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Formulation and *In-Vitro* Evaluation of Mucoadhesive Buccal Films of Glibenclamide

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Abstract

The present study was aimed to develop a new Mucoadhesive buccal film for the release of Glibenclamide with improved bioavailability, which is used as an oral hypoglycemic agent. The films were fabricated by solvent casting technique with different polymer combination and evaluated in terms of drug release, bioadhesive strength, content uniformity, film thickness, percentage elongation, surface pH and folding endurance. The release profile and bioadhesive strength were found to be the function of the type of polymers used. The formulation containing polymers Hydroxy Propyl Cellulose (HPC) and Polyvinyl Pyrrolidone (PVP) and Ethyl Cellulose (EC) showed better result.

Keywords: Glibenclamide, Mucoadhesive, Buccal films, hydroxy propyl cellulose

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Introduction

Diabetes mellitus is among the most widespread chronic disorder affecting mankind. Substantial efforts have recently been focused on delivery of drugs to or via mucous membrane by the use of muccoadhesive materials to overcome the limitation of conventional drug delivery system. Recently buccal mucoadhesive dosage form has shown lot of potential as a drug delivery system and it has generated lot of interest both in industry and in academics. Mucoadhesive drug delivery system is explored for various reasons such as prolonging the drug action, targeting the drug to a localized site, avoidance of degradation of drug in gastrointestinal tract, to deliver high molecular weight proteins and peptides systemically and to avoid first pass metabolism.[1,2] The present study attempts to develop a mucoadhesive buccal delivery system for Glibenclamide to improve and enhance its bioavailability, and to bypass the hepatic first pass effect by administering it through the buccal mucosa, which is richly perfused with blood vessels and offers greater permeability than skin. Buccoadhesive dosage forms utilize the mechanism of bioadhesion and produce

intimate contact with the membrane for longer time thus delivering the drug across the oral mucosa directly into the systemic circulation. [2]

Glibenclamide is an oral hypoglycemic agent belonging to sulphonyl ureas class [3]. The various physiochemical properties of Glibenclamide such as low molecular weight (494.0), dissociation constant (5.3), short biological half life (3 to 5 hrs), necessitates multiple dosing for maintaining therapeutic effect throughout the day [4]. Glibenclamide is having relatively high doses when given orally with only 45% to 50% of drug absorption. Absence of objectionable taste and odor made it a suitable candidate for buccal administration, which are capable of avoiding the first pass effects and gastrointestinal side effects with delayed release. The development of technology for release of drug at a controlled rate into a systemic circulation using buccal cavity as port of entry has become popular.

The goal of the present study was an attempt to design and evaluate mucoadhesive buccal films of Glibenclamide with different polymers viz. HPC, PVP and EC.

Materials and Methods

Glibenclamide B.P. was a gift sample from Ishaan Labs Pvt. Ltd., Bangalore. Hydroxy propyl cellulose M from E.Merk, Mumbai PVP 40,000 and Ethyl cellulose from Loba Chemicals, Mumbai; Propylene glycol from Nice Chemicals Pvt. Ltd., Cochin; Dibutyl phthalate from Loba Chemicals, Mumbai; Ethanol from PCL, Pune. All other reagents used were of analytical grade.

Preparation of buccal film:
Buccal films were prepared by the solvent casting technique. Polymers HPC-M, EC and PVP were used for the preparation of films. Propylene glycol was used as a plasticizer and penetration enhancer [5]. Rectangular films of 1.9 cm x 1.5 cm and containing 4.5 mg of Glibenclamide per film was cut out from the cast film using a sterile razor.

Estimation of Glibenclamide:
Glibenclamide content in the buccal film was estimated by using UV spectrophotometric method based on the measurement of absorbance at 300 nm in phosphate buffer pH 7.4. The method was validated for linearity, accuracy and precision. The methods obeyed Beer's law in concentration range 2 – 20 μg/ml [6].

