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Formulation and evaluation of antidiabetic drug of glipizide on transdermal patches

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ABSTRACT

Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged ill health and early death. It is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency and it is often combined with insulin resistance. Glipizide an important drug of the sulphonyl urea class, is currently available for treating hyperglycemia in Non-insulin dependent diabetes mellitus (NIDDM), but has been associated with severe and sometimes fatal hypoglycemia and gastric disturbances, such as nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy. Because anti diabetic drugs are usually intended to be taken over a long period, patient compliance is also very important. Glipizide (molecular weight 445.5 Daltons) showed favorable partition coefficients (log octanol/buffer: 0.36 ± 0.08; isopropyl myristate/buffer: 0.28 ± 0.12) and negligible skin degradation. Hence, in the present study, we have formulated membrane-moderated transdermal systems of Glipizide.

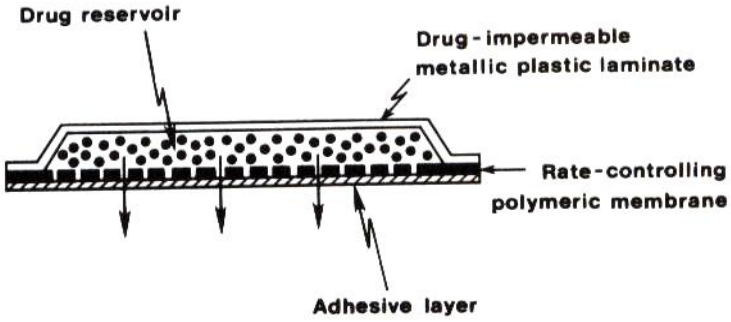
Keywords: Diabetes mellitus, Glipizide, Transdermal Patches, Eudragits, HPMC, NaCMC

INTRODUCTION[1 2 3 4]

Controlled release drug delivery systems are designed to release one or more drugs continuously in a predetermined pattern for a fixed period of time either systemically or to a specified target organ .Drug release from this system should be at a desired predictable and reproducible rate. The primary objectives of controlled release drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance, controlled release drug delivery systems have been designed for oral parental ,implantable and transdermal route. Literature on transdermal formulations of Glipizide and a comparative study of various rate controlling membranes and drug reservoirs is scanty. Hence there is a scope for continued interest and need for developing transdermal therapeutic systems for controlled release of glipizide. Hence studies have been undertaken in the present investigation on membrane moderated therapeutic systems by employing Eudragit RL100 , Eudragit RLPO and Eudragit RS 100 as a rate controlling membranes and HPMC, NaCMC, M.C and Carbopol as drug reservoir gels with an objective of developing transdermal formulations to obtain controlled release of Glipizide. Though the polymeric film and drug reservoirs have been studied for controlled release, no attempts were made to study the influence of casting solvent, polymer film and drug reservoir on permeability of Glipizide. The solvent employed in the preparation of polymer films is likely to influence the permeability of drug. In the present investigation the influence of four different solvents namely Acetone, DCM, Chloroform& Ethyl acetate, four in each case (Eudragit RL 100\ Eudragit RL PO \Eudragit RS 100) employed in the preparation on the permeability of polymer films was studied. For the design of membrane moderated Transdermal drug delivery systems a suitable rate controlling membrane is essential. Polymeric films prepared with various polymers can be used as rate controlling membranes. In the present work, Eudragit RL 100, Eudragit RL PO and Eudragit RS 100 films were prepared and

evaluated as rate controlling membrane for transdermal drug delivery systems. Solvent evaporation and Casting on mercury surface techniques were employed in the present work for the preparation of films. In each case films were prepared using solutions of the polymer in various solvents to evaluate the influence of the solvent used on the mechanical and permeability properties of the films. Continuous intravenous infusion is recognized as a superior mode of drug delivery not only to bypass hepatic ''first-pass" elimination, but also to maintain a constant, prolonged and therapeutically effective drug level in the body. A closely monitored intravenous infusion can provide the advantage of drug into the systemic. Circulation and control of circulating drug levels. However this mode of drug delivery involves certain risks and close medical supervision of medication. Recently there has been a growing recognition that the benefits of intravenous infusion can be closely duplicated without its hazards, by using the intact skin as the port of drug administration to provide continuous drug delivery into the systemic circulation[1]. This is known as the transdermal administration and the drug delivery systems are known as "transdermal therapeutic systems" or popularly as "transdermal patches". Transdermal therapeutic systems[2] are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery systems[3] are adhesive drug containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate.

Basic components of transdermal drug delivery system
Membrane Permeation–Controlled Systems



The Cross-sectional view of a membrane-moderated transdermal drug delivery system, showing various major structural components.

In this type of system drug reservoir is encapsulated in a shallow compartment moulded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate – controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed homogenously in a solid polymer matrix (e.g. Polyisobutylene adhesive) or suspended in an unbleachable, viscous liquid medium (e.g. Silicon fluids) to form a paste like suspension.

The rate of drug release from this type of system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane and adhesive. The constant release rate of the drug is the major advantage of membrane permeation controlled system. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or rapid release of entire drug content. Examples of this system are

Transderm – Nitro: Nitroglycerin – releasing transdermal system for once a day medication in angina pectoris.

