

Formulation and Evaluation of Gliclazide Transdermal Drug Delivery Application

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Abstract: A novel matrix controlled to release transdermal drug delivery system (TDDS) of GLICLAZIDE was prepared to use different ratios of poly vinyl alcohol (PVA) poly vinyl pyrrolidone (PVP) (3:1, 2:3, 4:1, 1:2, 2:1 and 1:4) by solvent casting (evaporating) method. Physicochemical parameters were characterized and dissolution studies of the formulated films were performed. In addition solubility studies at various pH, thickness test, moisture content test and flatness test were performed. *In vitro* permeation studies were done using modified Franz diffusion cells through animal skin utilizing in normal saline. Permeation studies were illustrated. Dimethyle sulfoxide (DMSO) was a good chemical enhancer. The prepared films were subjected to SEM, DSC and FT-IR spectral analysis. The present study resulted in optimized formulation.

Key words: Gliclazide, Transdermal patch, PVP, PVA, Dimethyl sulfoxide, Chemical enhancer.

1. Introduction

For Thousands of years, human civilizations have applied substance to the skin as cosmetic and medicinal agents. However, it was not until the twentieth century that the skin came to be used as a drug delivery route. In fact, Marian Webster dates the word “transdermal” to 1944 highlighting that it is a relatively recent concept in medical and Pharmaceutical practice ^[1]. TDDS delivers drugs through the skin as an alternative for more traditional route like orals, intravascular, subcutaneous and transmucosal ^[2]. A Transdermal Drug Delivery Systems (TDDS) or transdermal patch is defined as flexible, multilaminated, Pharmaceutical preparation of varying size containing one or more drug substance to be applied to the intact skin for systemic circulation to maintain the plasma level. This is normally formulated with pressure sensitive adhesive that assures the adhesion of the preparation for the skin ^[3]. In the present scenario, very few transdermal patches are commercially available. The Gliclazide being an anti-hyperglycemic agent requires chronic administration. Since the drug has an extensive hepatic first pass metabolism. An attempt was made to develop transdermal drug delivery systems for patient better compliance ^[4]. Simple drug-matrix dispersion type of transdermal drug delivery system (TDDS) of Gliclazide was formulated for prolonged periods of maintenance therapy alternatives to conventional oral dosages forms. Moreover, the physicochemical characteristics of Gliclazide also comply with the general requirement for formulating a TDDS to a good extent ^[5].

Gliclazide is classified as a type II anti-hyperglycemic agent. It has mean plasma half life of 2-3 hrs and only 40% of the orally administered drug reaches the systemic circulation due to hepatic metabolism. The present research was directed to examine the release rate of Gliclazide and see the enhancer effect of the

Dimethyle sulfoxide. This study was aimed at developing a suitable film formulation containing Gliclazide for transdermal use; the embedded drug should be released without any preferential binding to the polymer.

2. Materials and Methods

The Polyvinyl alcohol was supplied by SD fine-chem limited Mumbai. Polyvinylalcohol (PVA) and Polyvinylpyrrolidone (PVP) were obtained from B-pura lab Chennai. Dibutyl phthalate was procured from Loba Chemie Ltd, India. Formaldehyde was obtained commercially from Nice Chemicals Kochi, India. Fine chemicals Dimethyle sulfoxide Spectro chemicals Mumbai. Polyethylene glycol was purchased from SDFCL Mumbai. Gliclazide was received as a gift sample from Hetro Pharmaceutical Hyderabad India.

2.1. Preparation of Transdermal Patch

The TDDS composed of different ratios of PVP and PVA containing Gliclazide ($1\text{mg}/\text{cm}^2$) were prepared using glass plat mould solvent (casting) evaporation technique. The Dibutyl phthalate was incorporated as a plasticizer at concentration of 30%w/w of dry weight of polymer and 4% of Dimethyle sulphoxide (DMSO) was incorporated as a permeation enhancer. Backing membrane was casting by pouring and then evaporating 4% aqueous solution of PVA&PVP mixed with a solution and poured into glass molded plate and kept for 24 hrs at room temperature (25°C). The matrix was prepared by pouring the homogenous dispersion of drug with different blends of PVA with PVP in Water on the backing membrane in glass plate. The above dispersion was evaporated slowly at 40°C for 2 hrs to achieve drug polymer matrix patch. The dry patches were kept in desiccator's further investigation shown in (Table 1)

Table 1: Composition of PVA and PVP film Formulation.

