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Formulation Development and Characterization of Glipizide Transdermal Gels by Using Permeation Enhancers

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ABSTRACT

That in research paper an effort were made to formulate glipizide transdermal patches using different permeation enhancers. The results obtained determined the polymer and solvent victimized had an influence on drug diffusion and permeability of the films. These results obtained showed that the drug diffusion via Eudragit RLPO films was relatively high compared to Eudragit RS100 and Eudragit RL100 films (Eudragit RLPO> Eudragit RL100> Eudragit RS100). The Formulation G6 has shown a good release. The effects designated to the nonionic surfactant Tween 20 expands the permeability qualities of Glipizide when compared to the other permeation modifiers.

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INTRODUCTION

In the present study, we aimed to deliver anti-diabetic drug glipizide for developing transdermal therapeutic systems for controlled release. Hence studies have been undertaken in the current study on membrane moderated therapeutic systems by using HPMC, CAP, ethylcellulose, and Polypropylene glycol as a rate-controlling membrane and HPMC, Cellulose acetate phthalate, ethylcellulose as drug reservoir gels. The manner of biosimilars is certain to avoid chronic disorders specified diabetics, which need longer-term dosing to take care of therapeutically drug concentration. The transdermal patch is used for anti-diabetic activity that belongs to the class sulfonylurea used for type 2 diabetes [1].

MATERIALS AND METHODS

Glipizide was received as free sample from Hetero Drugs Limited, Hyderabad. Eudragit RS 100, Eudragit RL 100, and Eudragit RLPO, Sodium CMC, Sodium alginate and Methylcellulose used to be acquired from SD fine chemicals Ltd., Mumbai. All abundant chemical as well as chemical agent utilized in this study are of analytical grade.

Methodology

Drug-Excipients compatible studies

Incase of polymer used in the formulation is in the dispersion forms instead of dispersion dry polymer whose dispersions are used in the formulation were kept under stability conditions [2].

Preparation of drug-free films of Eudragit RS 100, Eudragit RL 100, and Eudragit RLPO Films

The flicks were arranged by polymerizing the poly-

mer in numerous solvents like Acetone, chloroform, dichloromethane, and ethyl acetate [Table 1].

Dibutyl phthalate at a concentration of 15% w/w of the polymer used to be used a plasticizer in the readying of films subsequent to 24 hours the dried fims give up out while stored in a desiccator [3].

Transdermal patch containing various permeation enhancers

In a 100ml glass beaker polymer was added and made up with water and was allowed to soak for 24 hours and Glipizide 400 mg was weighed and added to the gel by dissolving in ethanol by titration inorder to get a homogenous dispersion.

The permeation enhancers were incorporated by mixing with water.

The gel was brimming in the collapsable tubes and labeled [4].

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

Here the optimized film and gel are taken and different compositions of the polymer enhancers are added and these were evaluated (Table 2, Table 3 and Table 4) [5].

Preparation of transdermal patch with different gel composition

Here the optimized film and is taken and the different composition of gels are added to it and this composition was prepared and further evaluation (Table 5) [6].

Evaluation of Transdermal Films

Physical Appearance

By apparent watching free films sort out have been evaluated (Table 6) [7].

Thickness uniformity

It used to be sounded by screw gauge [7].

Folding Endurance

The no. of times the film that could be folded at the same place without breaking gave the exact value of folding endurance [8].

***In-Vitro* Skin Permeation**

In vitro studies helps in identifying the mechanism of skin permeation of the drug and later it can be formulated into a transdermal therapeutic system [9].

Kinetic Treatment

The data obtained from the *in vitro* dissolution studies acquire kinetic track record analysis [10].

Zero-order kinetics: $Q_t = Q_o + K_o t$

Korsmeyer-Peppas release model: $Mt / M_\infty = K \cdot t^n$

Permeability Coefficient

From the drug diffusion data, it was calculated using the following equation (Table 7, Table 8, Table 11 and Table 19) [11].

$$P_m = K_{app} \cdot \frac{H}{A}$$

Where, K_{app}= Diffusion rate constant (mg/h) calculated from the slope of the linear drug (d/p) diffusion profiles

H = Thickness of the film (cm)

A =Surfacearea of the film (cm^2)

Evaluation of Transdermal Gels

Drug content

The Glipizide gel used to be liquefied in 50 ml of phosphate buffer (pH 7.4). spectacular absorbance was sounded after suitable dilution at 223 nm [12].

pH and viscosity

The pH of the dispersion was measured using a pH meter. Viscosity of the gels was determined using a Brook field rheometer [13].