Transderm – Scop: Scopolamine – releasing transdermal system for 72 hrs. Prophylaxis of motion sickness.

Catapres: Clonidine-releasing transdermal system for 7 day therapy of hypertension.

Estraderm: Estradiol – releasing transdermal system for treatment of menopausal syndrome for 3 – 4 days.

The membrane permeation-controlled technology has also been used for controlled percutaneous absorption of prostaglandin-derivatives.

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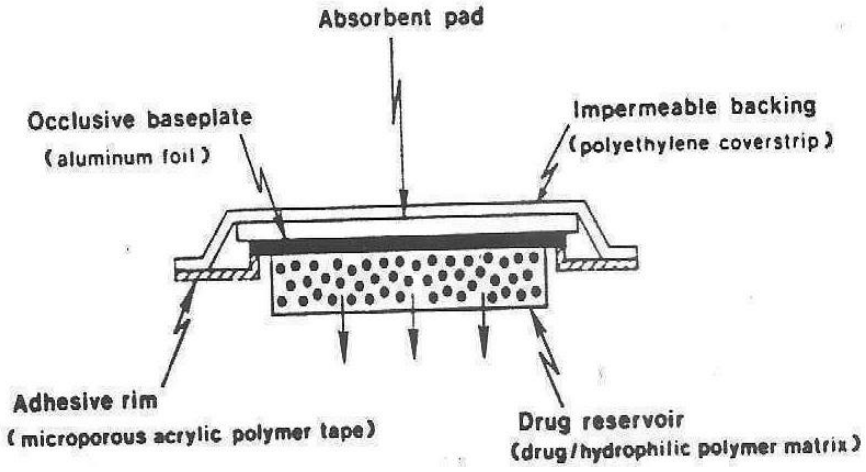


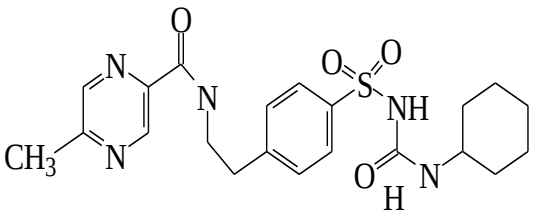
The cross-sectional view of a matrix dispersion-type transdermal drug delivery system, showing various major structural components

Micro reservoir type or Micro sealed Dissolution

The micro reservoir type drug delivery system can be considered a combination of the reservoir and matrix diffusion type drug delivery systems. In this approach, the drug reservoir is formed by first suspending the drug solids in the aqueous solution of water soluble liquid polymer (e.g. Polyethylene glycol) and then dispersing the drug suspension homogenously in lipophillic polymer viz. silicone elastomers by high energy dispersion technique to form several discrete, un leachable micro spheres of drug reservoirs. This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains in-situ, which produces a medicated polymer disc with a constant surface area and a fixed thickness. A transdermal therapeutic system is then produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim.

E.g., Nitroglycerin: Releasing transdermal therapeutic system for once – a day treatment of angina pectoris

Drug profile
Glipizide



Mol.Formula: $C_{21}H_{27}N_5O_4S$,
Mol. Wt.: 445.55
Discripton: A white or almost white, odorless or almost odorless crystalline powder.
Solubility: Practically insoluble in water and alcohol sparingly soluble in acetone, soluble in chloroform. It dissolves in dilute solutions of alkali hydroxides.
Treatment of adverse effects: In acute poisoning the stomach should be emptied by emesis or lavage. Hypoglycemia should be treated with urgency.
Therapeutic uses: Glipizide is used to control hyperglycemia in type-II diabetes. Usual initial dose in treatment of diabetes mellitus is 2.5 to 5 mg daily 3 or 4 times.

MATERIALS & METHODS

Glipizide, Eudragit RL 100, Eudragit RLPO, Acetone, Ethyl acetate, Dichloromethan, chloroform dibutylphthalate, Propylen glycol, Methanol, sodium cmc, Propylene, Sodium CMC (200-300cPs), Sodium Alginate, Methyl cellulose (28-32%), Sod, alginate, dichloromethane, Potassium Di Hydrogen Ortho Phosphate, PVP, DMSO, PEG100.

Equipments

1.	U. V. Spectrophotometer	Elico; Hyderabad; Model: SL 159
2.	Analytical Balance (200 D)	Dhona; Calcutta
3.	Ultra Sonicator	PCI Limited; Mumbai
4.	Magnetic Stirrer	Remi; Mumbai
5.	Hot Air Oven	Lawrence & Mayo; Sec'bad
6.	pH meter	Systronics Digital –DI-707

7.	Brook field Rheometer	LVDV III Ultra

METHODS

Preformulation studies

Solubility studies:
Drug excipient compatibility studies:
Organoleptic characters:

Solubility Studies: The solubility studies in 10ml water and chloroform the hihest amount of dose was accurately weighted and individual flask containing different solvents and stir well for some time

Preparation of drug free films of eudragit rs 100, eudragit rl 100 and eudragit RLPO films: Casting solvent technique was employed in the present work for the preparation of drug free films. The films were prepared by dissolving the polymer (Eudragit RS100, Eudragit RL100 and Eudragit RLPO) in various solvents namely Acetone, chloroform, dichloromethane and ethyl acetate. Dibutyl phthalate at a concentration of 15% w/w of the polymer was used as a plasticizer in the preparation of films. Eight ml of the casting solution was poured in a glass bangle (6.2 cm diameter) containing mercury placed on a horizontal flat surface. The rate of evaporation was controlled by inverting a funnel over the Petri plate. After 24 hours the dried films were taken out and stored in a desecrator.