S.No	Formula code	Polymeric blend	Drug mg/cm^2	Ratio(w/w)	Plasticizer Dibutyl phthalate	Permeation enhancer DMSO	Solvent system
1	GLZ 1	PVA: PVP	1	1:2	30%	1%	Water
2	GLZ 2	PVA : PVP	1	2:1	30%	1%	Water
3	GLZ 3	PVA : PVP	1	2:3	30%	1%	Water
4	GLZ 4	PVA : PVP	1	3:2	30%	1%	Water
5	GLZ 5	PVA : PVP	1	1:4	30%	1%	Water
6	GLZ 6	PVA : PVP	1	4:1	30%	1%	Water

2.2. Preparation of barriers: Human cadaver skin

The fresh, full thickness ($75\text{--}80\mu\text{m}$) human cadaver skin (of thigh region) of both sex and age group 20-45 years were obtained from the postmortem department of forensic medicine, Rajamuthaiya hospital. The skin was immersed in water at 60° for a period of 5 min. The epidermises were peeled from the dermis after the exposure. The isolated epidermises ($25\pm 5\mu\text{m}$) were rapidly rinsed with water and then either used or stored frozen (for not more than 48 hours) wrapped in aluminum foil.

2.3. Drug-Polymer interaction study

FTIR spectra of Gliclazide, PVA, PVP, transdermal film loaded with drug and adjuvant were taken using a Thermo Scientific Nicolet iS5 FT-IR Spectrophotometer (model iS5 KBr disk method). 10mg of the sample and 20mg of potassium bromide were taken in a mortar and triturated. The triturated samples (pellet) were kept in a holder and scanned between $400\text{--}4000\text{cm}^{-1}$. Here, the patches of specified size were taken directly for the study.

2.4. Scanning Electron Microscopy (SEM)

The external morphology of the transdermal patch was analyzed using a scanning electron microscope (JMS 6100 JEOL, Tokyo, Japan). The samples placed on the stubs were coated finally with gold palladium and examined under the microscope.

2.5. Differential Scanning Calorimetry (DSC)

A Thermogram of Gliclazide and preparation of patches was recorded using a Differential scanning calorimetry and were compared. The sample was hermetically sealed with flat-bottomed aluminum pans and heated over a temperature range of 40-240° at a rate of 10° using alumina as a reference standard.

2.6. Thickness Test

The aim of the present study was to check the uniformity of thickness of the formulated films. The thickness was measured at five different points of the film. Using BAKER Digital caliper the average of five readings was calculated.

2.7. Uniformity of weight Test

Five different patches of the individual batch were weighed and the average weight was calculated. The individual weight should not deviate significantly from the average weight of five. The tests were performed in films, which were dried at 60° for four hours prior to the testing.

2.8. Moisture content Test

The film was weight and kept in desiccators containing calcium chloride (fused) at 40° and dried for at least 24 hours. The film was weight until it showed a constant weight. The moisture content was the difference between the constant weights taken and the initial weight and was reported in terms of percentage (by weight) moisture content.

2.9. Flatness Test

The longitudinal patches were cut out of the prepared medicated film. The length of each strip was measured and then the variation in lengths due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered an equal to a hundred percent flatness.

$$\text{Constriction (\%)} = \frac{L_1 - L_2}{L_2} \times 100 \dots\dots (5)$$

Where L_1 = Final length of each strip and L_2 = initial length of each strip.

2.10. Moisture uptake Test

A weight film kept in a desiccator at 40° for 24 hours were taken out and exposed to different relative humidity of 75% (saturated solution of sodium/aluminum chloride) and 93% (saturated solution of ammonium hydrogen phosphate) respectively, at room temperature. Then, the weights were measured periodically to constants weights.

