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Formulation of Glimepiride Oral Films and Development of a Novel Disintegration Time Testing Method for its Evaluation

Hema A. Nair *, D. S. Pyla

Department of Pharmaceutics,Sri Venkateshwara College of Pharmacy, Hyderabad, Telangana 500081, India.

Email: hemajit@rediffmail.com

Abstract

Glimepiride is a low dose antidiabetic drug with poor aqueous solubility. The aim of the present work was to develop fast dissolving palatable films of glimepiride capable of presenting the drug in solution in the oral cavity itself and intended for quick onset of action coupled with convenience in portability and administration. The paper also presents a novel method for testing disintegration time of oral films. Glimepiride was complexed in a 1:3 molar ratio with sulphobutyl ether beta-cyclodextrin by kneading method to tackle both, mild bitterness and poor water solubility. The drug complex, pullulan as film forming polymer and other excipients, were dissolved in water and films were prepared by the solvent casting method. Dried films were cut into units, each containing 1 mg of drug, and evaluated for physicochemical, mechanical and performance-based attributes. The films were found to be elegant, non-tacky and flexible and uniform in weight, thickness and drug content. They disintegrated rapidly and provided all the drug in dissolved form within three minutes. The developed film thus provided a novel, convenient and suitable formulation for delivery of glimepiride. Concurrently, the work also describes a disintegration test conceived inhouse, based on a modification of the bulk densitometer, capable of accurately estimating the time taken by the film to disintegrate in the oral cavity. The method rendered disintegration time estimates statistically similar to results recorded from studies in human volunteers, due to the ability to mimic a mouth-like environment.

Keywords: Disintegration time testing, Glimepiride, Orally disintegrating film, Sulphobutyl ether beta-cyclodextrin,.

INTRODUCTION

Rapidly dissolving or quick mouth dissolving dosage forms, both tablets and films, have already acquired a favourable market share so that fast dissolving oral films are, as of today, a well proven and world-wide accepted technology for the systemic delivery of actives [1]. Generally, oral films are ultra-thin-strips of postage stamp size with an active pharmaceutical ingredient incorporated into a polymeric film along with other excipients. These films are supposed to simultaneously disintegrate and dissolve in the mouth and allow for rapid drug absorption partially via the mouth, but mostly through the rest of the git.

The rapid introduction of newer products and filing for patents in these classes of products are indicators of the growing popularity of oral films [2]. In the near future, more and more drugs are expected to be reformulated from conventional tablet / capsule dosage forms to the mouth dissolve types. The reasons for the increasing consumer acceptance of these dosage forms are attributed to their ability to overcome several of the drawbacks of tablet and capsule based products including, but not limited to, difficulty in swallowing, requirement for availability of water, difficulties in opening of packaging and difficulty in integrating the intake of the medicine into other everyday activities [3]. Low dose drugs administered orally, which are not very bitter in taste, are suitable for reformulation into mouth dissolve films, especially if they are intended for chronic administration. Revolutionary manufacturing technologies such as 3-D printing will soon make large scale manufacturing of films with reproducible attributes, facile [4].

Glimepiride is a potent oral antidiabetic belonging to the class of sulphonylureas. It is used with insulin or other oral antihyperglycemics to control high blood sugar. Glimepiride has a normal oral daily dose of 1 to 8 mg and is slightly bitter in taste. It is also used chronically and often by geriatric patients who present with swallowing difficulties. Hence, glimepiride was selected as a drug for formulation into oral films. Also, being a BCS class II drug, it was complexed with betacyclodextrin sulphobutyl ether; which was expected to yield a two-fold benefit of masking the mild bitterness of the drug and of increasing its solubility both in the aqueous casting solution used for film formation and in the salivary milieu.