Ingredients	F1	F2	F3	F4	F5	F6
Eudragit RL100(gm)	2	2	-	-	-	-
Eudragit RLPO(gm)	-	-	2	2	2	2
N-dibutyl phthalate (ml)	0.313	0.313	0.313	0.313	0.313	0.313
Aceton (ml)	-	-	25	-	-	-
Dichloro-methane (ml)	-	-	-	25	-	-
Chloroform (ml)	25	-	-	-	25	-
Ethyl acetate (ml)	-	25	-	-	-	25

Composition of Eudragit Rs100 Rl100rlpo Drug Free Films

Preparation of transdermal gels with various polymers

The polymer (quantity of each polymer with the drug was specified in table 5.6) was taken in a 100 ml glass beaker and water was added. This was allowed to soak for about 24 h and then Glipizide of about 400 mg was weighed and added to the gel by dissolving in ethanol with titration to get a homogenous dispersion of the drug in the gel.

INGREDIENTS	G1	G2	G3	G4	G5	G6
Glipizide (mg)	400	400	400	400	400	400
Sodium CMC(200-300cPs) (mg)	950	----	----	----	----	-----
Sodium Alginate (mg)	----	1200	----	-----	----	----
Methyl cellulose (28-32%) (mg)	----	----	750	----	----	----
HPMC (50cPs) (mg)	----	----	----	1750	----	----
Sodium CMC: PVP (2.4cP) (1:1) (mg)	-----	----	----	----	950	---
Sodium CMC: PEG6000 (1:1)(mg)	----	----	----	----	----	950
Alcohol (ml)	2	2	2	2	2	2
Distilled water (ml) up to	20	20	20	20	20	20

Composition of Transdermal Gels Containing Various Polymers

Composition of transdermal patches containing various permeation enhancers (2%)

The polymer (quantity of each polymer with the drug was specified in table 5.7) was taken in a 100 ml glass beaker and water was added. This was allowed to soak for about 24 h and then Glipizide of about 400 mg was weighed and added to the gel by dissolving in ethanol with triturating to get a homogenous dispersion of the drug in the gel. The permeation enhancers were incorporated by mixing with distilled water. The gel was then filled in the collapsible tubes and labeled.

INGREDIENTS	GP1	GP2	GP3	GP4
Glipizide (mg)	400	400	400	400
Sodium CMC: PEG6000 (mg) (1:1)	950	950	950	950
Tween 20(ml)	0.361	---	---	---
SLS (mg)	---	400	---	---
DMSO (ml)	---	---	0.363	---
PEG 400(ml)	---	---	---	0357
Glycerin (ml)	2	2	2	2
Distilled water (ml) up to	20	20	20	20

Composition of Transdermal Patch Containing Various Permeation Enhancers (2%)

Composition of transdermal patches containing various permeation enhancers (2%)

The optimized film and gel are taken and different composition of the polymer enhancers are added and these were evaluated

INGREDIENTS	**F6+GP1+G6** (P1)	**F6|+GP2+G6** (P2)	**F6+GP3+G6** (P3)	**F6+GP4+G6** (P4)
Glipizide (mg)	400	400	400	400
Sodium CMC: PEG6000 (mg) (1:1)	950	950	950	950
Tween 20(ml)	0.361	---	---	---
SLS (mg)	---	400	---	---
DMSO (ml)	---	---	0.363	---
PEG 400(ml)	---	---	---	0357
Glycerin (ml)	2	2	2	2
Distilled water (ml) up to	20	20	20	20

Preparation of Transdermal Patch Containing Various Permeation Enhancers

Preparation of trans dermal patch with various different gel composition

The optimized film and is taken and the different composition of gels are added to the it and these composition was prepared and further evaluation was made

INGREDIENTS	**F6+G1+GP1 (T1)**	**F6+G2+GP1 (T2)**	**F6+G3+GP1 (T3)**	**F6+G4+GP1 (T4)**	**F6+G5+GP1 (T5)**	**F6+G6+GP1 (T6)**
Glipizide (mg)	400	400	400	400	400	400
Sodium CMC(200-300cPs) (mg)	950	----	----	----	----	-----
Sodium Alginate (mg)	----	1200	----	-----	----	----
Methyl cellulose (28-32%) (mg)	----	----	750	----	----	----
HPMC (50cPs) (mg)	----	----	----	1750	----	----
Sodium CMC: PVP (2.4cP) (1:1) (mg)	-----	----	----	----	950	---
Sodium CMC: PEG6000 (1:1)(mg)	----	----	----	----	----	950
Alcohol (ml)	2	2	2	2	2	2
Distilled water (ml) up to	20	20	20	20	20	20

Preparation of Transdermal Patch Containing Various Permeation Enhancers

The factors that require consideration when selecting an in vitro system include:

1. The rate limiting process:Drug solubilization or diffusion in the vehicle, partitioning from the vehicle, diffusion through the test membrane or partitioning and removal by the receptor phase.
2. The intrinsic diffusivity of the permeate and apparent diffusivity.
3. The predominating route of diffusion during the experiment and the relative contents of drug binding and metabolism, occurring in the membrane, delivery and receptor phases.
4. The predominating route of diffusion during the experimentation and the relative extents of drug binding.
5. The intrinsic barrier potential of the membrane and the effects that vehicle components may have on retardative properties. Hydration of the membrane and the presence of penetration enhancers may be important here.