Drug release study:
A simple apparatus was used for *in vitro* release study. A 200 ml glass beaker was filled with isotonic phosphate buffer (1PB 7.4). Rectangular films measuring 1.9 cm x 1.5 cm containing 4.5 mg were cut. A thin coating of high vacuum silicone lubricant was applied to a 2.5 x 7.5 microscope slide, making sure that all edges adhered and no lubricant touched the exposed surface. Silicone lubricant was found superior to solvent-based adhesives by virtue of its non-interacting compatibility with the film. In addition to its capacity to maintain adhesion of film to the slide, its water repellency provided secondary assurance of only single surface release. The slide was placed at inclined angle into a 250 ml beaker on a 37^0C thermostat containing 200 ml of pH 7.4 buffer preheated to 37^0C. A non-agitated system was maintained to eliminate any effect of turbulence on the release rate as well as to assure that no disruption of the film occurred. Periodically samples were obtained by removing the slide, stirring the solution and pipetting a 5ml sample with a muslin cloth covered over the tip of the pipette. The slide was quickly reinserted, making sure that the film remained

completely immersed throughout the release study [6]. The beaker was kept covered throughout the run to prevent evaporation. The study was continued for 8 hrs. All samples were assayed by diluting suitably, by U.V. spectrophotometer at 226 nm.

Bioadhesive Strength:

In the present study hamster cheek pouch was used as a model mucosal surface for bioadhesion testing. The duration of bioadhesion was studied by measuring the time required for the formulation to erode completely or the time for which the formulation was maintained at its position without dislodging so bioadhesive strength is an index of bioadhesive strength of a film to the buccal mucosa till the complete drug releases. Bioadhesive strength of the film was measured using a modified double beam balance described by Gupta et al [7].

Percent elongation at break was determined using universal testing machine as described by Khanna et al [8]. The parameters longitudinal strain (LS, increase in length/ initial length) and percentage elongation at break (LS x 100) were calculated. A small strip of film was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the values of the folding endurance. The surface pH was measured by the method similar to that used by Bottenberg et al [9]. A combined glass electrode was used. The films were kept in contact with 0.5 ml of distilled water for 1 hr. pH was noted by bringing the electrode near the surface of the film and allowing it to equilibrate for 1 min.

All the polymers used for the fabrication of films gave good quality films. Method of casting on the petridish was found to be satisfactory. Buccal films with different polymers were transparent, smooth and flexible. Initially dummy films were prepared in order to determine the best combination of polymers, plasticizers and solvents required to get good formulation. Then, the formulations which showed complete homogenous smooth, flexible and non-sticky were selected for further studies and evaluated for in vitro drug release, bioadhesion strength, surface pH, percentage elongation, folding endurance and film thickness.

Results and Discussion

The results revealed that the release of drug is depended on the polymer type as well as on their concentration. Film containing HPC alone (F1 & F2) released the maximum drug. Incorporation of PVP or EC reduced the release rate of Glibenclamide from the buccal films. The plots of log cumulative percent drug retained against time (Fig. II) were found to be almost linear. This indicated that drug diffusion from these buccal films followed a first order kinetics. Cumulative percent drug release against root of time (Fig. III) gave the Higuchi's plot, which revealed that the release of drug was by diffusion. F1 & F2 followed non-Fickian release, whereas the remaining formulations showed Fickian release. The rank order of the drug release from different formulations is F1>F2>F3>F4. Formulation F1 showed 76.79% drug release at the end of 4 hr followed by F2 (74.26%), F3 (67.74%) and F4 (65.43%). The formulation F5 showed 54.49%, F6 (43.12%), F7 (39.13%) and F8 (37.44%) at the end of 8 hrs.

The bioadhesive strength of the formulation was found to be dependent on the type of polymers used. Results obtained showed that the formulation F2 exhibited maximum bioadhesion strength. The order of bioadhesion strength for all the formulations F2>F1>F4>F3>F5>F6>F7>F8. The adhesion strength for all the formulations was in the

range of 11 to 3 Gms for the buccal film F1 to F8. The content uniformity of all the films revealed the drug was uniformly distributed throughout the films.

