent sulphonyl urea with long duration of action. It is pharmacologically distinct from other sulphonylureas because of differences in receptor-binding properties and potentially selective effects on ATP-sensitive K^+ channels [9]. It is Preferred

Sulfonylurea in view of the reduced mortality (all-cause and CV mortality), better CV outcomes (composite of acute myocardial infarction, stroke, and CV mortality), and renal protection, in patients at increased risk of hypoglycemia, in obese or overweight patients, in patients with moderate or severe hepatic or renal impairments (reduction in dosing interval). It can be used during Ramadan, with appropriate counseling and dose modification, as it confers a lower risk of hypoglycemia [10]. It belongs to class II of Biopharmaceutical classification system showing poor aqueous solubility (0.0082 mmol) and high permeability. Several attempts have been made to improve solubility of Glimpiride using approaches like solid dispersion [11] inclusion complexation and co-solvency [12]. This project is aimed to formulate innovative preparation of glimepiride in the form of thin film.

The very poor aqueous solubility and wettability of glimepiride give rise to difficulties in the design of pharmaceutical formulations and led to variable oral bioavailability so it is beneficial to prepare it into a new dosage form which should be fast dissolving, in order to attain highest level of therapeutic efficacy. HPMC is used as polymer, Sodium Lauryl Sulfate as surfactant, Polyethylene glycol as plasticizer, mannitol is added as sweetening agent. The purpose of addition of water-soluble polymer is to generate a formulation that dissolves fastly when come in contact with saliva.

METHOD USED FOR PREPARATION OF GLIMEPIRIDE ORAL THIN FILMS (GOTFS)

Selection of Solvent System

Glimpiride was the Active Pharmaceutical Ingredient or API, Hydroxypropyl Methyl Cellulose (HPMC) was the selected polymer. Sodium Lauryl Sulfate was added as surfactant while Polyethylene Glycol was the plasticizer.

Preparation of Polymeric Suspension

Glimpiride loaded nanosuspension was prepared using high shear homogenization method. Stabilizer solution was prepared using 1% HPMC and 12% SDS. The solution was stirred using high shear homogenizer at 4000 rpm for 15 min. Glimpiride (0.4 g) was then added to this solution while stirring and homogenization was continued at 8000 rpm for 150 min at ambient conditions.

Casting of Suspension

OTFs of optimized glimepiride nanosuspension were prepared by solvent casting method. We added accurately weighed quantities of HPMC E-15 (1 g) and PEG 400 (0.15 g) to glimepiride nanosuspension formulation (equivalent to 40 mg of glimepiride) and stirred using magnetic stirrer for 30 min. The final mixture was then casted on a glass plate with the help of doctor's blade [13, 14].

Drying of Casted Suspension

It was dried at room temperature for 48 hours.

Peeling and Cutting and Packing of prepared Films

After drying, films were removed with the help of the sharp blade, we cut them in the suitable sizes containing glimepiride equivalent to 2 mg, then packed in aluminum foil and kept in a desiccator till further evaluation.

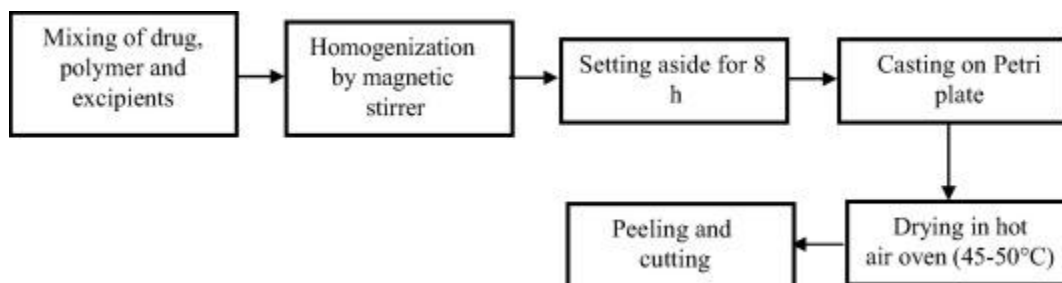


Figure 1: Preparation of GOTFs.

Disintegration Test

Disintegration time is defined as the time (second) at which a film breaks when brought into contact with water or saliva. The disintegration time is the time when a film starts to break or disintegrate. Thickness and mass play a role in determining the dissolvable film's physical properties [15]. Disintegration test was performed in the USP Disintegration apparatus. Simulated salivary fluid (pH 6.8) was used as the

medium. We placed the films in the tubes of the container, and the disks were placed over it and disintegration time was calculated [14]. A film is placed onto 2 ml distilled water taken in petri dish. Time taken by the film to dissolve completely is considered as the disintegrating time.