The kinetics of skin permeation can be more precisely analyzed by studying the time course for the permeation of drug across a freshly excised skin mounted on a diffusion cell, such as the Franz diffusion cell. Keshary and Chien have pointed out certain deficiencies in the Franz cell and modified to obtain closer approximation to in vivo conditions. Some diffusion cells are designed to hold the skin at a vertical position between donor and receptor chambers. A more recent example is the valia, Chien cell, which is superior to similar earlier models in that it does not expose both, the donor and the receptor phases to the same temperature, and does not allow solvent loss from either phase. Moreover, the design overcomes another inadequacy of the Franz cell, namely the susceptibility of its donor phase to the changes in ambient temperature. Finally the donor compartment contents may be stirred which makes the cell suitable for transdermal drug delivery from solutions and suspensions. Various types of in vitro apparatus for measuring drug permeation profiles across the skin have been reported in the literature.

RESULTS

Pre-formulation Studies

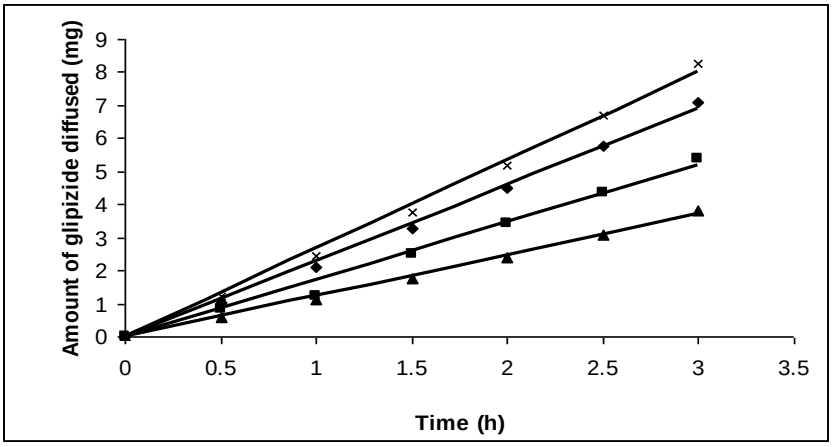


Fig 1: Characterization Properties of Eudragit Rl100 Films

POLYMER	CASTING SOLVENT	Permeability Coefficient ($PmX10^3$ mg/cm.h)
EUDRAGIT RL100	F5	**1.8**
	F6	**1.4**
	F7	**0.9**
	F8	**2.1**

Permeability Coefficient Values Of Glipizide From Eudragit Rl100 Films Prepared With Various Casting Solvents

POLYMER	CASTING SOLVENT	THICKNESS (µm)	FOLDING ENDURANCE
EUDRAGIT RLPO	F9	36.60+0.15	254
	F10	37.60+0.14	238
	F11	37.20+0.13	208
	F12	38.00+0.14	182

POLYMER	CASTING SOLVENT	WATER VAPOUR TRANSMISSION RATE Q X 10^4 g/cm 24 hrs
EUDRAGIT RLPO	F9	4.394
	F10	3.748
	F11	3.376
	F12	4.744

TIME (h)	AMOUNTOF GLIPIZIDE DIFFUSED (mg) (X± s d) solvent employed			
	Acetone	Dichloromethane	Chloroform	Ethyl Acetate
0	0	0	0	0
0.5	1.155 ± 0.05	0.990 ±0.05	0.705 ±0.05	1.410 ± 0.02
1	2.327 ±0.01	1.986 ±0.01	1.382 ±0.04	2.854 ± 0.02
1.5	3.602 ±0.04	3.089 ±0.02	2.116 ±0.02	4.388 ± 0.03
2	4.952 ±0.02	4.227 ±0.04	2.878 ±0.04	6.012 ± 0.05
2.5	6.452 ±0.02	5.428 ±0.02	3.712 ±0.07	7.744 ± 0.03
3	7.777 ±0.04	6.677 ±0.02	4.575 ±0.06	9.546 ± 0.02

