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Development and Characterization of Mucoadhesive patches of Glimepiride for buccal administration

Subhranshu Panda*, Sheetal acharya, Jyoti Gandhi, Nishith Patel

LJ Institute of Pharmacy & Research Center, Ahmedabad

ABSTRACT:

Glimiperide, a third-generation sulfonylurea is poorly soluble anti-diabetic drug. In preformulation study solid dispersions by solvent evaporation technique were prepared to enhance solubility. Different ratios of PEG 6000 to Glimperide were taken for solid dispersion. The Films of Glimepiride solid dispersion equivalent to 2mg Glimiperide , were developed by solvent casting method using different Polymers, HPMC K4M, Sodium CMC, carbopol 971P and polyox. The prepared mucoadhesive buccal patches were evaluated for Swelling index, Residence time, Folding endurance, Tensile strength and Mucoadhesive strength. *In vitro* release was carried out in simulated saliva solution using modified USP type II apparatus at 50 rpm. *Ex vivo* release studies were performed with few selected batches and its results along with evaluation parameter were taken in to account to select optimized batch. The release of Glimepiride from developed formulations was found to be fickian diffusion controlled. A Short-term accelerated stability study was carried out for one month and the formulation found stable for that period of time.

Keywords: Glimiperide, Solid dispersion, Buccal patch, Mucoadhesion

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For Correspondence:

Dr. Subhranshu Panda

Department of Pharmaceutics and Pharmaceutical Technology, LJ Institute of Pharmacy & Research Center, Nr.sarkhej circle, S. G. Road, Ahmedabad-382210, India

Email:subhranshu021075@yahoo.co.in

Introduction:

Type II diabetes is characterized by progressive deterioration of normal pancreatic b-cell function. Initially, hepatic and muscle tissues lose sensitivity to the action of insulin. In the early stages of the disease, the b-cells of the pancreatic islets compensate for decreased insulin sensitivity by increasing insulin secretion. As the disease progresses, b-cell decomposition with impaired insulin secretion follows and sensitivity to insulin continues to decrease. Sulfonylureas directly stimulate insulin secretion [1]. Glimepiride, an anti-diabetic drug, is a very potent medium-to-long acting third-generation sulfonylurea. It stimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites.

Among all sulphonylureas, Glimepiride shows a minimal influence on risk of blockage of calcium channels in myocardial cells and data about the safety of use of Glimepiride in patients with coronary artery disease is available. Glimepiride appears to have a lower risk of hypoglycemia, compared to the other [2].

For the management of type II diabetes many efforts have been devoted to the area towards a development of optimal therapeutic regimens. To control hyperglycemia in patients with type II diabetes, the Sustained release formulations have been tried. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of the body, to achieve promptly and then maintain the desired therapeutic drug concentration that elicits the desired

pharmacological action and to minimize the incidence and the severity of unwanted adverse effects. To achieve this goal, it would be advantageous and more convenient to maintain a dosing frequency to once, or at most, a twice-daily regimen. An appropriately designed sustain release dosage form can be a major advance in this direction compared to conventional immediate release dosage forms [3]. The development of improved method of drug delivery has received a lot of attention in the last two decades [4].

To prepare a sustained release, matrix tablet approaches are most popular form. But there are some disadvantages of these tablets like first pass metabolism, instability in the acidic environment of the stomach or are destroyed at the enzymatic or alkaline environment of the intestine, food influence on absorption. To overcome these disadvantages, transmucosal drug delivery is an alternative [5]. The oral cavity is easily accessible for self administration, stopping of drug is feasible if required, safe and, hence is well accepted by patients [5]. This study focuses on the suitability of the buccal mucosa to achieve systemic drug concentrations of glimepiride for a sustained release.

To avoid the swallowing of dosage form or dose dumping, bioadhesive polymers have received considerable attention for platforms of buccal controlled delivery [6]. Due to bioadhesion, the immobilization of drug carrying particles at the mucosal surface would result in, a prolonged residence time at a site of absorption or action, a localization of the drug delivery system at a given target site and Increase in the drug concentration gradient due to the instant contact of the particles with mucosal surface [7].

