ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 6, Suppl 5, 2013

ISSN - 0974-2441

Research Article

EFFECT OF CHEMICAL ENHANCERS ON THE RELEASE OF GLIPIZIDE IN A MATRIX DISPERSION TRANSDERMAL SYSTEM

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Received: 21 August 2013, Revised and Accepted: 17 September 2013

ABSTRACT

Glipizide is one of the most commonly prescribed drugs for treatment of type 2 diabetes. Oral therapy with Glipizide comprises problems of bioavailability fluctuations and may be associated with severe hypoglycaemia and gastric disturbances. As a potential for convenient, safe and effective antidiabetic therapy, the rationale of this study is to develop a transdermal delivery system for Glipizide in order to improve its therapeutic efficacy. In the preparation of films, chitosan was used as polymer. Inclusion complex of glipizide with β-Cyclodextrin was formed. The role of different permeation enhancers in the formulation was also studied. The films were characterized for thickness, tensile strength, drug content, moisture uptake, moisture content, and drug release. *In vivo* and skin irritation studies were performed for the optimized film.

Formulation F12 containing Chitosan (1.5% w/v) and combination of permeation enhancers (Oleic acid: ethanol 1:1.5) showed the highest drug content 99.95% and the drug release was 99.39% in a period of 24 hours. The release data fitted into kinetic equations, yielded Higuchi plot and diffusion mechanism of drug release. The physical evaluation indicated the formation of smooth, flexible and translucent films. No skin irritation occurred on rat skin and the infrared studies showed the compatibility of the drug with the formulation excipients. The *ex vivo* study revealed a constant permeation of drug for long period. The best permeation enhancer was F12 (Oleic acid: ethanol 1:1.5). The obtained results indicated the feasibility for transdermal delivery of Glipizide using Chitosan.

Keywords: Glipizide, Diabetes, Transdermal Drug Delivery, β-cyclodextrin, Chitosan, *in vitro* permeation

INTRODUCTION

Diabetes Mellitus (DM) is a major health problem worldwide causing prolonged illness and death [1]. It is a chronic metabolic disorder characterized by high blood glucose level (hyperglycemia) caused due to insulin deficiency or insulin resistance. Most of those diagnosed have type 2 Non Insulin Dependent Diabetes Mellitus (NIDDM) and are usually 45 years of age or older. Studies show that the most important complication of type 2 DM is cardiovascular [2 - 4]. Oral administration of sulphonyl urea drugs have serious problems in maintaining the blood levels of drug and glucose leading to different complications and high inter individual variations [5].

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks mainly poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses. One of the methods most often utilized has been transdermal drug delivery: meaning transport of therapeutic substances through the skin for systemic effect [6].

Glipizide is one of the most commonly prescribed drugs for treatment of type 2 diabetes. It acts by decreasing the amount of sugar made in liver [7]. Oral therapy with Glipizide comprises problems of bioavailability fluctuations and may be associated with severe hypoglycaemia and gastric disturbances. As a potential for convenient, safe and effective antidiabetic therapy, the rationale of this study was to develop a transdermal delivery system for Glipizide. Chitosan was used as the polymer which has film forming ability, bioadhesive and absorption enhancing properties [8]. Aimed at optimizing the drug delivery and circumventing the skin barrier function, inclusion complexation of glipizide with β-CycloDextrin was formed. The physicochemical properties of the prepared films were also investigated [9, 10]. The best formulation of our previous studies (F4, without permeation enhancer), was compared with different permeation enhancers in the formulation, F7 – F13.

MATERIALS AND METHODS

Materials

Glipizide was purchased from Supra Chemicals, (Thane, Mumbai, India). Chitosan was the gift sample from Indian Sea Foods, (Cochin, India). Beta cyclodextrin, Acetic acid, Lactic acid and Propylene glycol were purchased from Yarrow Chemicals, (Mumbai, India). All other chemicals and reagents used were of laboratory or analytical grade.

Methods

Compatibility study

Glipizide and the polymer Chitosan were mixed separately and corresponding pellets were prepared. The FTIR spectra (NICOLET 6700 FTIR, USA) was taken and analysed for any interaction between the drug and the polymer.