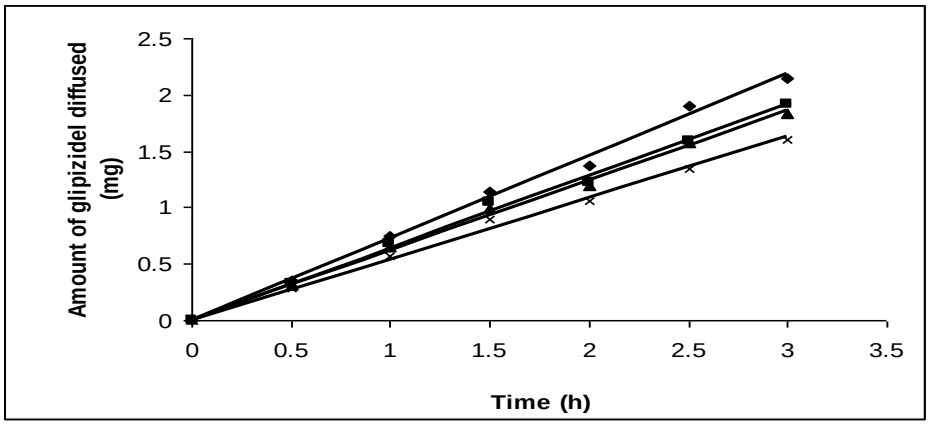
SOLVENT EMPLOYED	CORRELATION COEFFICIENT (R) VALUES		DIFFUSIONRATE CONSTANT (K) VALUE (mg/h)	DIFFUSION EXPONENT VALUE (n)	T_{50} (h)
	ZERO ORDER	PEPPAS MODEL			
F9	0.9990	0.9991	2.611	1.077	3.829
F10	0.9990	0.9996	2.225	1.067	4.494
F11	0.9989	0.9994	1.517	1.044	6.592
F12	0.9989	0.9997	3.176	1.067	3.149

Characterstics of gels formulated with different polymers

Formulation	Drug content (%)	Viscosity (cPs)	Extrudability (N)	Spreadability (g.cm/sec.)	pH		Homogeneity	Irritation
					Before Drug incorporation	After		
G1	99.03	1581	14.91	28.4	7.20	7.12	***	--
G2	98.48	4776	15.17	31.64	7.42	7.25	***	--
G3	99.34	1320	15.66	32.89	7.35	7.16	***	--
G4	99.49	1570	16.16	29.76	7.18	7.14	***	--
G5	99.58	2878	15.41	30.86	7.22	7.26	***	--
G6	99.19	2634	16.28	30.12	7.54	7.12	***	--

Diffusion data of glipizide from various transdermal gels through eudragit rlpo films

TIME (h)	AMOUNT OF GLIPZIDE DIFFUSED(mg) $\overline{X}$ ± s d					
	T1	T2	T3	T4	T5	T6
0	0	0	0	0	0	0
0.5	0.360±0.06	0.330±0.06	0.315±0.02	0.285±0.03	0.435±0.05	0.495±0.03
1	0.744±0.03	0.682±0.08	0.651±0.03	0.574±0.05	0.899±0.06	1.008±0.06
1.5	1.137±0.05	1.041±0.05	1.993±0.05	0.896±0.06	1.257±0.03	1.433±0.05
2	1.373±0.04	1.226±0.03	1.190±0.02	1.057±0.04	1.680±0.02	2.972±0.09
2.5	2.905±0.02	1.584±0.01	1.576±0.03	1.345±0.03	2.171±0.04	2.511±0.04
3	2.152±0.07	1.916±0.02	1.833±0.04	1.603±0.04	2.658±0.06	3.078±0.07



Diffusion Profiles Of Glipizide From Various Transdermal Gels Through Eudragit RLPO Films

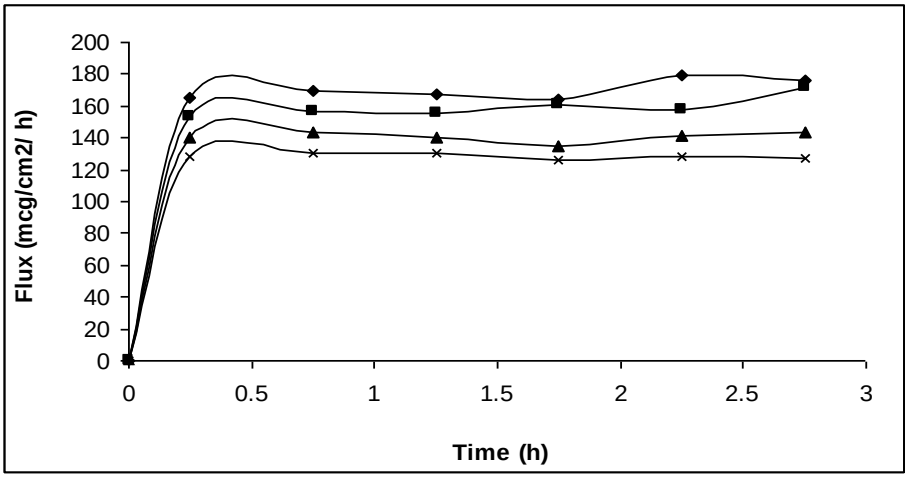
(-♦-) T1 (Transdermal gel prepared with Na CMC),
(-■-)T2(Transdermal gel prepared with Na Alginate)
(-▲-)T3 (Transdermal gel prepared with Methyl cellulose)
(-×-)T4(Transdermal gel prepared with HPMC)

Diffusion characteristics of glipizide from various transdermal gels through eudragit rlpo films

