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Research Article

Formulation and Evaluation of Matrix Type Transdermal Patches of Glibenclamide

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ABSTRACT

Matrix type transdermal patches containing Glibenclamide were prepared using three different polymers by solvent evaporation technique. Aluminium foil cup method was used as a substrate. Polyethylene glycol (PEG) 400 was used as plasticizer and Dimethyl sulfoxide (DMSO) was used as penetration enhancer. The physicochemical parameters like weight variation, thickness, folding endurance, drug content, % moisture absorption and % moisture loss were evaluated. *In vitro* drug release studies and skin permeation studies were carried out using Franz diffusion cell. Cumulative amount of drug released in 12 hours from the six formulations were 55.467, 52.633, 47.157, 53.394, 49.139 and 45.597 %, respectively. The corresponding values for cumulative amount of drug permeated for the said formulation were 43.013, 40.429, 37.793, 41.522, 37.450 and 34.656 %, respectively. On the basis of *in vitro* drug release and skin permeation performance, formulation HP-1 was found to be better than other formulations and it was selected as the optimized formulation.

Keywords: Glibenclamide, matrix type transdermal drug delivery system, physical evaluation, *in vitro* drug release, *in vitro* drug permeation.

INTRODUCTION

Most recently, there is an increasing recognition that the skin can also serve as the port of administration for systemically-active drugs. In this case, the drug applied topically will be absorbed first into the blood circulation and then be transported to target tissues, which could be rather remote from the site of drug application, to achieve its therapeutic purposes. [1] Recently, it is becoming evident that the benefits of i.v. drug infusion can be closely duplicated, without its hazards, by using the skin as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation. [2] To provide continuous drug infusion through on intact skin, several transdermal therapeutic systems have been developed for topical application on to the intact skin surface to control the delivery of drug and its subsequent permeation through the skin tissue.

Transdermal therapeutic systems are defined as self-contained, discrete dosage forms when applied to the intact skin, deliver the drug(s) through the skin at a controlled rate to the systemic circulation. One of the approaches of transdermal therapeutic systems (TTS) is the maintenance of the blood concentration of drug at therapeutic level by means of controlled permeation throughout the skin (therefore avoiding the first-pass effect) during a long period of time and using only one administration. [3]

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The advantages of delivering drugs across the skin for systemic therapy are well documented. Some of the main advantages of transdermal drug delivery system are to deliver steady infusion of drug over an extended period of time, to increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g. GI irritation, low absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc. Application and removal of transdermal patch produce the optimal sequence of pharmacological effect. The drug input can be terminated at any point of time by removing transdermal patch because self administration is possible with these systems. [4]

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentration, hyperglycemia caused by insulin deficiency, often combined with insulin resistance. Glibenclamide is a potent oral sulfonylurea hypoglycemic agent. It is currently available for treating hyperglycemia in Non-Insulin Dependent Diabetes Mellitus (NIDDM-type II). The drug inhibits ATP-sensitive potassium channels in pancreatic beta cells. This inhibition causes cell membrane depolarization, opening of voltage dependent calcium channels, thus, triggering. The most frequently reported side effects of glibenclamide are gastric disturbance like nausea, vomiting, heartburn, anorexia, and increased appetite after oral therapy. [5] Since these drugs are usually intended to be taken for a long period, patient compliance are also very important. For a systemically-active drug to reach a target tissue remote from the site of drug

administration on the skin surface, it has to possess some physicochemical properties which are capable of facilitating the sorption of drug by the stratum corneum, the penetration of the drug through various skin tissues, and also the uptake of the drug by the capillary network in the dermal papillary layer.

Glibenclamide (M.W. 494.004 g:mol) showed the favourable logarithmic value of partition coefficient (log octanol / phosphate buffer pH 7.4) 0.3617 and negligible skin degradation. The plasma half life is about 4-6 hours which makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for a long term treatment. [6-7] Therefore, controlled release transdermal preparation of glibenclamide was prepared to give a sustained effect as compared to the conventional multiple oral dosing.

In the present investigation six formulations were formulated using hydroxy propyl methyl cellulose, polyvinylpyrrolidone-K30 and Eudragit-RS100 polymers by solvent evaporation techniques employing aluminium foil as substrate polyethylene glycol 400 (PEG-400) was incorporated at concentration of 36 % w/w of polymers as plasticizer and Dimethylsulfoxide (DMSO) was incorporated at the concentration of 12 % w/w of polymer as penetration enhancer. The transdermal patches were evaluated for their physicochemical characteristics such as thickness, weight variation, drug content % moisture loss, % moisture absorption, and folding endurance.