Preparation of Glipizide transdermal films

The polymers composition in the transdermal film is given in table 1. Chitosan (1.5% w/v) was dissolved in water containing 2 % w/v of a 1:1 mixture of lactic acid and acetic acid solution and stirred overnight using a magnetic stirrer. The resulting solution was filtered through a muslin cloth to remove the extraneous matter. The resulting solution was medicated with the glipizide followed by sonication for 2 hours. The mixtures were then casted on glass moulds and dried in an incubator at 25°C for 24 hours. The mixture was spread uniformly. After drying, the films were carefully peeled off. The films were stored in tight glass containers maintained at room temperature until further investigations.

Table 1: It shows the formulae used for the preparation of Glipizide TDDS

Sl.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Glipizide	750mg	750mg	750mg	750mg	750mg	750mg
2	Chitosan	0.5%w/v	0.5%w/v	1%w/v	1.5%w/v	2%w/v	2.5%w/v
3	β-cyclodextrin	-----	750mg	750mg	750mg	750mg	750mg
4	Lactic acid	2%w/v	2% w/v	2% w/v	2% w/v	2% w/v	2% w/v
5	Acetic acid	2% w/v	2% w/v	2% w/v	2%	2% w/v	2% w/v
6	Propylene glycol	30%w/w of polymer	30%w/w of polymer	30%w/w of polymer	30%w/w of polymer	30%w/w of polymer	30%w/w of polymer
7	SLS	----	----	----	----	----	----
8	DMSO	----	----	----	----	----	----
9	Urea	----	----	----	----	----	----
10	Oleic acid	----	----	----	----	----	----
11	Ethanol	----	----	----	----	----	----
12	Water	Upto 50ml	Upto 50ml	Upto 50ml	Upto 50ml	Upto 50ml	Upto 50ml

Preparation of the Glipizide - β -CyD Inclusion Complex

Inclusion complex of Glipizide in β -CyD was prepared by kneading method, whereby Glipizide was added to the β-CyD in a molar ratio equivalent to its corresponding stoichiometric ratio in the complex (1:1), kneaded thoroughly with least amount of water to obtain a paste which was then dried under vacuum at room temperature in presence of phosphorus pentoxide as a drying agent [11].

Preparation of TDDS Containing Glipizide - β -CyD Inclusion Complex

Chitosan in varying quantities was dissolved in water containing 2 % w/v of a 1:1 mixture of lactic acid and acetic acid solution and stirred overnight using a magnetic stirrer. The resulting solution was filtered through a muslin cloth to remove the extraneous matter. The resulting solution was medicated with the equivalent amount of Glipizide-β-CyD complex followed by sonication for 2 hours. Permeation enhancers were added at this step in the corresponding concentrations followed by sonication for 1 hour shown in Table 2.

Table 2: It shows the formulae for the preparation of Glipizide TDDS to study the enhancing effect of different permeation enhancers

Sl. No	Ingredients	F7	F8	F9	F10	F11	F12	F13
1	Glipizide	750mg	750mg	750mg	750mg	750mg	750mg	750mg
2	Chitosan	1.5%w/v	1.5%w/v	1.5%w/v	1.5%w/v	1.5%w/v	1.5%w/v	1.5%w/v
3	β-cyclodextrin	750mg	750mg	750mg	750mg	750mg	750mg	750mg
4	Lactic acid	2%w/v	2% w/v	2% w/v	2% w/v	2% w/v	2% w/v	2% w/v
5	Acetic acid	2% w/v	2% w/v	2% w/v	2%	2% w/v	2% w/v	2% w/v
6	Propylene glycol	30% w/w of polymer	30% w/w of polymer	30% w/w of polymer	30% w/w of polymer	30% w/w of polymer	30% w/w of polymer	30% w/w of polymer
7	SLS	10%w/w of drug	----	----	----	----	----	----
8	DMSO	----	10%w/w of drug	----	----	----	----	----
9	Urea	----	----	10%w/w of drug	----	----	----	----
10	Oleic acid	----	----	----	10%w/w of drug	10%w/w of drug	10%w/w of drug	10%w/w of drug
11	Ethanol	----	----	----	10%w/w of drug	5%w/w of drug	15%w/w of drug	20%w/w of drug
12	Water	Upto50ml	Upto50ml	Upto50ml	Upto50ml	Upto 50ml	Upto50ml	Upto 50ml

The mixtures were then casted on glass moulds and dried in an incubator at 25°C for 24 hours [12]. The mixture was spread uniformly. After drying, the films were carefully peeled off. The films were stored in tight glass containers maintained at room temperature.