The folding endurance gives the idea of flexible nature of films. Formulations F1, F2, F3 and F4 showed folding endurance above 300. F8 showed minimum folding endurance. However all the films showed satisfactory flexibility.

The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity. Acidic or alkaline pH is bound to cause irritation to the buccal mucosa. Attempt was made to keep the surface pH close to the neutral pH. The surface pH of all the formulations was found to be within ±1.5 units of neutral pH. Hence it is assumed that these formulations cause no irritation in the oral cavity.

Flexibility of the films affects mucoadhesion[10]. Films with good percent elongation are essential. Formulation F1 showed maximum percent elongation and formulation F8 showed minimum percent elongation. The rank order of the percent elongation is F1>F2>F4>F3>F5>F6>F7>F8. Thickness of films was found to be in the range of 0.20 to 0.24 (nm) for all the films. The rank order were F5>F2>F4>F1>F6>F7>F3>F8.The results are shown in Table No.2.

The results obtained in the present investigation indicate that the films exhibited satisfactory physical and mechanical properties. F1 and F3 showed good acceptability . Formulation F5 delivered 54.49% of drug for extended period of time. To improve the release of drug from these films, necessary alteration in composition could be done and can be used as a good device for buccal delivery of Glibenclamide.

The present study was a satisfactory attempt to develop erodible buccoadhesive films, which will overcome the inherent drawbacks associated with conventional drug delivery of Glibenclamide and will have an improved bioavailability, therapeutic efficacy and patient compliance.

Further, *in vivo* release studies need to be carried out on suitable animal models in order to establish an *in vitro – in vivo* correlation. Also there is challenge for manufacturer to device suitable manufacturing process to enable large-scale production and willingness of the pharmaceutical industry to take up potential candidates so as to offer an alternative to conventional drug therapy.

Table 1. Mucoadhesive Film Composition

Ingredients	**Formulations**							
	F1	***F2***	***F3***	***F4***	***F5***	***F6***	***F7***	***F8***
Glibenclamide (mg)	60	60	60	60	60	60	60	60
Hydroxy propyl cellulose-M (mg)	700	800	650	700	400	300	--	--
Polyvinyl pyrrolidone, 40,000 (mg)	--	--	150	100	--	--	200	150
Ethyl cellulose, 18-22 cps, (mg)	--	--	--	--	400	500	600	650
Propylene glycol (ml)	0.1	0.1	0.1	0.1	0.1	0.1	--	--
Dibutyl phthalate (ml)	--	--	--	--	--	--	0.3	0.3
Ethanol (95%) (ml)	27	30	27	27	20	20	20	20

Table 2. Data obtained from evaluation of mucoadhesive formulations (±SD)*

FORMULATION CODE	Film Thickness	Bioadhesive Strength (gm)	Surface pH	% Elongation	Folding Endurance	Drug Content Uniformity
F1	0.210±0.005	11.2±0.6	6.5	57.5±2.5	300	4.440±0.018
F2	0.245±0.025	12.4±0.4	6.4	54.1±1.4	300	4.346±0.002
F3	0.205±0.004	8.5±0.9	6.7	53.3±2.8	300	4.349±0.014
F4	0.238±0.007	8.9±0.7	6.6	44.1±1.4	300	4.425±0.009
F5	0.246±0.008	7.1±0.5	7.1	36.6±1.4	259±11.93	4.348±0.024
F6	0.208±0.002	6.8±0.6	7.0	31.6±2.8	238±7.0	4.334±0.035
F7	0.207±0.003	3.5±0.1	5.8	22.5±2.5	80±7.09	4.362±0.018
F8	0.205±0.006	3.2±0.08	5.5	21.1±2.1	69.0±7.21	4.382±0.017