The aim of the present study is to formulate the matrix type transdermal patches of glibenclamide as a model drug with combination of HPMC, EC, PVP K-30 and ERS-100 to minimize the dose of the drug for lesser side effects.

Materials and Methods

Glibenclamide was obtained as a kind gift from Ingla Laboratories Pvt. Ltd., Mumbai. The other chemicals were obtained form authenticated manufacturers ie. HPMC (Pharmasynth Formulation, Haridwar), PVP K-30 (Loba Chemical Ltd., Mumbai), Eudragit RS-100 (Rohm Pharma, Germany), PEG-400 (CDH, New Delhi) Dimethyl sulfoxide, DMSO (CDH, New Delhi), Chloroform (Merck, India), Methanol (Merck, India), Potassium dihydrogen phosphate (CDH, New Delhi) and Sodium hydroxide (CDH, New Delhi).

Preparation of transdermal patches

Matrix type transdermal patches composed of different ratios of HPMC, PVP K-30, Eudragit RS-100 with drug (Table 1) were prepared by solvent evaporation technique in a glass ring. The bottom of the ring was wrapped with aluminium foil [8] by adhesive and placed in a petridish of area 23.75 cm^2. A fixed volume (5 ml) of polymeric solution with drug and plasticizer was poured on to the petridish and an inverted funnel was placed on the petridish to facilitate the evaporation of solvent at a controlled rate over the drying period of 24 h at room temperature. The dried films were removed and cut into 2.009 cm^2 area and kept in a desiccator until used.

Evaluation of transdermal patches

The transdermal patches were evaluated for their physicochemical characteristics such as weight variation, thickness, % moisture loss, % moisture absorption, folding endurance, *in vitro* drug release, *in vitro* drug permeation studies [9] and drug content. [10]

Thickness

The thickness of the film was measured at three different points using a screw gauge and average thickness was observed.

Weight variation

Five films from each batch were weighed individually and the average weight was calculated.

Percentage moisture absorption

The films were weighed accurately and placed in the desiccator containing 100 ml of saturated solution of aluminium chloride, which maintains 79.50 % RH. After 3 days the films were taken out and weighed.

Percentage moisture loss

The films were weighed accurately and kept in a desiccator containing anhydrous calcious chloride, after 3 days, the films were taken out and weighed.

Folding endurance

It was determined by repeatedly folding the film at the same place until it broke. The number of times of film could be folded at the same place without breaking/cracking gave the value of folding endurance.

Drug content

A film of 2.009 cm^2 area was cut into small pieces and taken in a 100 ml volumetric flask and dissolved in 25 ml methanol. The solution was filtered and the drug was determined spectroscopically at λ_{max} 225 nm after suitable dilution.

In vitro drug release studies

A modified Franz diffusion cell was fabricated to study the *in vitro* release profile as well as the permeation of glibenclamide from the matrix films. [11] For this study the patches were stuck to an aluminum foil which was slightly larger than patch fixed using water impermeable adhesive to ensure that the receptor fluid could not come in contact with the sides of the film. The faces with lower drug concentration was placed in contact with the receptor fluid pH 5.0 buffer with 20 % w/v PEG-400 for maintaining sink condition. Before placing the patch fixed on alluminium foil on to the diffusion cell, the mouth of the cell was coated with a thin layer of silicon grease to prevent leakage of the receptor fluid. 0.5 ml of the receptor fluid was withdrawn at an interval of 12 h. It was immediately replaced with 0.5ml of fresh drug free buffer solution containing 20 % w/v PEG-400 to maintain constant volume. The removed fluid, after suitable dilution with phosphate buffer was analysed spectrophotometricaly at λ_{max} 228 nm and concentration was observed from the calibration curve.

In vitro skin permeation studies

In permeation studies too, modified Franz diffusion cell with the diffusion area of 2.009 cm^2 was used. The skin was removed from the abdominal portion of the mouse skin after killing the mouse by treating overdose of inhalation of chloroform. The hair and fat were removed after treating the skin with 0.32mol l^{-1} ammonia solution for 35 minutes. [12] The stratum corneum side of the skin was kept in intimate contact with the release surface of the films.