FORMULATION	CORRELATION COEFFICIENT (R) VALUES		DIFFUSION RATE CONSTANT (K) VALUE (mg/h)	DIFFUSION EXPONENT VALUE(n)	T_{50} (h)
	ZERO ORDER	PEPPAS MODEL			
T1	0.9976	0.9982	0.7268	1.012	13.759
T2	0.9982	0.9979	0.6286	0.964	15.908
T3	0.9985	0.9984	0.6114	0.978	16.3559
T4	0.9980	0.9981	0.5294	0.955	18.8893
T5	0.9992	0.9991	0.8734	0.996	11.4495
T6	0.9993	0.9994	1.0164	1.010	9.8386

Diffusion flux of glipizide from transdermal gels containing various permeation enhancers through eudragit rlpo films

TIME (h)	AMOUNT OF GLIPIZIDE DIFFUSED(mg) $\overline{X}$ ± s d			
	P1	P2	P3	P4
0	0	0	0	0
0.25	164.97	152.75	140.53	128.31
0.75	169.86	156.82	143.79	130.75
1.25	167.68	155.61	139.98	130.90
1.75	163.74	160.49	134.42	126.39
2.25	178.82	157.23	140.86	128.31
2.75	175.97	171.49	143.38	127.05



Diffusion flux of glipizide from transdermal gels containing various permeation enhancers through eudragit rlpo films.

(-♦-) P1 (Transdermal gel prepared with Tween 20)
(-■-)P2 (Transdermal gel prepared with SLS)
(-▲-)P3 (Transdermal gel prepared with DMSO)
(-×-)P4 (Transdermal gel prepared with PEG 400)

Diffusion Characteristics of GlipzideFrom Transdermal Gels Containing Various Permeation Enhancers Through Eudragit RLPO Films

FORMULATION	CORRELATION COEFFICIENT (R) VALUES		DIFFUSION RATE CONSTANT (K) VALUE (mg/h)	DIFFUSION EXPONENT VALUE (n)	T_{50} (h)
	ZERO ORDER	PEPPAS MODEL			
P1	0.9995	0.9993	0.8022	0.9905	12.47
P2	0.9989	0.9986	0.7322	0.9817	13.66
P3	0.9994	0.9992	0.6622	0.9717	15.10
P4	0.9996	0.9996	0.6343	1.001	15.77

PERMEATION ENHANCERS	PERMEABILITY OEFFICIENT ($PmX10^4$ mg/cm.h)
P1	6.177
P2	5.638
P3	5.099
P4	4.884

DISCUSSIONS

Transdermal formulations can be fabricated as membrane controlled, matrix, micro reservoir and adhesive type drug delivery system. Membrane controlled systems are designed for the present investigation, as they were found to yield zero order release. In membrane controlled drug delivery system, the drug reservoir will be sandwiched in between rate controlling and drug impermeable membrane. In the present investigation Eudragit RS 100, Eudragit RL 100 and Eudragit RLPO films were selected as rate controlling membranes and HPMC ,NaCMC, MC and Na Alginate gels were used as drug reservoirs. The influence of casting solvents on permeability of drug, comparison of different polymers and reservoirs was studied in the present research work. Glipizide which is prone to under go first pass metabolism and having a short biological half life is selected as a suitable candidate for the present work. The literature on these drug delivery systems is scanty. Though few reports are available on transdermal formulations of Glipizide, no attempts were made to study the influence of casting solvent, polymer employed to form rate controlling membrane and affect of drug reservoir film on the drug release from the transdermal films. Polymeric films can be prepared by various methods such as melt extrusion, bubbling, air spray, thermo setting, casting on mercuric surface and solvent evaporation methods. Among the various methods, solvent evaporation and casting on mercuric surface methods are convenient and most suitable for laboratory purpose. Hence in the present work, casting on mercuric surface technique employed for the preparation of film

Comparision of eudragit rs100, eudragit rl100 and eudragit rlpo films

In order to compare the films, they have to be formulated with same casting solvents and plasticizers. Hence in this investigation, of Eudragit RS100, Eudragit RL100 and Eudragit RLPO drug free films were fabricated with the common solvent Ethyl acetate and the plasticizer dibutyl phthalate. The water vapour transmission coefficient and Glipizide permeability coefficient values were showed in below table.

POLYMER	Q X 10^4gm/Cm^2 24 Hrs	$PmX10^3$ mg/cm.h
EUDRAGIT RS100	4.199	1.9
EUDRAGIT RL100	4.502	2.1
EUDRAGIT RLPO	4.744	2.4

Water Vapour Transmission Coefficient (Q) And Permeability Coefficient Values (Pm) Of Different Films Prepared With Ethylacetate

Based on the water vapour transmission coefficient (Q) and permeability coefficient (Pm) values the formulations can be arranged as Eudragit RLPO.> Eudragit RL100.> Eudragit RS100. Among all the films, Eudragit RLPO films prepared with Ethylacetate showed the desired permeability coefficient (Pm) when compared to other films. Hence the Eudragit RLPO films prepared with Ethylacetate was used in further studies.