Glimepiride has the lower molecular weight compare to the other third generation sulphonylurea and shorter half life (6-8 h) which make suitability for development of buccal dosage form. It 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 37^0C (<0.004 mg/ml). In media pH>7, solubility of drug is slightly increased to 0.02 mg/ml. This poor solubility may cause poor dissolution and unpredicted bioavailability [8]. However, only a few attempts have been made to improve its bioavailability.

To penetrate the mucosa to a significant degree, a drug should have relatively low molecular weight and should exhibit biphasic solubility patterns i.e. the drug should be soluble in the aqueous salivary fluid and shows penetration through lipid membrane [9]. Glimepiride shows practically insolubility in aqueous fluid. Hence in this study, solid dispersions of Glimepiride were prepared to obtain a biphasic solubility pattern.

The cellulose derivative- Hydroxypropylmethylcellulose (HPMC) is an uncharged synthetic bioadhesive polymer for the matrix system. Sodium carboxymethylcellulose (SCMC) shows good erodible property and carbopol 971P is one of the excellent mucoadhesive polymers. Polyethylene Oxide (Polyox™) is the good alternative of HPMC for the matrix system and shows the good swelling and mucoadhesive property. Polyox™ N 80 is one of the moderate viscosity grades while Polyox™ WSR 303 is highest viscosity grade.[10, 11]

In the present investigation, Buccal films were prepared with 2 mg Glimepiride (twice a day) to develop a sustain release formulation for treatment of type 2 diabetes. For patient compliance the patches were adhered to mucous membrane of buccal cavity two times a day and the therapeutic efficacy will be maintained for 24 h. Glimepiride shows the high protein binding capacity and influence of food on absorption in conventional tablet dosage form, which can be terminated by buccal dosage form. Thus use of Glimepiride mucoadhesive films for type 2 diabetes would be beneficial to get sustain release and to enhance bioavailability.

MATERIALS AND METHODS

Materials

Carbopol 971 P was a gift from Corel Pharma Chem., Ahmedabad. Hydroxy propyl methyl cellulose K4M (HPMC K4M), polyethylene oxide (PEO) WSR 303 and polyethylene oxide (PEO) N80 were provided by Union carbide corporation, Bhopal. Polyethylene glycol 6000(PEG 6000), polyethylene glycol 400(PEG 400), polyethylene glycol 400(PEG 400), propylene glycol, sodium carboxy methyl cellulose (SCMC) 1500±400cps and ethyl cellulose were purchased from Astron Chemicals, Ahmedabad. All other chemicals were of analytical grade and were used without further purification.

Preparation of Solid dispersion of Glimepiride

Different ratios of drug to polymer 1:1(SD 1) and 1:2 (SD 2) of solid dispersion were prepared by solvent evaporation method. Glimepiride and PEG 6000 both are soluble in dichloromethane. Glimepiride was dissolved in dichloromethane then carrier was dissolved in the drug solution. Solvent was removed by keeping the solution mixture at room temperature till the solvent evaporated. It was passed through 80 mesh sieve. It was dried further at 40°C in tray dryer.

Physical mixtures of Glimepiride (PM 1 and PM 2) were prepared by mixing Glimepiride with the hydrophilic carriers PFG 6000 in 1:1 and 1:2 respectively for 5 minute in a mortar until a homogenous mixture was obtained.

FTIR Spectroscopy

The prepared solid dispersion along with the physical mixtures were analyzed by FTIR spectrophotometer (Shimadzu-8400S, Japan) to check any influence of polymer on the glimepride.