The donor compartment was kept on the receptor compartment and secured tightly with the help of rubber bands. Phosphate buffer pH 7.4 containing 20 % w/v PEG-400 and 0.002 % gentamycin as an antibacterial agent serving as the elution medium was used as the receptor fluid. It was filled into the receptor compartment through the sampling port and checked for the absence of any air bubble under the skin. A magnetic bead was rotated at a constant

Table 1: Composition of transdermal patches

Formulation code	Polymer ratio			Plasticizer (PEG-400) % of polymer wt.	Drug (% of polymer wt.)	Enhancer (DMSO) % of polymer wt.	Solvent
	HPMC	PVPK-30	ERS-100				
HP-1	9	1	–	36%	20%	12%	chloroform: methanol (1:1)
HP-2	8	2	–	36%	20%	12%	chloroform: methanol (1:1)
HP-3	7	3	–	36%	20%	12%	chloroform: methanol (1:1)
A-1	9	–	1	36%	20%	12%	chloroform: methanol (1:1)
A-2	8	–	2	36%	20%	12%	chloroform: methanol (1:1)
A-3	7	–	3	36%	20%	12%	

Area of the patches = 23.75cm^2
Amount of drug incorporated= 50mg
Weight of polymers = 250mg

Table 2: Physical characterisation of transdermal patches

S. No.	Formulation Code	Thickness (mm) ±SD[a]	WEIGHT (mg) ±SD[b]	Drug content (mg/2.009 cm^2) ± SD[a]	%Moisture loss ± SD[a]	%Moisture absorbance± SD[a]	Folding endurance
1	HP-1	0.054±0.0037	51.9±0.87	4.15±0.0510	4.13±0.0852	7.827±0.0854	>200
2	HP-2	0.041±0.0022	51.1±0.71	4.11±0.0216	3.984±0.0712	7.577±0.0991	>200
3	HP-3	0.035±0.0043	50.8±0.88	4.10±0.0432	3.370±0.1518	7.00±0.0944	>150
4	A-1	0.046±0.0036	51.3±1.07	4.13±0.0356	3.773±0.0557	5.724±0.1320	>200
5	A-2	0.035±0.0043	50.9±1.18	4.10±0.0283	3.683±0.1798	4.194±0.1365	>200
6	A-3	0.042±0.0064	51.2±2.35	4.12±0.0432	2.687±0.0662	3.939±0.0494	>200

a = mean of three observations
b = mean of five observations

Table 3: Kinetic model for *in vitro* drug release studies

Model		HP-1	HP-2	HP-3	A-1	A-2	A-3
Zero order	R	0.7951	0.8238	0.8651	0.8330	0.8519	0.8479
	SSQ	1227	1002	666	953	774	892
	K	5.6958	5.4099	4.8104	5.4791	5.0342	4.6823
First Order	R	0.9076	0.9180	0.9313	0.9197	0.9273	0.9163
	SSQ	540	443	306	398	348	343
	K	-0.0785	-0.073	-0.0624	-0.0745	-0.0663	-0.0601
Matrix	R	0.9903	0.9978	0.9908	0.9758	0.9920	0.9892
	SSQ	64	50	48	96	45	53
	K	16.8897	16.0031	14.1689	16.1604	14.8503	13.8168
Peppas	R	0.9803	0.9820	0.9808	0.9118	0.9839	0.9786
	SSQ	83	83	93	293	80	98
	K	16.2968	14.4947	11.2014	12.64500	12.5328	11.2688
Hix Crow	R	0.8763	0.8915	0.9122	0.895	0.9058	0.8964
	SSQ	720	590	402	541	461	438
	K	-0.0234	-0.0219	-0.0190	-0.0223	-0.0201	-0.0184

Best fit model matrix for selected formulation

Table 4: Kinetic model for *in vitro* drug permeation studies containing enhancers

		HP-1	HP-2	HP-3	A-1	A-2	A-3
Zero order	R	0.9441	0.8941	0.8906	0.9588	0.9688	0.9607
	SSQ	255	408	358	172	104	114
	K	4.2383	4.1157	3.8001	3.9811	3.5198	3.3176
First Order	R	0.9771	0.9405	0.9351	0.9853	0.9891	0.9825
	SSQ	91	202	193	57	37	48
	K	-0.0532	-0.0510	-0.0462	-0.0492	-0.0423	-0.0394
Matrix	R	0.9853	0.9894	0.9899	0.9824	0.9796	0.9820
	SSQ	68	43	35	75	68	53
	K	12.3324	12.0767	11.1562	11.5467	10.1831	1.6179
Peppas	R	0.9953	0.9863	0.9850	0.9977	0.9988	0.9977
	SSQ	34	65	56	14	3	6
	K	8.0434	8.8605	8.2626	7.4143	6.7765	6.4745
Hix Crow	R	0.9680	0.9269	0.9219	0.9782	0.9837	0.9763
	SSQ	133	259	239	87	54	66
	K	-0.0164	-0.0158	-0.0144	-0.0153	-0.0132	-0.0124