A quality attribute critical to the performance and patient acceptance of the mouth dissolve films is their ability to dissolve/ disintegrate rapidly in presence of the limited moisture available on the tongue without the need for biting or chewing, to give a palatable mass. For e.g. the labelling instructions accompanying mouth dissolving films such as Zuplenz (having ondensteron as the active) state that the patient should remove the film from its pouch and immediately place it on top of the tongue where it dissolves in 4 to 20 seconds, then swallow with saliva [5]. Although several products have been approved and commercialized [6], there are no standard or compendial methods to evaluate the disintegration time of the films on the tongue, typically designed to be a few seconds. Moreover, methods commonly reported, are unable to mimic the mouth conditions.

The present studies were directed towards development of a palatable oral film for delivery of glimepiride and also includes the development of a suitable *in vitro* test for estimation of disintegration time of the oral films in a manner predictive of the actual time for disintegration of the film when placed on the tongue.

MATERIALS AND METHODS

Glimepiride and Captisol® (Beta cyclodextrin sulfobutyl ether sodium) (BCDSBE) were kindly gifted by Ipca Laboratories Ltd. Mumbai, India and Cydex Pharmaceuticals, USA respectively. All other formulation ingredients purchased including pullulan (Hayashibara Co. Ltd., Japan), citric acid (Nice Chemicals, India), crospovidone and glycerine (SDFCL, India) and sodium saccharin (N. R. Chemicals, India) were used as received. All solvents and other ingredients used including buffer salts were of analytical grade.

Phase Solubility Studies:

Phase solubility studies for effect of beta cyclodextrin sulfobutyl ether sodium (BCDSBE) on the solubility of glimepiride was carried out according to the method reported by Higuchi and Connors [7]. An excess of glimepiride (50mg) was added to 20 ml portions of pH 6.8 buffer, each containing increasing amounts of BCDSBE as 0.02, 0.04, 0.06, 0.08 and 0.1 and 0.12 % w/v. All the above solutions were shaken on a rota shaker at 25°C for 72 hours. Next, the solutions were filtered and their absorbance was noted at 230 nm. The concentration of glimepiride in every solution was calculated from a validated standard plot and phase solubility diagram plotted between the amount of glimepiride dissolved at various concentrations of BCDSBE, both expressed in millimoles. The plot was used to determine the type of glimepiride: BCDSBE complex. Also, the linear part of the curve was used to extrapolate the slope of the line and this in turn was used to estimate the stability constant K1:1 of a 1:1 glimepiride cyclodextrin complex as an indicator of the overall stability of the prepared combine, using the equation [8]

K1:1 = slope/So(1-slope).

Preparation and characterization of glimepiride BCDSBE complex:

The glimepiride – cyclodextrin complex was prepared by the kneading method. Weighed amount of BCDSBE was transferred to a glass mortar. A small quantity of water was added while triturating to obtain a slurry like consistency. Next, glimepiride (drug : BCDSBE molar ratio 1:3) was incorporated into the slurry and trituration was further continued for one hour. Slurry was then air dried at 25°C for 24 hours to give the glimepiride – cyclodextrin complex.

FTIR spectra of glimepiride, BCDSBE and the complex prepared as above were recorded (Shimadzu) using a KBR pellet prepared by mixing 2 mg sample with about 200 mg fine KBr powder and then compressing the mixture in a pellet-forming die.

Preparation of mouth dissolving glimepiride film:

Dose of glimepiride per film was 1mg. Oral films of glimepiride were prepared by solvent casting method and films were cast in Teflon plates with a radius of 3.45 cm. Since each film was intended to be 2.5 x 2.5 cm^2 in size, this corresponded to each petriplate yielding 6 films.

The ingredients used for preparation of the film and the purpose of inclusion in the formulation are listed in **Table 1**. From the dried powder of glimepiride BCDSBE complex, 84 mg corresponding to 6 mg glimepiride was dissolved in 7 ml water. To the above drug solution, polymer and other excipients were added to form a homogenous mixture and the volume was made up to 10 ml. The resultant solution was poured into the Teflon coated petriplate placed on a leveled surface and dried in a hot air oven at 60°C for 7 hr. The film was subsequently peeled, cut into 2.5 x 2.5 cm^2 dimension and evaluated.