Extrudability

It is the measurement of the flow ability of gels from tubes(collapsible). Comparison among the different formulations can be made regarding the effect of filling under various stress conditions and ease of extrusion. The results for all the formulations were recorded as extrusion pressure in grams [14].

Spreadability

It was determined by an apparatus that consists of a wooden block provided with two glass slides. The lower slide was fixed on a wooden block and the upper slide with one end was tied to a glass slide and the other end tied to a weight pan. A gel quantity of 2.5g was placed between two slides and a 1000g weight was placed over it for 5 minutes to press the sample to a uniform thickness [15].

RESULTS AND DISCUSSION

In Physical observation of drug and excipients at the temperature of 40°C/75% RH there are no changes in White Crystalline Powder & Free flow no aggregation (Table 26).

All the films prepared were evaluated for thickness uniformity, folding endurance (Table 10 and Table 14). Drug diffusion from these films was studied with 10 ml of 0.20%W/V Glipizide solution by using Franz diffusion cell (Table 9 and Table 15). The correlation coefficient values (r) were tabulated in Table 13 and Table 16 consequently for Eudragit RS100, Eudragit RL100, and Eudragit RLPO. The

Table 1: Composition of Eudragit RS 100 RL100 & RLPO Drug Free Films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Eudragit RS100 (gm)	2	2	2	2	-	-	-	-	-	-	-	-
Eudragit RL100 (gm)	-	-	-	-	2	2	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	0.313	0.313	0.313	0.313	0.313	0.313
Acetone (ml)	25	—	—	—	25	—	—	—	25	—	—	—
Dichloro-methane (ml)	—	25	—	—	—	25	—	—	—	25	—	—
Chloroform (ml)	—	—	25	—	—	—	25	—	—	—	25	—
Ethyl acetate (ml)	—	—	—	25	—	—	—	25	—	—	—	25

Table 2: Composition of transdermal gels containing various polymers

Ingredients	G1	G2	G3	G4	G5	G6
Glipizide (mg)	400	400	400	400	400	400
Sodium CMC (mg)	900	–	-	-	-	-
Sodium Alginate (mg)	-	1100	-	-	-	-
Methylcellulose (mg)	-	-	800	-	-	-
HPMC (mg)	-	-	-	1600	-	-
Sodium CMC: PVP (2.4cP) (1:1) (mg)	-	-	-	-	900	-
Sodium CMC: PEG6000 (1:1) (mg)	-	-	-	-	–	900
Alcohol (ml)	5	5	5	5	5	5
Distilled water (ml)	25	25	25	25	25	25

Table 3: Composition of transdermal Patch Containing Permeation Enhancers

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

Table 4: Ingredients of Transdermal Patch with Permeation Enhancers

Ingredients	F12+GP1+ G6(P1)	F12+GP2+ G6(P2)	F12+GP3+ G6(P3)	F12+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)	20	20	20	20

Table 5: Preparation of Glipizide Transdermal Patch Containing Gel

Ingredients	F12+G1+GP (T1)	F12+G2+ GP1 (T2)	F12+G3+ GP1 (T3)	F12+G+ GP1 (T4)	F12+G5+ GP1 (T5)	F12+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

Table 6: Drug - Excipient Compatibility Studies – Physical Observation

Name of the sample	Ratio	Observation		
		Initial	RT Initial	40°C / 75% RH (4 weeks)
API	-	**	**	**
API + eudragit RS 100	1:1.5	**	**	**
API + RL 100	1:1.5	**	**	**
API + RLP0	1:1.5	**	**	**
API + HPMC	1:1.5	**	**	**
API + Sodium alginate	1:1.5	**	**	**
API + NACMC	1:1.5	**	**	**
API +PVP6000	1:1.5	**	**	**
API + Methylcellulose	1:1.5	**	**	**

** White Crystalline Powder. Free flow no aggregation

Table 7: Diffusion Data of Glipizide From Eudragit RS 100 Films

Time (h)	Amount of Glipizide Diffused (mg) (X± s d) Solvent Employed			
	F1	F2	F3	F4
0	0	0	0	0
0.5	0.915 ± 0.05	0.750 ±0.05	0.525 ±0.05	1.125 ± 0.02
1	1.816 ±0.01	1.490 ±0.01	1.025 ±0.04	2.280 ± 0.02
1.5	2.788 ±0.04	2.291 ±0.02	1.541 ±0.02	3.490 ± 0.03
2	3.817 ±0.02	3.124 ±0.04	2.117 ±0.04	4.773 ± 0.05
2.5	4.903 ±0.02	4.013 ±0.02	2.710 ±0.07	6.112 ± 0.03
3	6.061 ±0.04	4.944 ±0.02	3.349 ±0.06	7.566 ± 0.02