3. Result and Discussion

FTIR spectra analysis shows that, all the peak of Gliclazide, indicating that, there was no interaction between the drug and formulation components. The compatibility between Gliclazide and polymers were confirmed by FTIR Spectrophotometer Fig. 1. FTIR studies of drug and excipients revealed that there was no interaction between the selected drug and polymers.

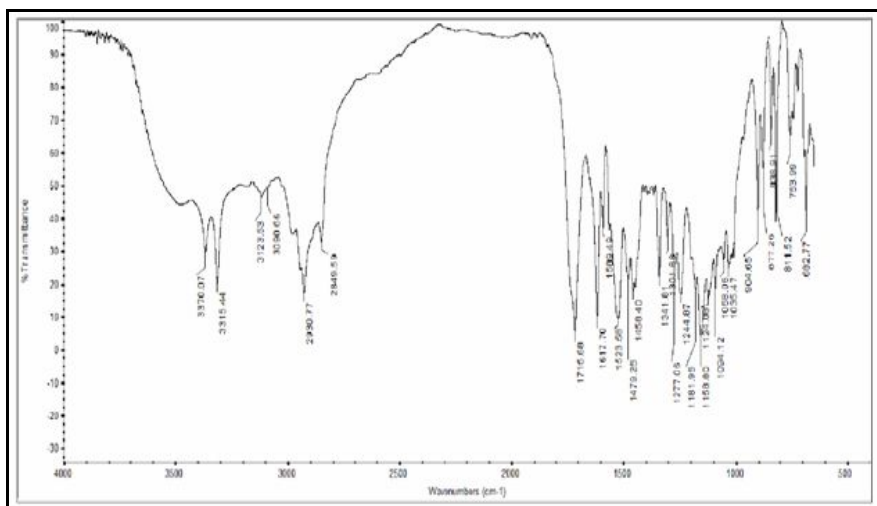


Fig 1. FT-IR report Gliclazide

The formulated Gliclazide transdermal patches were evaluated for thickness test, weight variation test, drug content test were observed in Table. 2.

Table 2: Characterization of Gliclazide PVA and PVP films

S. No	Formulation Code	Thickness (n=5)(mm)	Weight Variation(n=5) (mg)	Percentage of elongation(n=5)	Drug content 1cm ² patch(n=5)
1	GLZ 1	0.23	28	100%	96.44%
2	GLZ 2	0.22	14	100%	95.70%
3	GLZ 3	0.11	15	100%	97.76%
4	GLZ 4	0.25	16	100%	96.00%
5	GLZ 5	0.24	22	100%	94.66%
6	GLZ 6	0.12	15	100%	95.55%

The external morphology of the transdermal patch was analyzed using a scanning electron microscope. The samples placed on the stubs were coated finally with gold palladium and examined under the microscope at 1000X and 1500X Fig.2

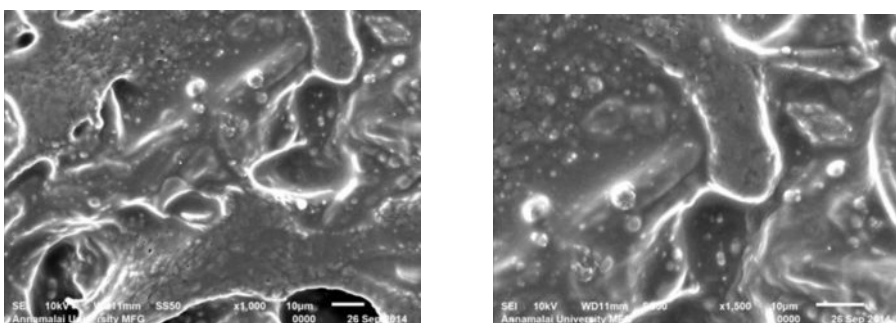


Fig 2. SEM images of Gliclazide TDDS Patch

The matrix kind of transdermal film of Gliclazide was prepared by solvent casting (evaporation) method using a combination of hydrophilic and lipophilic polymer. PVP is added to an insoluble film former, PVA that tends to increase its release rate. The resultant can be contributed to the leaching of soluble components, which leads to the formation of pore and then decrease in the mean diffusion path length of the drug molecules. PVP acts as a nucleating agent that retards the crystallization of the drug and enhances the solubility of the drug in the matrix by sustaining it in an amorphous form.