Preparation of Mucoadhesive film

Glimepiride mucoadhesive buccal films were prepared by solvent casting technique. Different polymers were used in

Table 1 Formulation of film Using HPMC K4M in Different ratio

Ingredients	Batch 01	Batch 02	Batch03
Glimepiride, (mg)	120	120	120
HPMC K4M ,(mg)	480	600	720
Propylene glycol(ml)	0.12	0.14	0.16
Ethanol: water(3:1)	20	20	20
Swelling Index(2h)	45.2	46.4	46.9
Residence time (h)	4.05	4.55	5.30
Folding endurance	162	165	167
Tensile strength	130	150	160
Mucoadhesive strength	0.29	0.32	0.33

different concentrations to get good sustained release of drug. In this study the films for Glimepiride 2 mg were developed, using HPMC K4M. Three different batches were prepared varying the ratios of HPMC K4M (Table 1). Among these batches the batch 2 was selected for further study. For modification of the drug release property and mucoadhesive property respectively the quantity of HPMC K4 M was partially substituted with other excipients like sodium CMC, carbopol 971P and polyox® (Table 2). Two grades of polyox, N80 and WSR 303 were used. Polymers and concentration of polymers were optimized for mucoadhesive buccal film. Baking layer of the buccal films was prepared using ethyl cellulose and adheres to the buccal film.

Dissolution studies

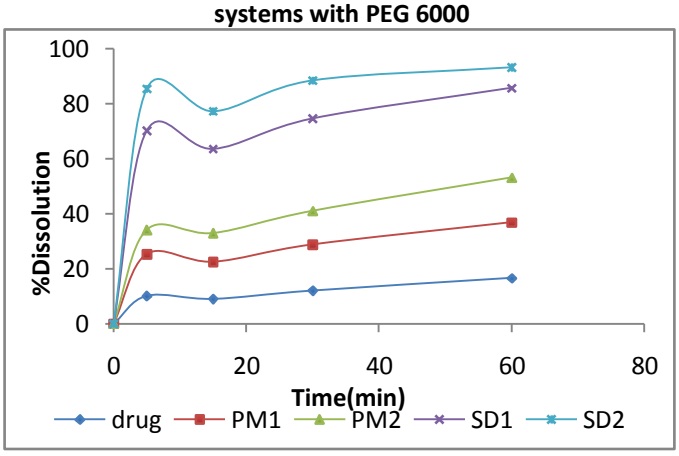
All film formulations were evaluated for non-pharmacopoeial (industry specified) tests. The films were characterized for their physical characteristics, bioadhesive performance, release characteristics, thickness, folding endurance, drug content uniformity percentage swelling and surface pH. For mucoadhesive buccal films, *in vitro* release was carried out in simulated saliva solution using modified USP type II apparatus at 50 rpm (Singhla Scientific Industries, Ambala). The selected batches were taken for *ex vivo* permeation study using franz diffusion apparatus (Orchid Scientifics FDC 00, Nasik). Short-term accelerated stability study of optimized formulations of Glimepride 2 mg buccal patch was carried out at 40 ± 2 °C and at 75 ± 5 % RH for one month.

Kinetics and Mechanism of drug release

The mechanism of drug release and the release from mucoadhesive film is studied as per Korsmeyer and Peppas model [13] $Mt/M\infty = kt^n$

where *M /M∞,* percent drug released at time *t*; *k*, apparent rate constant characteristic of the formulation run; *n*, an exponent which characterizes the mechanism of drug release, i.e. for cylindrical systems *n*=0.45 for purely Fickian diffusion, 0.45<*n*<0.89 for anomalous (Non-Fickian transport).