Evaluation of film:

***Uniformity of weight*:** Five films were randomly selected and their average weights measured. Individual films were weighed and mean weight and standard deviation were calculated.

***Uniformity of thickness*:** Five films were randomly sampled. The thickness of each film was measured using digital screw gauge, at four corners and in the centre. Average of all readings was taken as thickness of film and the standard deviation was calculated.

***Uniformity of drug content*:** A 2.5 x 2.5 cm^2 section of the film corresponding to 1 mg of glimepiride was dissolved in 10 ml of distilled water. The solution was suitably diluted with pH 6.8 buffer and the absorbance measured at 230 nm by UV visible spectrophotometry. The exercise was repeated on another five sections of films prepared from separate solutions. A blank film was similarly treated and the absorbance recorded to rule out any interference due to the excipients.

***Folding endurance*:** The folding endurance of oral films was measured manually. Films were repeatedly folded at the same place till they broke. The number of times the film could be folded in case of 5 films was counted and the mean count was recorded as the folding endurance.

***Tensile strength*:** The tensile strength of the developed films was measured on a Maxwell tensile testing machine. For measurement of tensile strength films were prepared in larger petriplates and a proportionate volume of film forming solution was used for casting. The test sample (17 mm x 13 mm with a thickness of 0.14 mm) was securely held by top and bottom grips and the grips were moved apart at a constant rate of 10 mm/min resulting in stretching of the specimen. The force on the specimen and its displacement was continuously monitored and plotted on a stress-strain curve until the strip broke.

The tensile strength was calculated using the formula:

Tensile strength = load at breakage × film width/ film thickness

And the extent of elongation undergone by the film at breaking point was expressed as

Percent elongation = increase in length ×100/original length

***Tackiness*:** 10 films were stacked one above the other. The top most film was protected by covering with a piece of butter paper and a weight of 5 gms was placed on it. The arrangement was allowed to remain for 7 days at 25°C after which attempts were made to separate the films from each other.

***Surface pH*:** The film was placed in a petridish and wetted with 1 ml of distilled water. The electrode of a calibrated pH meter was immediately brought in contact with the surface of the film and the pH was determined.

***Test for in vitro drug dissolution*:** The USP apparatus II was modified for the dissolution studies. The bottom of a glass petriplate was inserted into the hemispherical

bottom of the dissolution vessel in an inverted position to function as a base for holding a 500 mL glass beaker which served to contain the dissolution medium. Dissolution was carried out in 150 mL pH 6.8 phosphate buffer maintained at 37±0.5°C. The outer dissolution vessel was filled with water till a level which allowed the beaker to stand steadily in it. The film was placed at the bottom of the beaker with forceps and the paddle was operated at 50 rpm. Aliquots (5mL) of the dissolution medium were withdrawn at 30sec, 1min, 2min, 4min, 6min, 8min, 10min time intervals and was replaced with an equal volume of fresh medium. The samples were filtered through Whatman filter paper, diluted suitably and analyzed using UV– spectrophotometry at 230 nm.

***Disintegration time testing: Development of novel method mimicking oral conditions*:** A novel test for disintegration of films capable of mimicking the conditions prevailing in the mouth was devised based on a modification of a powder densitometer. A piece of cardboard covered with aluminum on its lower surface served as the equivalent of the upper palate and was affixed at a height of 3 cm above the holders provided for the measuring cylinder in the densitometer as shown in **Figure 1**. The film was placed in a petri plate, which in turn was placed on the holder. A limited volume (1.5 ml) water in the petriplate served to mimic the moist conditions on the tongue. The mechanical apparatus was immediately switched on so that the film was raised and lowered at a rate of 20 times a minute in such a manner that at its upper-most position it contacted the foil covered surface. Time required by the film to disintegrate completely was noted.

Figure 1 shows actual pictures of the modified apparatus. For the sake of image clarity, colored film was prepared and used only for procurement of the pictures.