Table 8: Permeability Coefficient of Glipizide From Eudragit RS 100 Films

Polymer	Casting solvent	Permeability Coefficient ($PmX10^3$ mg/cm.h)
Eudragit RS100 Films	F1	1.5
	F2	1.3
	F3	0.8
	F4	1.9

Table 9: Release order kinetics of glipizide from eudragit RS 100 films

Solvents	Correlation coefficient (r) values		Diffusion rate constant (k) value (mg/h)	Diffusion exponent value (n)	T_{50} (h)
	Zero Order	Peppas Model			
F1	0.998	0.999	2.011	1.055	4.973
F2	0.999	0.999	1.642	1.052	6.090
F3	0.999	0.999	1.108	1.033	9.025
F4	0.998	0.999	2.512	1.061	3.981

Table 10: Thickness and Folding endurance of Glipizide From Eudragit RL 100 Films

Polymer	Casting solvent	Thickness (μm)	Folding endurance
Eudragit RL100	F5	34.40+0.65	112
	F6	37.80+0.37	188
	F7	36.80+0.15	216
	F8	37.60+0.28	119

Table 11: Diffusion Data of Glipizide From Eudragit RL 100 Films

Time (h)	Amount of Glipizide Diffused (mg) (X± s d) Solvent Employed			
	Acetone	Dichloromethane	Chloroform	Ethyl Acetate
0	0	0	0	0
0.5	1.050 ± 0.05	0.825 ±0.05	0.585 ±0.05	1.230 ± 0.02
1	2.125 ±0.01	1.240 ±0.01	1.149 ±0.04	2.467 ± 0.02
1.5	3.267 ±0.04	2.474 ±0.02	1.763 ±0.02	3.781 ± 0.03
2	4.476 ±0.02	3.410 ±0.04	2.410 ±0.04	5.202 ± 0.05
2.5	5.752 ±0.02	4.368 ±0.02	3.101 ±0.07	6.687 ± 0.03
3	7.110 ±0.04	5.391 ±0.02	3.823 ±0.06	8.280 ± 0.02

Table 12: Permeability Coefficient Values of Glipizide From Eudragit RL 100 Films

Polymer	Casting Solvent	Permeability coefficient (pmx10^3 mg/cm.h)
Eudragit RL 100	F5	1.8
	F6	1.4
	F7	0.9
	F8	2.1

Table 13: Correction Coefficient of Glipizide From Eudragit RL 100 Films

Solvent	Correlation Coefficient (R) Values		Rate Constant Value (Mg/H)	Exponent Value (N)	T_{50} (H)
	Zero Order	Peppas Model			
F5	0.9989	0.9996	2.363	1.066	4.232
F6	0.9952	0.9969	1.816	1.098	5.507
F7	0.9989	0.9994	1.268	1.047	7.886
F8	0.9987	0.9995	2.749	1.063	3.638

Table 14: Thickness & Folding Endurance of Eudragit RLPO Film

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

Table 15: Diffusion Data of Glipizide From Eudragit RLPO Films

Time (h)	Amount of 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

Table 16: Correlation Coefficient of Glipizide From Eudragit RLPO Films

Solvent Emplo	Correlation Coefficient (R) Values		Rate Constant (K) Value (Mg/H)	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

Table 17: Permeability Coefficient Values of Glipizide

Polymer	Casting Solvent	PermeabilityCoefficient ($PmX10^3$ mg/cm.h)
Eudragit RLPO	Acetone	2.00
	Dichloromethane	1.7
	Chloroform	1.2
	Ethyl Acetate	2.4

Table 18: Characteristics of gels formulated with different polymers

Formulation	Drug content (%)	Viscosity (cPs)	Extrudabilit (N)	Spreadability (g.cm/sec.)	pH
G1	99.03	1581	14.91	28.4	7.12
G2	98.48	4776	15.17	31.64	7.25
G3	99.34	1320	15.66	32.89	7.16
G4	99.49	1570	16.16	29.76	7.14
G5	99.58	2878	15.41	30.86	7.26
G6	99.19	2634	16.28	30.12	7.12