Figure 1 Dissolution profile of Glimepiride and its binary systems with PEG 6000



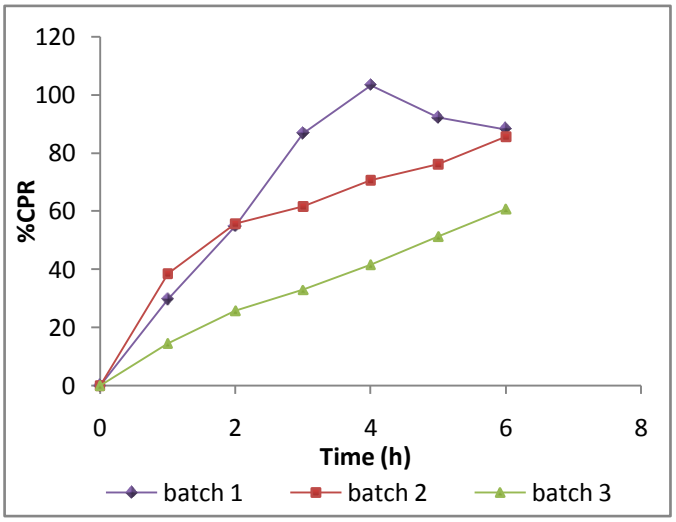


Figure 3 Comparison of *in vitro* release of Glimepiride from batch 01 to 03

RESULTS AND DISCUSSION

Solid dispersion of Glimepiride

In vitro dissolution studies were carried out for prepared solid dispersion batches [Figure 1] and based on the release study, the optimized ratio of the solid dispersion of Glimepiride and PEG 6000 was find out with SD 2 containing drug and carrier in ratio of 1:2. During dissolution studies, it was noted that drug carrier system sinks immediately, whereas pure drug keeps floating on the surface for a longer time interval. Further, kneading results in uniform distribution of drug in the polymer crust and when such a system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in increase dissolution embedded drug. Moreover, other factors such as absence of aggregation and/or reagglomeration phenomenon during dissolution and particle size reduction could be attributed to a better dissolution profile [12].

Table 2 Modified Formulation of Batch B2 (Batch 4 to Batch 15)

Formulation	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15
Glimepiride,(mg)	120	120	120	120	120	120	120	120	120	120	120	120
HPMC K4M ,(mg)	540	420	300	540	420	300	540	420	300	540	420	300
SCMC,(mg)	60	180	300	-	-	-	-	-	-	-	-	-
Carbopol 971P, (mg)	-	-	-	60	180	300	-	-	-	-	-	-
PEO WSR 303,(mg)	-	-	-	-	-	-	60	180	300	-	-	-
PEO N80,(mg)	-	-	-	-	-	-	-	-	-	60	180	300
Propylene glycol (ml)	0.12	0.14	0.16	0.12	0.14	0.16	-	-	-	-	-	-
PEG 400(ml)	-	-	-	-	-	-	0.12	0.14	0.16	0.12	0.14	0.16
Swelling Index(2h)	49.6	52.4	53.5	30.4	31.6	31.7	47.6	48.4	50.8	45.4	46.6	47.2
Residence time (h)	4.00	4.25	4.50	6.25	7.05	7.55	6.35	5.45	5.05	5.50	5.10	4.40
Folding endurance	223	232	240	223	232	240	130	128	125	132	128	127
Tensile strength (gm/mm^2)	140	160	200	150	170	250	120	140	180	120	160	180
Mucoadhesive strength	0.26	0.26	0.28	0.62	0.64	0.65	1.11	1.13	1.10	0.65	0.67	0.68

*B4 to B6 contains water 20 ml, B7 to B9 contains ethanol: water (3:1) 20 ml and B10 to B15 contains Ethanol: DCM (3:1) 20 ml

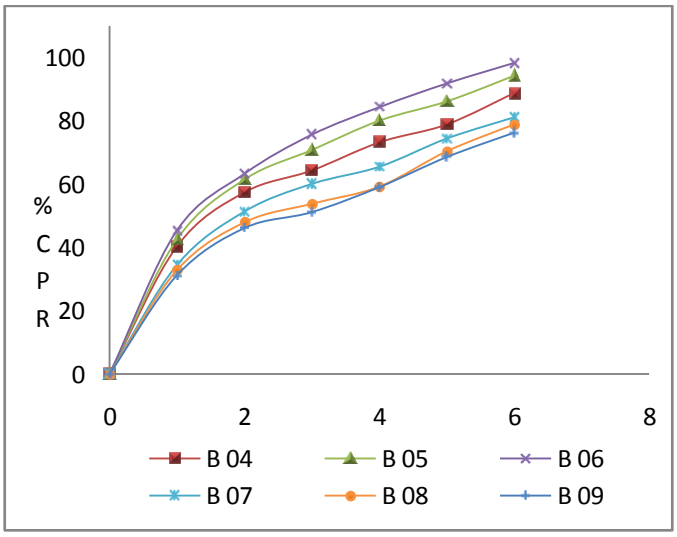


Figure 4 Comparison of *in vitro* release of Glimepiride from batch 04 to batch 09