In addition, the disintegration time of the films was also measured by the traditional petriplate method, wherein, a petri plate (6.9 cm in diameter) was filled with 10 ml of water. The film was carefully placed in the center of the petri plate. The time for the film to completely disintegrate was noted.

Finally, in order to validate the utility of the developed *in vitro* disintegration time testing apparatus developed, a preliminary *in vivo* evaluation was also carried out. The study was designed as per earlier reports on limited *in vivo* studies for evaluation of disintegration time of placebo mouth dissolve tablets [9]. Each film was evaluated for time to disintegrate by 5 volunteers. The volunteers were instructed to take a sip of water just prior to the test. A placebo orally dissolving film was placed on the tongue of the volunteer. The participants were instructed to move the film against the upper roof of the mouth with their tongue gently without chewing or tumbling the film from side to side. They were instructed to report the instant when the film dissolved completely on the tongue and the time required was measured using a stop watch and recorded. Volunteers were also instructed to spit and discard the disintegrated film.

To enable better comparison of the disintegration testing methods, in addition to the placebo version of the film described in this study, 4 more drug free films with varying disintegration times which were examined during the preliminary studies leading to the present formulation, were subjected to the disintegration tests as described above including the *in vivo* evaluation test. These films were all having the same quantitative composition of ingredients by weight, but were prepared using different polymers and superdisintegrants. In case of the *in vivo* studies, all 5 formulations were tested on each volunteer and the tests were carried out over a period of 5 days with each volunteer testing only 1 film per day.

The statistical significance of the difference between the disintegration time of the films as recorded by the three test methods was ascertained through a two way ANOVA test. A post hoc Tukeys test was also included to further analyze the difference between the mean disintegration times for the films.

RESULTS AND DISCUSSION:

Glimepiride is a BCS class II drug with poor aqueous solubility. In order to enable the preparation of films in feasible volumes of aqueous casting solution, it was necessary to solubilize the drug. Also, it would be advantageous to have the drug in solubilized form in the mouth itself to promote rapid absorption. Reports of solubilization of glimepiride as cyclodextrin complexes prompted the exploration of BCDSBE for increasing aqueous solubility of glimepiride [10]. The selection of β – cyclodextrin sulfobutyl ether was based on literature reports of its superior safety profile and drug solubilization properties [11]. Additionally, although glimepiride is only reported to be slightly bitter, inclusion into the cyclodextrin complex can also achieve taste masking [12]. Initially, to adjudge the type of complex and to estimate its stability, phase solubility studies were undertaken

Solubility of glimepiride in acidic and neutral aqueous media is reported to be less than 0.004 mg/mL at 37°C. In media pH>7, solubility of drug is slightly increased to 0.02 mg/mL [13]. The solubility of glimepiride in phosphate buffer pH 6.8 as measured during the phase solubility study was 0.0196 mg/mL, well within the above reported values of solubility.

The phase solubility studies clearly showed an increase in solubility of glimepiride in presence of increasing amounts of the complexing agent. The increase however was linear only up to a cyclodextrin concentration of 0.007 mM **(Fig. 2)**. Beyond this, the phase solubility profile revealed a greater increase in solubility resulting in an Ap-type- curve as per the classification of complexes proposed by Higuchi and Connors based their effect on substrate solubility [7]. Such a profile is indicative of presence of a higher order species with respect to BCDSBE.

Such higher complexes are believed to occur because of association of a 1:1 complex with additional cyclodextrin molecules resulting in stepwise binding constants. If this were the case, the stability constant of the initially formed 1:1 complex may be obtained from the linear part of the curve and from the present studies, this was calculated to be 2525 Lit/Mole indicating good stability [8].