Dissolution Test

Dissolution is defined as the amount of drug substance that goes into solution per unit time under

standardized conditions of liquid/solid interface, temperature and solvent composition. *In vitro* method is carried out in modified USP XXIII apparatus. *In vitro* dissolution studies of GOTF (containing pure Glimepiride) were performed in 900 ml of pH 1.2 HCl buffer at 37±0.5 °C using USP Type II (Paddle) Dissolution apparatus at 75 rpm. Aliquots (5 ml) were collected at specific time intervals and the volume was made up by adding fresh dissolution medium [14, 15] the average dissolution time of film was determined.

Thickness

The thickness of the films was measured using the digital micrometer screw guage with an accuracy of 0.001 mm. Thickness was measured for 10 different films and determined the average thickness. The average thickness was determined.

Weight Uniformity

Weight variation was studied by individually weighing 10 randomly selected film strips and calculating the average weight by digital weighing balance. We took ten films of 2x2 cm² size and weight of ten films was 30 mg and the average weight was calculated.

Surface pH

Surface pH of film was determined to check whether the film causes irritation to the mucosa. The surface pH study was carried out by selecting 3 films randomly, by using electrode [14].

Morphology Study

The morphology of the films was studied for their appearance, texture and clarity. The appearance of film and texture was determined.

Folding Endurance

Number of times a film can be folded at the same place without breaking or cracking gives the value of folding endurance. We determined it by repeatedly folding the films at the same place until it broke. The film was folded ten times at the same place.

Tensile Strength and Percent Elongation

Tensile strength was determined using lab scale tensile strength to measure instrument. Films of dimension 2x2 cm² and free from physical imperfections were used for the study. The films were held between two clamps at a distance of 3 cm. Films were pulled by the upper clamp at the rate of 5 mm per minute until it tears with the addition of weight at regular intervals. Measurements were done in triplicate. Tensile strength is the ratio of maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture to the cross-sectional area of the fractured film as a mean of three measurements and described in the equation:

$$\text{Tensile strength} = \frac{\text{Breaking force}}{\text{Cross sectional area of sample}}$$

$$\text{Percent elongation} = \frac{\text{Increase in length at breaking point}}{\text{Original length}}$$

Drug Content Uniformity

Three films were randomly selected from the prepared ones were checked for dimensions and weight. Sample film of 4 cm² was cut into small pieces and transferred to 100 ml volumetric flask. 100 ml of phosphate buffer pH 6.8 was added in the volumetric flask and this solution was sonicated for 30 minutes and the volume was made up to the mark using same solvent, filtered and the absorbance of the solution was recorded at 228 nm by UV Spectroscopy.

Table 1: Tests performed on GOTFs.

Tests	Results
Morphology	Smooth texture
pH	6.2
Weight uniformity	3mg (average weight)
Disintegration time	3 sec
Dissolution time	10 sec
Thickness	0.1mm
Appearance	Transparent
Tensile strength	7 N/mm ²
Percent elongation	19 %

RESULTS AND DISCUSSION

Organoleptic evaluation was done, and the appearance of film was transparent, and texture was smooth. The average disintegration time of six films was noted. Film was disintegrated within 3 seconds, which provides confirmation of the films being fast disintegrating [16]. *In vitro* dissolution studies of GOTF (containing pure Glimepiride) were performed, the average dissolution time of 10 GOTFs was 10 seconds. The thickness of the films was

measured, thickness was measured for 10 different films and average thickness was determined, and the average thickness was 0.1mm. The average weight of film was 3 mg. Folding endurance was determined, and the film endured 10 attempts of breakage [17]. The tensile strength of film was 7 N/mm² and percent elongation was 19%. **CONCLUSION**

In the present study oral fast dissolving drug delivery system of Glimepiride was successfully developed which offers a suitable and practical approach in

serving desired objective of faster disintegration and dissolution characteristics with increase in patient compliance. The drug and polymer compatibility was appreciable in terms of fast dissolution of the prepared films. The results were positive in developing a novel oral fast dissolving film of Glimepiride however; there is scope for an extensive pharmacokinetic and pharmacodynamic evaluation.

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