Best fit model – Peppas for selected formulation

speed for maintaining the hydrodynamics of the receptor fluid constant throughout the study and the temperature of the receptor fluid was maintained at 37±1°C with the help of a thermostate.

The amount of drug that was permeated through the skin was determined by removing 0.5 ml samples periodically. The samples were replaced with the same volume of drug free phosphate buffer containing 20 % PEG-400 to keep the volume of the receptor compartment constant and also to ensure an intimate contact between the dermal surface of the skin and the receptor solution. As the skin specimen degraded with time, the contents started leaching out from

the skin to the medium was increasing with time, there could be bacterial growth in the receptor solution. As the skin specimen degraded with time the contents leaching out from the skin to the medium were increasing with time, there could be bacterial growth in the receptor solution contributing to the turbidity which was effectively controlled using 0.002 % gentamycin in the receptor fluid. The aliquots removed were assayed spectrophotometrically after suitable dilution and the absorbance were observed at λ_{max} 228 nm using the drug free phosphate buffer (the reagent blank).

RESULTS

Transdermal patches of Glibenclamide were prepared by solvents evaporation technique employing aluminium foil as a substrate. Different formulations of HPMC / PVP-K30 and HPMC / ERS-100 were prepared containing glibenclamide to the desired the optimum drug release via the most suitable choice of polymeric blends of HPMC/PVPK-30 and HPMC/ ERS-100 among the formulation studies.

The prepared transdermal patches were transparent, smooth, uniform and flexible. The thickness of the patches was varied from 0.054±0.0037mm to 0.035±0.0043mm. Low standard deviation values in the film thickness measurements ensured uniformity of the patches prepared by solvent evaporation technique. The film prepared by HPMC/ PVP-K30 were relatively more transparent and flexible than HPMC/ERS-100. % moisture loss was found to be between 4.13±0.0854 to 2.687±0.0662 and % moisture absorption was found to be between 7.827±0.0854 to 3.939±0.0494. The result revealed that the moisture loss/moisture absorption was found to increase with increasing concentration of hydrophilic polymers. The small moisture loss in the formulations help the films to remain stable, brittle and free from complete drying. Again low moisture absorption protects the material from microbial contamination and bulkiness of the patches. [13] Folding endurance was found to be >150 that is satisfactory weight of the patches were varied between 51.9±0.87 mg to 50.8±0.87mg drug contents was found to be 4.15±0.0510mg to 4.10±.0.0283 (Table 2).

In vitro drug release studies

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance. [14] For *in vitro* release studies Franz diffusion cell was used. The result indicated that the release of drug from patches increases with increasing concentration of HPMC. The cumulative percent of drug release in 12 hours was found to be the highest (55.467±0.66 %) from formulation HP-1 carrying HPMC and PVP- K30 in ratio 9:1 (Table1, Fig.1) and minimum (45.591±0.64%) from formulation A-3 carrying HPMC and ERS-100 in ratio 7:3 (Fig.1). The drug release was found to increase on increasing the concentration of hydrophilic polymers in the polymer matrix (Fig. 1). This is due to the fact that dissolution of aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to decrease the mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate.

In vitro skin permeation studies

Release of drug from transdermal patches is controlled by chemical properties of drug and delivery by physiological as well as physicochemical properties of the biological membrane. [15] In *in vitro* skin permeation experiment, the amount of drug permeated was increased with increasing concentration of hydrophilic polymer. It might be result of initial rapid dissolution of the hydrophilic polymer when the patch was in contact with the hydrated skin, which resulted in accumulation of high amounts of drug on the skin surface and thus led to the saturation of skin with drug at all time. The cumulative percentage of drug permeated in 12 hours was found to be maximum (43.013±0.56) from formulation HP-1 and minimum (34.656±0.34) from formulation A3. (Fig.2). These formulations contained enhancers DMSO However, drug release and permeation studies showed initial burst effect. The initial quick release (burst effect) would be beneficial since it would help to achieve the therapeutic plasma concentration of drug in minimum time and later on the constant release would then provide a sustained and controlled release of drug. Burst effect might be due to the initial migration of the drug towards the surface of the matrix. Linear curves were obtained on plotting the graph of cumulative % of drug released vs. square root of time suggesting the Higuchian matrix diffusion mechanism of drug release from the TDDS formulation. Also lower RSD values were fit for Higuchi model and Peppas model, (Table 3 a 4).