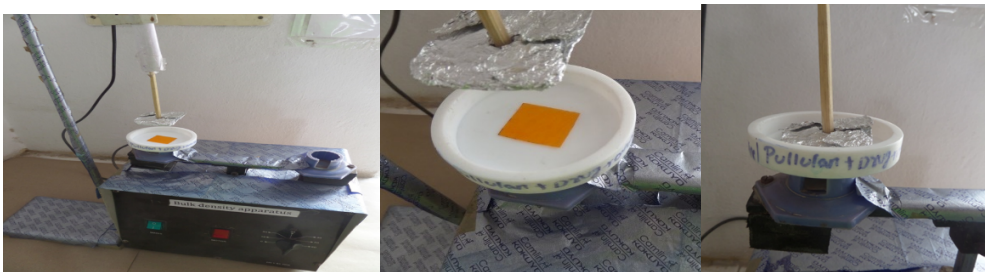

Fig 1: Apparatus for *in vitro* disintegration time testing of oral films developed by modification of densitometer.

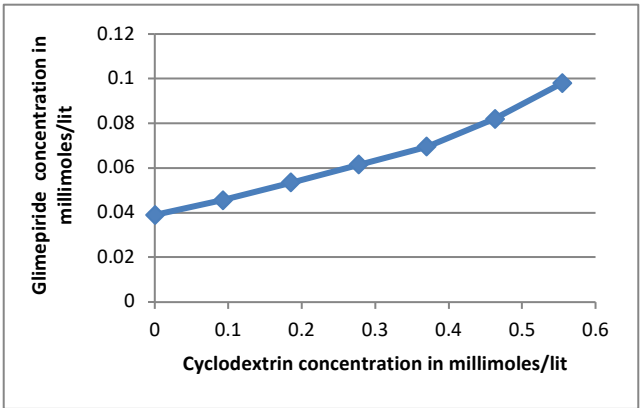

Fig. 2. Solubility of Glimepiride in presence of increasing amounts of beta cyclodextrin sulphobutyl ether.

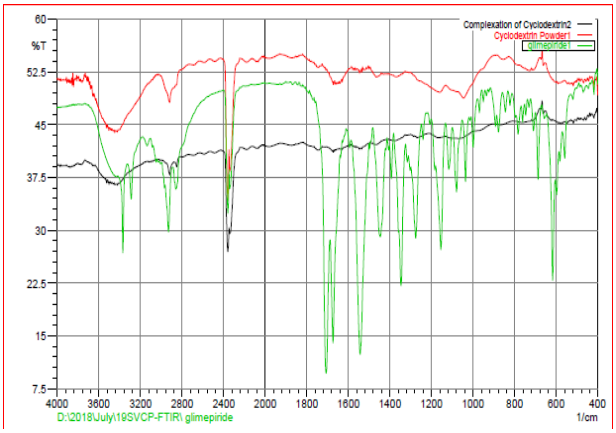

Fig.3. Overlay of IR spectra of glimepiride, BCDSBE and the complex.

Glimepiride
Betacyclodextrin Sulphobutylether
Glimepiride – BCDSBE complex

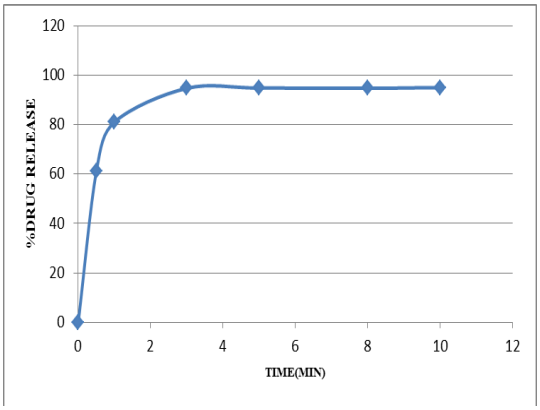

Fig. 4. Dissolution of glimepiride from the oral film.

Table 1: Formula card for preparation of the glimepiride mouth dissolving films with justification.

*Added as 84 mg of the complex preprepared by kneading method.