Studies on drug reservoir gels

The design of membrane moderated TDD systems requires a suitable rate controlling membrane and a drug reservoir. The results discussed in earlier indicated that Eudragit RLPO films could be used as rate controlling membranes for the design of TDD systems. The drug reservoir can be in either solid, semisolid or solution form. Drug from this reservoir diffuses slowly over extended periods of time at a constant rate. With a view to design a suitable drug reservoir, various types of gel formulations were prepared and evaluated by studying drug diffusion from these formulations through Eudragit RLPO membrane. Out of the various semisolids dosage forms, the gels are becoming more popular due to ease of application and better percutaneous absorption, than other semisolids preparations. Gels can resist the physiological stress caused by skin flexion, blinking and mucociliary movement, adopting the shape of the applied area, and controlling drug release. Gel formulations were prepared with an intention of increasing the contact time of the drug with the skin so that glipizide is released in prolonged manner for an extended period of time.In the present study efforts were made to prepare transdermal gels of glipizide using polymers like HPMC, NaCMC, MC and Na Alginate. Transdermal gels prepared with HPMC found to be white, translucent and homogenous. But gels prepared with NaCMC, MC and Na Alginate was found to be off white and homogenous. Drug content values of the formulations were well with in the range between 98.48-99.97 % The pH of all formulations was around the skin pH 7.12 to 7.60 reflecting no risk of skin irritation which was further confirmed by skin irritation testing. The viscosity of various formulated glipizide gels was measured using a Brook field rheometer with spindle SC4-18 and operated with various shear rates (in between 10-90% torque) to construct the rheogram. Viscosities of different formulations are presented in table 28 and 32. All gels were found to exhibit plastic flow. It was observed that the gel

formulations showed good extrudability, homogeneity and spreadability and the data was presented in tables.
The correlation coefficient values (r) were reported in Table 30. These values revealed that the diffusion profiles follows zero order kinetics and the mechanism of drug release was governed by peppas model. The diffusion exponent of release profiles (slope) has a value of 0.955-1.010 (n>1), which indicates case II transport diffusion. Permeability coefficient values (Pm) of the films towards the glipizide gel was calculated from the drug diffusion data and the results were given in table.
The gel formulations can be graded in the following order with respect to the rates of release of glipizide from them:
(HPMC) < (MC) < (Na alginate) < (NaCMC) < (NaCMC +PVP)< (NaCMC+ PEG-6000).
Based on permeability coefficient values, NaCMC gels were selected for further studies as these gels offered high permeability of glipizide.

Influences of permeation enhancers

The stratum corneum has evolved primarily for barrier function. This creates difficulties in the formulation of TDDS which aims to delivery the drug via skin in therapeutic quantities. The search for solutions to this problem led investigators to employ several enhancement techniques. One approach is the co administration of skin permeation enhancers. Ideally, permeation enhancers are a chemical entity which reduces reversibly the barrier resistance of the stratum corneum without damaging the viable cells. A large number of substances have been evaluated as permeation enhancers and research is extending with the growing need for safe, effective accelerants. The permeation enhancers such as 2% w/w of SLS, 2% w/v of PEG400, DMSO and Tween 20 were used in this work improves the permeation of drug. The results of the in-vitro diffusion study from different gels containing various permeation enhancers across the Eudragit RLPO films prepared with Ethyl acetate are reported in table 33 and are shown in figure 16. Diffusion flux was calculated and same were reported in table 34 and shown in figure 17.The correlation coefficient values (r) were reported in table 35 These values revealed that the dissolution profiles follows zero order kinetics (in fig 18) and the mechanism of drug release was governed by peppas model (fig 19). The diffusion exponent of release profiles (slope) has a value of 0.9717-1.001 (n>1), which indicates case II transport diffusion. Permeability coefficient values (Pm) of the films towards the glipizide gel was calculated from the drug diffusion data and the results were given in table 36. The permeation enhancers like SLS,PEG400,DMSO and Tween 20 used for increasing the permeation of drug could be arranged in the following increasing order according to their permeation rates : Tween 20> SLS> PEG400> DMSO. The increased permeation rate in all these enhancers may be due to surfactant action .These results indicated that the non ionic surfactant Tween 20 improves the permeability characteristics of glipizide when compared with the other permeation enhancers. Hence the formulation containing Tween 20 was used in further studies.

Stability studies

The Stability studies were carried out for the formulation GP_1 (NaCMC + PEG – 6000 + Tween 20) at different temperature conditions like: 4^0(refrigerator temperature), 25^0 (ambient temperature) and 37^0(incubator temperature) for 6 weeks. Known amounts of gels were taken out at regular time intervals of 1week for 6weeks and analyzed for drug content, physical appearance, pH, viscosity, extrudability, spreadability and degradation rate constant(K). The results of stability studies are shown in table 37, 38 and 40. There were no significant changes in the drug content, physical appearance, pH, viscosity, extrudability and spreadability. The degradation rate constant (k) values for formulation GP_1 (NaCMC + PEG-6000+Tween 20) at different temperature conditions like: 4^0 (refrigerator temperature), 25^0 (ambient temperature) and 37^0 (incubator temperature) were 0.00008, 0.0001, 0.000106 per day respectively.