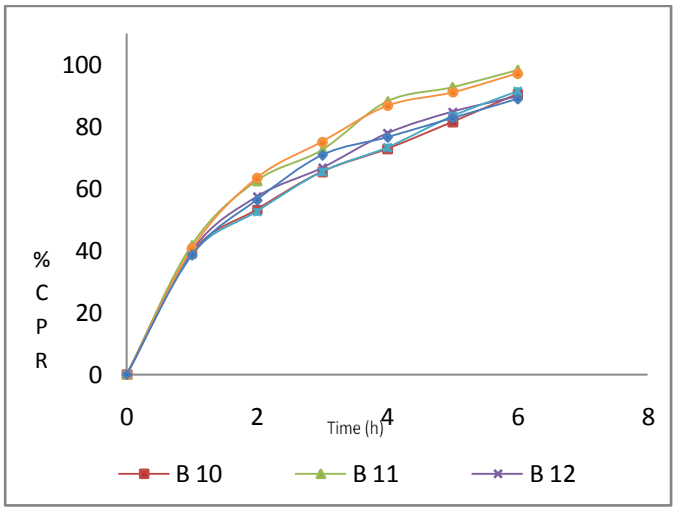


Figure 5 Comparison of in vitro release of Glimepiride from batch 10 to batch 15

Mucoadhesive film formation

Using the solid dispersion of Glimepiride (SD 2), the buccal films containing HPMC K4M were prepared with three different concentrations [Figure 3]. The batch 2 was further chosen as it showed comparatively good drug release profile but not satisfactory as per operational objective. So, modification in the properties of film of batch 2 was needed. For that some proportions of HPMC K4M were substituted with SCMC, Carbopol 971P and Polyox N80 and WSR 303.

The surface pH of all the films was within the range of salivary pH with no significant difference. *In vitro* release studies of various formulations were performed using simulated saliva as dissolution medium and measuring drug concentration using UV visible spectrophotometer (Shimadzu-8400S) at 228 nm. During dissolution, SCMC containing films swelled to form a gel layer on the exposed film surfaces [Figurre4]. The loosely bound polymer molecules in these films were readily eroded, allowing the easy release of Glimepiride as compared to batch containing carbopol 971P. Upon hydration, polyox® containing films formed hydrogel that control the drug release via diffusion mechanism [13]. As the strength of hydrogel is molecular weight dependent on molecular weight hence, Polyox WSR 303 showed good release profile [Figure 5].

***Table 3 Ex vivo* permeation release of Glimepiride of optimized batches**

Time of sampling in hours	Cumulative % drug release		
	Batch 06	Batch 11	Batch 14
1	39.52	38.69	33.52
2	57.26	52.48	41.26
3	71.73	65.37	65.73
4	77.54	73.22	76.54
5	83.71	83.32	85.71
6	89.85	91.38	92.4

The Sodium CMC containing films showed higher percent swelling due to presence of more hydroxyl group in the SCMC molecules compared to carbopol 971P containing batches with HPMC K4 M. The reason for decreasing swelling rate of carbopol 971P and HPMC K4M might be the formation of the hydrogen bonds between them. Buccal films made up of PEOs and HPMC K4M swelled rapidly and formed a weaker gel, which tended to be eroded more quickly. Carbopol 971P showed good residence time as compare to the SCMC. Polyox WSR 303 offered greater mucoadhesion among all. PEOs contain a long linear chain structure which allows them to form a strong interpenetrating network with mucus [11]. HPMC K4M concentration was varied with different concentration of polymers.