Ingredient	Quantity per 15 ml (intended for 6 films)	Justification of quantity
Glimepiride*	6 mg	Most common single oral dose being 1mg
BCDSBE *	78 mg	Accounting for a 3:1 molar ratio with drug
Pullulan	0.5 gm	Film forming polymer giving film of suitable thickness
Citric acid	25 mg	Salivary stimulating agent added to the extent of 5% w/w of polymer
Cross povidone	25 mg	Super-disintegrant added to the extent of 5% w/w of polymer
Sodium saccharin	12 mg	Sweetener added to the extent of 2 mg/ film
Glycerine	100 mg	Plasticizer added as 20% w/w of polymer
Peppermint oil	q.s	Flavoring agent
Water q.s	10 ml	Vehicle for casting

Table 2: Parameters used for evaluation of glimepiride oral films and the corresponding results.

Sr. No	Property evaluated and units of measurement	Mean ± S.D.
Parameters indicative of physicochemical uniformity of the films		
1	Weight per film (mg) (n=5)	121.33±0.12
2	Thickness of films (mm) (n = 5 x 5)	0.372± 0.059
3	Drug Content (% of labelled content) (n =5)	93.58 ±1.98
Parameters indicative of physical/mechanical properties of film		
4	Folding endurance (n = 5)	90+
5	Tensile strength (N/mm^2) (n = 5)	7.28± 2.52
6	Elongation at break (Percentage) (n = 5)	123.45±48.59
7	Test for Tackiness	Non-tacky
Parameters indicative of *in vivo* acceptability and performance		
7	Surface pH	6.4
	Dissolution	Nearly 100% within 3 min
9	Disintegration time (seconds) Petriplate method Developed novel test method	 65.2 ± 1.5 35 ± 0.2

Table 3: Time for disintegration of placebo films evaluated by different techniques.

	Average disintegration time in minutes ± s.d. (n=5)		
Formulation code*	**Traditional petriplate method**	**Developed alternate method**	***In vivo* test in human volunteers**
HC	3.00 ± 0.70	2.14 ± 0.11	1.56 ± 0.33
HM	2.74 ± 0.44	1.50 ± 0.46	1.34 ± 0.15
HS	6.79 ± 1.41	4.32 ± 1.29	3.91 ± 0.80
VC	21.80 ± 3.46	13.00 ± 2.42	11.00 ± 2.64
PC (Developed film as placebo)	1.25 ± 0.39	0.37 ± 0.07	0.30 ± 0.03

*All placebo films were quantitatively similar with respect to content by weight of polymer and superdisintegrant although the nature of both excipients were varied as shown in the code:
Polymer: H – HPMC E-15, V - PVA , P – PULLULAN
Superdisintergant: C – Crospovidone , M – Sodium croscarmellose, S – Sodium starch glycolate

Apart from forming the stepwise complexes, cyclodextrins and their complexes may form micelle like aggregates which in turn can solubilize further lipophilic molecules through non-inclusion complexation resulting in deviations from 1:1 ratio expected of an inclusion complex.

A study using the Jobs plot prepared using UV absorbance to decipher the glimepiride – BCDSBE complex reports a 1 : 3 ratio of drug : BCDSBE [14]. Hence, for the present studies too, this ratio was used to prepare glimepiride – BCDSBE complex by kneading method for incorporation into the film. The successful formation of the complex was evident from the IR spectra **(Fig. 3)** wherein the characteristic peaks of the drug were masked in the complex.

Oral films are generally stamp size. For the present studies, square patches of size 2.5 x 2.5 cm^2 was chosen as a suitable size based upon dose, ease of handling and administration. The patches were prepared by the laboratory friendly solvent casting method. The polymer chosen was water soluble due to the requirement for rapid dissolution of the film when placed on the tongue without the intake of water. Pullulan was selected because preliminary trials revealed that the films were more transparent and elegant when compared to films cast from aqueous solutions of polyvinyl alcohol or hydroxyl propyl methyl cellulose E-15. Also, pullulan is edible and non-toxic [15]. It can be made into very thin films of high tensile strength which are stable over a range of temperatures upto 60°C for 7 hrs. Glycerol was selected as a plasticizer after screening of other materials and the

and drug content measurements in multiple samples. The low values of standard deviation for all the measured parameters is an indicator of the uniformity of the films. The average drug content was 93.58% ±1.98 of the intended strength of 1 mg/film; indicating that the drug remained homogenously distributed in the polymer matrix during the drying process and the content per film does not deviate significantly from the theoretical content.