CONCLUSION

The results obtained in the present study thus indicated that the polymer and solvent used has significant influence on the water vapour transmission, drug diffusion and permeability of the films. These results indicated that the drug diffusion through Eudragit RLPO films was relatively high when compared to Eudragit RS100and Eudragit RL100 films. Based on the diffusion rate the formulations can be arranged as Eudragit RLPO> EudragitRL100> Eudragit RS100. Among all the films, Eudragit RLPO films prepared with Ethylacetate shown high Permeability when compared to other films. The rate of permeability coefficient was decreased in the order of films in various solvents is as follows. Ethyl acetate > acetone> dichloromethane> chloroform. The gel formulations can be graded in the following order with respect to the rates of release of Glipizide from them: (HPMC) < (MC) < (Na alginate) < (NaCMC) < (NaCMC +PVP)< (NaCMC+ PEG-6000).

REFERENCES

1. Shaw JE, Chandrasekaran SK, Campbell P. Percutaneous Absorption: Controlled Drug Delivery For Topical or Systemic Therapy. J Investig Dermatol. 1976;67(5):677-8. doi: 10.1111/1523-1747.ep12544519.
2. Monkhouse DC, Huq AS. Transdermal Drug Delivery – Problems and Promises. Drug Dev Ind Pharm. 1988;14(2-3):183-209. doi: 10.3109/03639048809151970.
3. Cronin CM, Mitrano EA, Wilder RS, Harmon EP, Zusman RM. Comparative evaluation of the three commercially available transdermal nitroglycerin delivery systems. Drug Intell Clin Pharm. 1987;21(7-8):642-4. doi: 10.1177/1060028087021007-816, PMID 3111812.

4. Guy RH, Hadgraft J, Bucks DAW. Transdermal drug delivery and cutaneous metabolism. Xenobiotica. 1987;17(3):325-43. doi: 10.3109/00498258709043943, PMID 3107225.
5. Barry BW. Dermatological formulations, percutaneous absorption. New York: Marcel Dekker; 1983.
6. Mishra B, Pandit JK, Bhattacharya SK. Recent trends in drug delivery systems: transdermal drug delivery. Ind J Exp Biol. 1990;28(11):1001-7. Available from: https://pubmed.ncbi.nlm.nih.gov/2283165/
7. Harpin VA, Rutter N. Barrier properties of the newborn infant's skin. J Pediatr. 1983;102(3):419-25. doi: 10.1016/s0022-3476(83)80669-6, PMID 6827416.
8. Jacob SA, Francone CA. Structure and function of man. 2nd ed. Philadelphia: W B Saunders Company; 1970. p. 55.
9. Chien YW. Logics of Transdermal Controlled Drug Administration. Drug Dev Ind Pharm. 1983;9(4):497-520. doi: 10.3109/03639048309044691.
10. Jain NK. Controlled and novel drug delivery, CBS publishers and distributors. Vol. 107; 2002.
11. Kydonieus AF. Transdermal delivery of drugs. Vol. I. FL: CRC Press; 1987. p. 3.
12. Guy RH, Hadgraft J, Bucks DA. A.W. Xenobiotica. 1987;17(3):325-43. doi: 10.3109/00498258709043943, PMID 3107225.
13. Knuston K, Potts RO, Guzek DB, Golden GM, Mckie JE, Lambert W. J. and Higuchi. W.I. J Control Rel. 1985;2(10):67.
14. Potts RO. In: Hadgraft J, Guy RH, editors. Transdermal drug delivery. New York: Marcel Dekker; 1989. p. 23.
15. Rolf D. Pharm Technol. 1988;12:131.
16. Good WR. Transder®-Nitro Controlled Delivery of Nitroglycerin via the Transdermal Route. Drug Dev Ind Pharm. 1983;9(4):647-70. doi: 10.3109/03639048309044697.
17. Keshary PR, Chien YW. Mechanisms of Transdermal Controlled Nitroglycerin Administration (I): Development of a Finite-Dosing Skin Permeation System. Drug Dev Ind Pharm. 1984;10(6):883-913. doi: 10.3109/03639048409040788.
18. Durrheim H, Flynn GL, Higuchi WI, Behl CR. Permeation of hairless mouse skin I: experimental methods and comparison with human epidermal permeation by alkanols. J Pharm Sci. 1980;69(7):781-6. doi: 10.1002/jps.2600690709, PMID 7391939.
19. Chien YW, Valia KH. Drug Dev Ind Pharm. 1984;9(4):575.
20. Scheuplein RJ. Mechanism of percutaneous adsorption. I. Routes of penetration and the influence of solubility. J Invest Dermatol. 1965;45(5):334-46. doi: 10.1038/jid.1965.140, PMID 5847304.
21. Chien YW, Valia KH. Development of a Dynamic Skin Permeation System for Long-Term Permeation Studies. Drug Dev Ind Pharm. 1984;10(4):575-99. doi: 10.3109/03639048409041408.
22. Jonathan H, Guy RH. Transdermal. Drug Deliv. 1989;179.
23. USP 27. NF 22, The United States of America Pharmacopeial Convention, Rockville. Vol. 2309; 2004.
24. Guy RH, Hadgraft J. A theoretical description relating skin penetration to the thickness of the applied medicament. Int J Pharm. 1980;6(3-4):321-32. doi: 10.1016/0378-5173(80)90115-5.
25. Guy RH, Hadgraft J. Percutaneous metabolism with saturable enzyme kinetics. Int J Pharm. 1982;11(3):187-97. doi: 10.1016/0378-5173(82)90037-0.