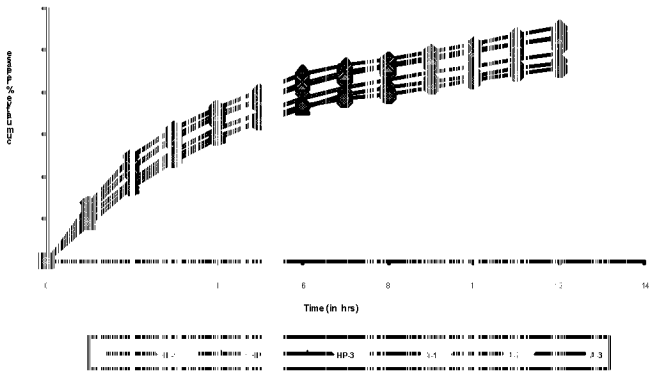

Fig. : *In vitro* drug release profile of formulation HP-1 HP-2, HP-3, A-1, A & A-3

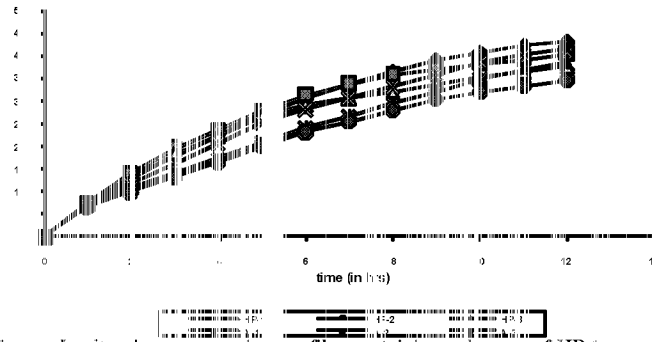

Fig. : *In vitro* drug permeation profiles containing enhancer of HP-1, HP-2, HP-3, A-1, A-2 and A-3.

DISCUSSION

Transdermal drug delivery system is a most suitable system for a long-term treatment or for a multi-dose treatment because transdermal patches are prepared for a long period of time in a single dose providing treatment from a day to even up to seven days. Transdermal drug delivery system also increases the bioavailability of drug by avoiding the first pass

metabolism and increases the therapeutic efficacy of drug by reaching into the systemic circulation.

Glibenclamide is a potent oral sulfonylurea class of drug currently available in the market for treatment of Non-Insulin Dependent Diabetes Mellitus (NIDDM). Polymers HPMC, PVPK-30 and Eudragit RS-100 were selected on the basis of their adhering property and non toxicity. The result of the finding showed excellent adhering property and controlled release. Further result of the contents of drug within the patch was in the range of 4.10-4.15 mg. The cumulative percentage of drug release in 12 hours were found to be 55.46±0.66 % for *in vitro* drug release, 45.591±0.64 % for *in vitro* skin permeation release and 43.013±0.56 % for *in vitro* skin permeation release containing enhancer DMSO for best formulation HP-1. Glibenclamide transdermal patches were prepared with combination of these polymers and evaluated it for physical parameters such as thickness, drug content, weight variation, % moisture loss and % moisture absorption. From these evaluation it was found that thickness, drug content, weight variation, low moisture loss, low moisture absorption were suitable for maximum stability of the prepared formulations.

Maximum *in vitro* drug release, *in vitro* skin permeation and *in vitro* skin permeation with DMSO for formulation HP-1 made suitable for further studies. According to the above observations it was concluded that Glibenclamide was suitable for transdermal drug delivery system.

Result from present study concluded that Glibenclamide in combination with HPMC, PVP –K30 and ERS-100 and with incorporation of PEG-400 (36 %) and DMSO (12 %) produced smooth, flexible and transparent film. The release rate of drug through films and permeation across skin increased when the concentration of hydrophilic polymer was increased. In view of the overall results reported in the present study, it is proposed that Glibenclamide can be used in the formulation of matrix type transdermal drug delivery system to prolong the drug release.

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