*±SD = Standard Deviation

Fig. I: In vitro release profiles from different mucoadhesive films

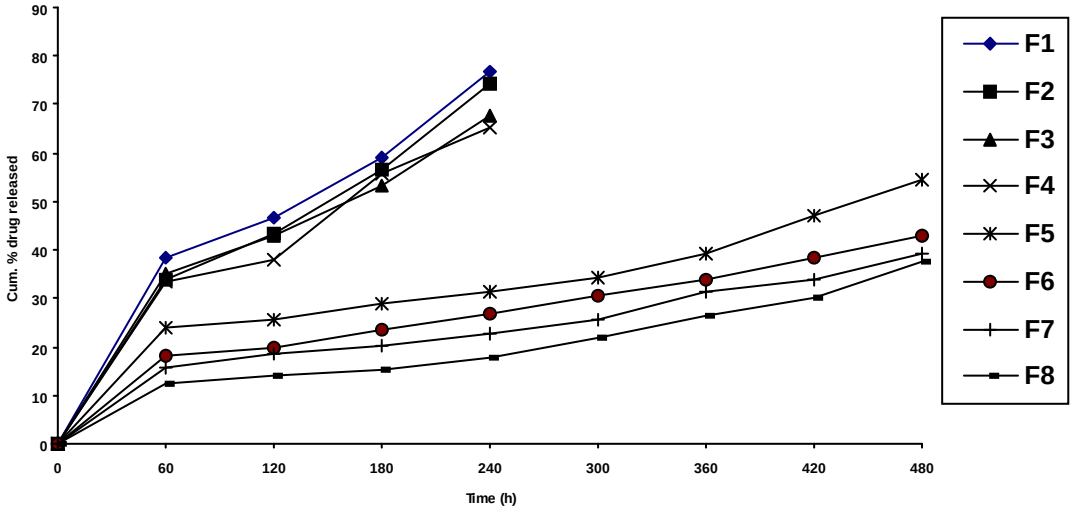


Fig. II: Plots of log cumulative percent drug remained as a function of time for buccal films