In vitro drug diffusion studies were carried out for the different formulations using Franz diffusion cell. The medicated films showed that drug release study in % cumulative release. The relationship can be established as $GLZ1 > GLZ6 > GLZ3 > GLZ2 > GLZ4 > GLZ5$. Because different ratios of polymer in film the percentage release can be varied. Drug polymer affinity will be a main factor that controls the release of drug from the formulation. Maximum percentage of drug release (i.e. 98.42%) was observed with formulation GLZ1 and the minimum (i.e. 48.21%) was found with formulation GLZ5. The addition of hydrophilic components such as PVP and PVA in to the formulation produces constant drug release. Thus they play a significant role in improving the solubility of a drug and sustaining the drug release by penetration in to the dissolution medium. The formulated Gliclazide transdermal patches were evaluated for drug diffusion studies observed in Table.3

TABLE 3: The *In-vitro* Diffusion Studies (Drug Release) of Gliclazide through male wistar rat skin with PVP vs. PVA

S.No	Time in hrs	Cumulative Percentage of different ratio drug Diffused in mcg/cm ²					
		GLZ-1 (1:2)	GLZ- 2 (2:1)	GLZ-3 (2:3)	GLZ-4 (3:2)	GLZ-5 (1:4)	GLZ-6 (4:1)
1	10 min	25.15±0.25	18.77±0.78	19.03±0.81	20.36±0.58	15.24±0.95	13.25±0.50
2	30 min	30.35±0.51	23.29±0.56	25.30±0.75	25.77±0.76	21.42±1.04	17.10±0.44
3	1 hr	35.78±1.35	31.31±0.64	32.34±0.90	32.11±0.55	30.07±1.13	26.40±0.08
4	2 hr	44.78±0.54	36.40±1.01	37.06±0.92	42.07±0.64	38.73±0.64	35.60±0.58
5	4 hr	55.72±1.72	40.05±0.66	45.14±0.45	48.65±0.85	46.45±0.45	46.60±0.59
6	8 hr	59.56±0.36	48.84±0.74	52.33±0.72	55.63±0.64	52.72±0.72	52.40±0.66
7	12 hr	65.56±0.57	54.35±1.04	59.19±0.55	64.21±0.98	58.04±0.18	62.10±0.45
8	24 hr	79.81±0.23	62.74±0.87	66.55±0.61	79.50±0.32	66.12±1.56	71.23±0.66

4. Conclusion

In this study, different ratio of PVA and PVP transdermal Gliclazide patches were formulated using DMSO as a permeation enhancer. It can be reasonably concluded that Gliclazide could formulate into transdermal polymeric patches to prolong its release characteristics. Thus, the formulation GLZ 1 (PVA: PVP, 1:2) was found to be the best form of sustained release once a day formulation. PVP acts as nucleating agents that retards the crystallization of the drug and this plays a significant role in improving the solubility of the drug in the matrix by sustaining the drug in amorphous form. It undergoes rapid solubilization by penetrating into the dissolution medium. Thus, PVP was incorporated into film using mixture of other polymers & the suitability of the films was studied.

The transdermal drug delivery system of Gliclazide was prepared by solvent casting (evaporation) technique. In, thus we can obtain film of good quality in both physical & chemical characteristic and found to be cost effective. The permeability studies, diffusion studies and physicochemical characteristics of formulating films indicated that DMSO is a good enhancer for transdermal drug delivery systems.

Thus, the formulation of transdermal drug delivery systems of Gliclazide with the above said polymer with enhancer can be used to get the optimum release kinetics.

The *in vitro* drug diffusion study of optimized formulation GLZ1 (1:2) was 98.42±0.52 %. So the maximum effect attained in this formulation.

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