The mechanical properties of the film also indicate a flexible film with good tensile strength. Tack is defined as the force with which the film adheres to an accessory that has been pressed into contact with the film. It has been evaluated qualitatively by gently pressing the film between fingertips [17] or as the ability of a film to get adhered to a piece of paper pressed between strips [18]. For the present study, the cohesive tack between the films was evaluated. Films were subjected to a test conceived in house wherein the stacked films were allowed to rest for a period of 1 week under a 5 gm weight. However, the films were found to be tack free and easily separable after being subjected to the test.

Orally dissolving films are intended to disintegrate/dissolve very rapidly, within a few seconds when placed on the tongue and achieving this property in the developed product is a key to its success. Although guidelines suggest using the conventional disintegration testing apparatus for determination of the disintegration time of orally dissolving tablets, no official methods are available for evaluating disintegration time of ODTFs. The USP official disintegration apparatus has been used in some studies [19], but preliminary experimentation during the present studies revealed that it was nearly impossible to judge the time point when the transparent thin film completely disintegrates within the apparatus. Similarly, methods of placing the film in limited water in petriplates with / without swirling [20] have also been employed which was followed as a traditional method for the present studies as well. The inadequacy of the petriplate method in judging *in vivo* disintegration time has also been pointed out by other reports [21].

Thus, a need for a method which can simulate the oral conditions better was found to be lacking and an attempt was therefore made to develop the same. A novel test for disintegration of films based on a modification of the bulk densitometer was devised and the disintegration times for a few selected placebo films were compared with results from tests carried out on the films using conventional method as well as with the results of an *in vivo* testing of placebo films in human volunteers **(Table 3**). A two-way ANOVA test showed that the disintegration time of the different formulations tested were significantly different from each other ($p < 0.05$) and that the methods tested were also significantly different from each other ($p < 0.01$). Also, a post hoc Tukeys test revealed that the petri plate method yielded disintegration time estimates which were higher and significantly different from the newly developed method ($p < 0.01$) as well as from the results of the *in vivo* measurements ($p< 0.05$) whereas, film disintegration time measured by the newly developed method and the *in vivo* results of disintegration time were not significantly different from each other ($p< 0.05$).

The novel disintegration test developed was simple and rendered disintegration time estimates which were statistically similar to the results recorded from studies in human volunteers unlike the longer disintegration times given by the conventionally reported static methods. The alternative test developed as part of the study can serve as a more accurate tool for judging the disintegration time of the film.

The surface pH of was compatible with oral mucosal lining indicating that the film would not lead to any discomfort for the mucosal lining.

The *in vitro* dissolution of glimepiride from films was followed using 150 ml pH 6.8 phosphate buffer as the medium in USP apparatus II. The buffer was selected since it is the dissolution medium prescribed by IP for dissolution test of glimepiride tablets. The films provided for nearly complete drug release at the end of 3 mins **(Fig. 4)**.

The rapid release indicates that the drug is available in a solution form in the oral cavity itself. Glimepiride has been reported to have a permeability of 0.27 mg hr^{-1} cm^{-2} when studied in ex-vivo excised sheep buccal mucosa [22]. Studies on buccal and sublingual dosage forms have also claimed avoidance of first pass metabolism and rapid bioavailability of glimepiride when administered via these routes [23]. Hence in the present studies also the developed ODFs may offer dual benefits of convenience and improved bioavailability in terms of both rate and extent of drug available in the systemic circulation.

CONCLUSION:

The orally dissolving films developed in this study may serve as a suitable and more convenient means of delivery of glimepiride. Also, the developed disintegration test is simple and was found to successfully mimic mouth-like conditions during the test. As more and more oral films reach commercialization, the development of appropriate tests may contribute to the development of compendial testing methods as and when oral films make their way into the official list of formulations.

CONFLICT OF INTEREST:

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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