Table 19: Diffusion data of glipizide transdermal gels

	Amount of glipizide diffused(mg) X ± s d					
Time(h)	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

Table 20: Correlation Coefficient of Glipizide From Various Transdermal Gels

Formulation	Correlation coefficient (r) values		Rate constant (k) value (mg/h)	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

Table 21: Permeability Coefficient Values of Glipizide From Various Transdermal Gels

Formulation	Permeability Coefficient ($PmX10^4$ mg/cm.h)
T1	5.59
T2	4.84
T3	4.708
T4	4.076
T5	6.725
T6	7.826

Table 22: Characteristics of gels formulated with different permeation enhancers

Formulation	Drug content (%)	Viscosity (cPs)	Extrudability (N)	Spreadability (g.cm/sec.)	pH
GP1	99.39	1100	15.89	29.06	7.32
GP2	99.54	1673	16.06	32.05	7.25
GP3	99.79	1010	15.74	33.78	7.14
GP4	99.97	993	16.46	32.46	7.23

Table 23: Diffusion Data of Glipizide From Transdermal Gels Containing Various Permeation Enhancers Through Eudragit RLPO Films

	Amount of glipizide diffused (mg) X ± s d			
Time (h)	P1	P2	P3	P4
0	0	0	0	0
0.5	0.405±0.02	0.375±0.05	0.345±0.05	0.315±0.06
1	0.822±0.06	0.760±0.06	0.698±0.03	0.636±0.08
1.5	1.160±0.05	1.034±0.0	1.968±0.09	0.977±0.09
2	1.562±0.07	1.428±0.03	1.298±0.02	1.248±0.04
2.5	2.001±60.06	1.814±0.04	1.661±0.04	1.563±0.06
3	2.433±0.02	2.235±0.06	2.013±0.06	1.924±0.04

Table 24: Correlation coefficient of Glipizide From Transdermal Gels Containing Various Permeation Enhancers Through Eudragit RLPO Films

Formulation	Correlation coefficient (r) values		Rate constant value (mg/h) (k)	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

Table 25: Permeability coefficient values of glipizide from various transdermal gels containing various permeation enhancers through eudragit RLPO films

Permeation Enhancers	Permeability Coefficient ($Pmx10^4$ Mg/Cm.H)
P1	6.177
P2	5.638
P3	5.099
P4	4.884

Table 26: Physicochemical Properties of Gel (GP1) at 37°C Temperature

S.No	Parameter	0	1	2	3	4	5	6
1	Drug content (%)	99.68	99.40	99.24	99.08	98.92	98.76	98.64
2	Viscosity (cps)	1085	1079	1072	1069	1064	1058	1051
3	pH	7.47	7.45	7.41	7.39	7.36	7.32	7.29
4	Spreadability (g.cm/sec)	29.46	29.38	29.34	29.28	29.26	29.23	29.21
5	Extrudability (N)	17.78	17.67	17.65	17.62	17.59	17.55	17.51

diffusion exponent of release profiles (slope) for the polymer Eudragit RS100, RL100 AND RLPO has a value of 1.033-1.061; 1.047-1.093, and 1.044-1.077 respectively. Permeability coefficient values of the films towards the Glipizide (Table 8, Table 12, Table 17, Table 24 and Table 25).

Gel formulations prepared with NaCMC, MC, and Na Alginate were found to be off-white and homogenous (Table 18). Drug content integrity of your formulations have been well in the range between 98.48-99.97 %. The pH of all formulations have been around the skin pH 7.12 to 7.60 [Table 22]. It was well tried so the gel formulations displayed to good extrudability, and spreadability and the data (Table 22). The *in-vitro* diffusion study of different gels across the Eudragit RLPO films prepared with Ethyl acetate (Table 23). These values proved that the diffusion profiles follow zero-order kinetics and Peppas model (Table 24 and Table 25).

CONCLUSION

The current research indicated that the drug diffusion through Eudragit RLPO films was higher than Eudragit RS100and Eudragit RL100 films. Among all the films, Eudragit RLPO films prepared with Ethyl acetate proved high Permeability in comparison to abundant sort out films. These results indicated that the non-ionic surfactant Tween 20 improves the permeability characteristics of Glipizide compared to the opposite permeation enhancers used in the study.

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Conflict of Interest

The authors attest that they have no conflict of interest in this study.

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