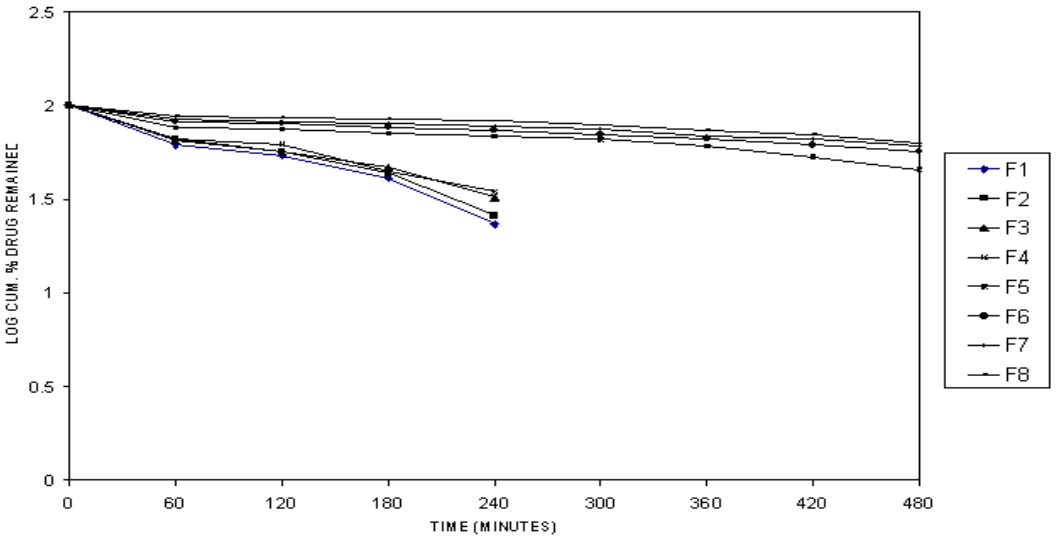
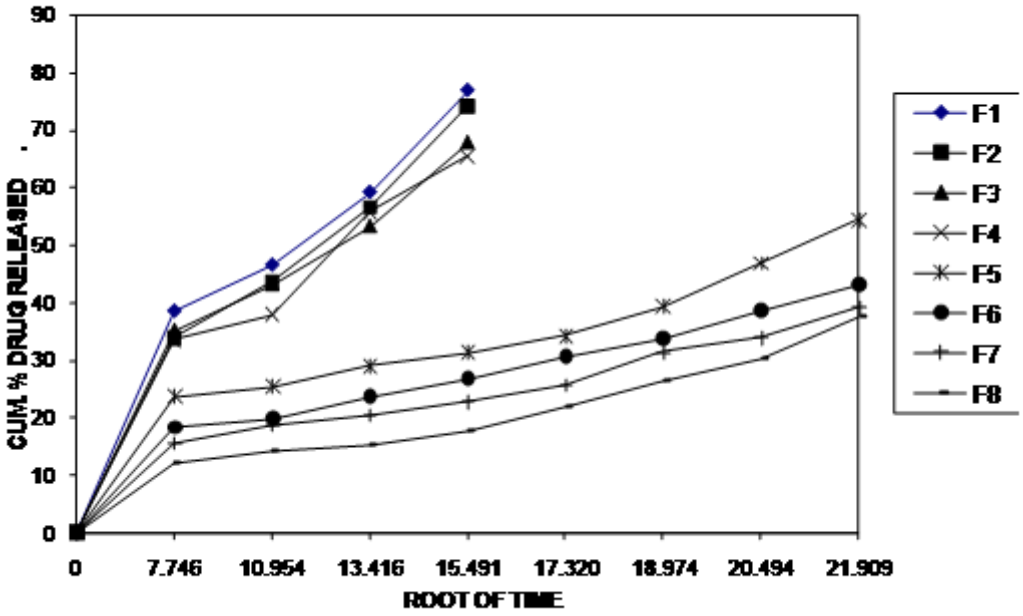


Fig. III: Higuchi's diffusion plots showing release of Glibenclamide from buccal films



References

[1] Khanna R.; Agarwal S.P.; and Ahuja A. *Indian J. Pharm. Sci*. **1998**, 60(1), 1.
[2] Rathbon J.; Michael, Ed., Marcel Dekker, Inc., New York, **1996.**
[3] John R.N; Campbell R.K; Herfindal E.T., Gourley, D.R., Eds; William and Wilkins, Marland, **1996**, 357.
[4] Tripati K.D. Jaypee Brothers Medical Publications (P) Ltd., New Delhi, **2001**, 278.
[5] Khanna R.; Agarwal S.P.; and Ahuja A. *Indian J. Pharm. Sci.* **1997**, 59(6), 299.
[6] Ilango R. et al. *Indian J. Pharm. Sci.* **1997,** 59(5), 232.
[7] Gupta A.; Garg S. and Khar R.K. *Indian Drugs*, **1992**, 30, 152.
[8] Khanna R.; Agarwal S.P. and Ahuja A. *Indian J. Pharm. Sci.*, **1997,** 59(6), 299.
[9] Bottenberg P. et al. *J. Pharm. Pharmacol*. **1991,** 43, 457.
[10] Ahuja A.; Khar R.K and Ali J. *Drug Develop, Ind. Pharmacy*, **1997**, 23, 489.
[11] Ali J.; Khar R.K and Ahuja A. *Indian J. Pharm. Sci*. **1998**, 60(5), 322.
[12] Khurana R.; Ahuja A. and Khar R.K. *Indian J. Pharm. Sci*., **2000,** 62(6), 447.
[13] Chandira M. et al *Der Pharmacia Lettre*; **2009**, 1 (1):83-91.
[14] Pandey S. et al *Der Pharmacia Lettre*, **2009**, 1 (2) 255-261.