Ex vivo dissolution studies

On the basis of release pattern, swelling, residence time and mucoadhesivenes, batch06, batch 11 and batch14 formulations were selected for *ex vivo* study. In e*x vivo* study, drug permeation through the buccal mucosa was determined for formulations. The drug permeation was found to be 89.85 %, 91.38 % and 92.4% in after 6 h [Table3]. In all buccal film batches containing HPMC K4M and polyox WSR 303 as polymers in batch 11 was optimized on the base of evaluation and result.

FTIR Spectroscopy

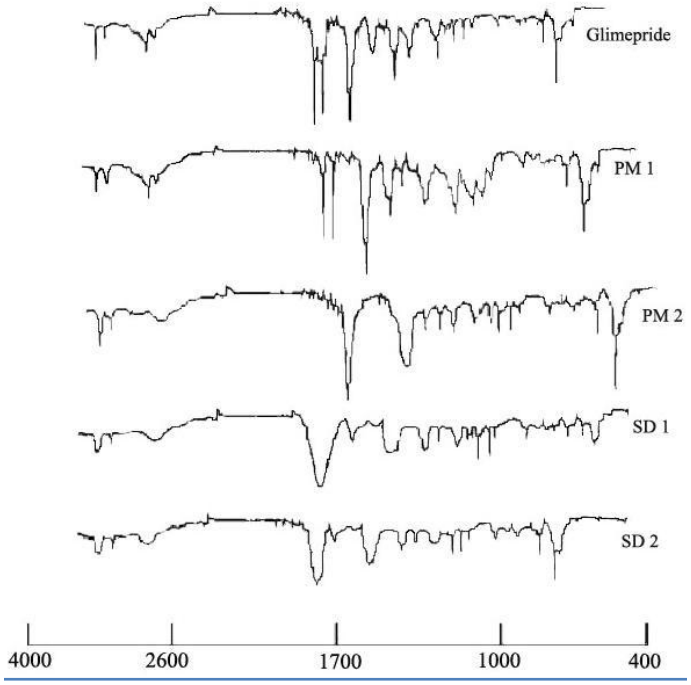


Figure 2 FTIR Spectra of Glimepiride and various binary systems with PEG

Figure 2 shows FTIR spectra for Drug, PM 1, PM 2, SD 1, and SD 2 respectively.

Kinetics and Mechanism of drug release

The release rate kinetic data for optimized batches are shown in Table 4. The drug release data showed good fit into the Higuchi equation. Value of release exponent "n" determined less than 0.5. It was concluded that the release of drug from the films followed the diffusion controlled mechanism in all the formulations. It was concluded that the release of Glimepiride from the films followed first order kinetics. Negative values of the correlation coefficient indicate negative slope for the plot. The release was found to be highly dependent on hydration and swelling properties. Diffusion of the drug was the main mechanism for drug release for formulation.

Table 4 Pharmacokinetics of optimized batch 6, batch 11, batch14

Batches	Zero order plots Correlation coeff. (R^2)	first order plots Correlation coeff. (R^2)	Higuchi's plots Correlation coeff. (R^2)	Hixson Crowell plots	Diffusion exponent (n)	Order of release
B 6	0.97951	0.950939	0.996875	-0.97951	0.431664	Fickian (diffusion)
B 11	0.971162	0.940186	0.991199	-0.97116	0.481756	Fickian (diffusion)
B 14	0.961513	0.922889	0.987631	-0.96151	0.483408	Fickian (diffusion)

CONCLUSION

Glimepiride mucoadhesive films could be satisfactory to ensure optimum Glimepiride levels for prolonged duration of time (360 minutes). Buccal patches of Glimepiride were successfully prepared using HPMC K4M, SCMC, carbopol 971P, PEO N80, and PEO WSR 303 as polymers and by solvent casting techniques. The patches were evaluated for various industry specified tests. The prepared Glimepiride buccal films were optimized based upon their physicochemical characteristics. Based on the results, batch containing drug and combination of HPMC K4M and PEO-WSR 303, was investigated as better formulation amongst all formulation. It shows good mucoadhesive time, swelling property and controlled drug release. Drug release from the developed formulations follows first- order kinetics. After one month of accelerated stability studies of developed formulations were also found to be stable.

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