Characterization of Glipizide Transdermal films

Thickness

The thickness of the films was measured using screw gauge with a least count of 0.01 mm at different spots of the films and average was taken and SEM was calculated [13].

Folding Endurance

Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gave the value of folding endurance [13].

Percentage of Moisture Content

The films were weighed individually and kept in desiccator containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight [13].

Percentage of Moisture Uptake

The weighed film kept in desiccator at room temperature for 24 hrs was taken out and exposed to 84% relative humidity (a saturated solution of ammonium chloride) in a desiccator until a constant weight of the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [13].

Drug Content Analysis

The films (n = 6) of specified area were taken into a 100 ml volumetric flask and dissolved in 10 ml water containing 2 % w/v of a 1:1 mixture of lactic acid and acetic acid solution and volume was made up with PBS pH 7.4. Subsequent dilutions were made and analyzed by UV spectrophotometer at 275.6 nm.

Tensile Strength

The films were cut into strips of 1cm width and 8cm length. The films were fixed onto the Tensile strength apparatus in such a way that the length of film between the jaws was initially 4 cm. The trials where the breakage occurred at the jaw were invalid and the result was repeated on another strip. The Tensile strength was calculated by the formula,

$$\text{Tensile strength} = \frac{\text{Break force } (1+\text{change in length})}{(\text{Width})(\text{Breadth})(\text{Initial length of the film})}$$

The percent elongation was determined by noting the length just before the break point and substituting in the formula

$$\% \text{ Elongation} = \frac{(\text{Final length} - \text{Initial length}) \times 100}{\text{Initial length}}$$

The three disks of 2×2 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and to check the batch- to- batch variation.

***In vitro* drug release study**

Chitosan films, of 2×2 cm^2 surface area were applied on a glass slide and covered with stainless steel mesh screen and clamped together. The assembly was placed at the bottom of the USP dissolution tester. The release studies were carried out according to the paddle method [14]. The height of the paddle from the surface of the assembly was adjusted to 2.5 cm. The vessel contained 900 ml PBS (pH=7.4), the temperature was adjusted at 32 °C and the speed was fixed at 50 rpm. Aliquots of 5ml were withdrawn from the release medium at each time interval through sintered glass filter and replaced by equivalent amounts of the buffer solution. The amount of drug released from the patch was determined spectrophotometrically at 275.6 nm using Shimadzu UV Spectrophotometer (2401/PC), Japan.

Kinetic Data Analysis

Zero order model: Data obtained from *in vitro* drug release studies were plotted as cumulative percentage of drug released versus time [15].

First Order model: Data obtained were plotted as log cumulative percentage of drug remaining versus time.

Higuchi model: Data obtained were plotted as cumulative percentage drug release versus square root of time.

***Ex vivo* Permeation Studies through Full Thickness Rat Abdominal Skin**

The abdominal hair of male Wistar albino rats (200 to 250 g) was removed carefully using electric razors. After the animals were sacrificed, the abdominal skin was excised and the adhering fat eliminated. The whole skin was equilibrated in PBS (pH = 7.4) for 1 hr before the beginning of each experiment. The skin used was of thickness 0.8 ± 0.05 mm. Skin was mounted on vertical Franz-type diffusion cell with the dermis facing the receptor compartment, while the donor side was charged with the medicated film. The jacketed cells were circulated with thermostated water maintained at 37°C. Samples of receptor fluid (1ml) were withdrawn periodically, up to 24 hours, and replenished with fresh buffer solution. Steady-state flux was estimated from the slope of the straight-line portion of the cumulative amount of drug permeated against time profiles [14, 16]. Permission was obtained from the institutional animal ethical committee held for these experiments (Registration code SDCP/IAEC-13/2010-11).

Skin Irritation Studies

A primary skin irritation test was performed since skin is a vital organ through which drug is transported. The test was carried out on 6 healthy rats weighing 1.5 to 2.0 kg and age around 24 months. Best Formulation (F12) was subjected to the study; the plain polymer film was used as control. The dorsal surface of the rat was cleared and hairs were removed by shaving. The skin was cleaned with rectified spirit. The films were placed over skin with the help of adhesive tape. The films were removed after 24hrs and the skin was examined for erythema and oedema.

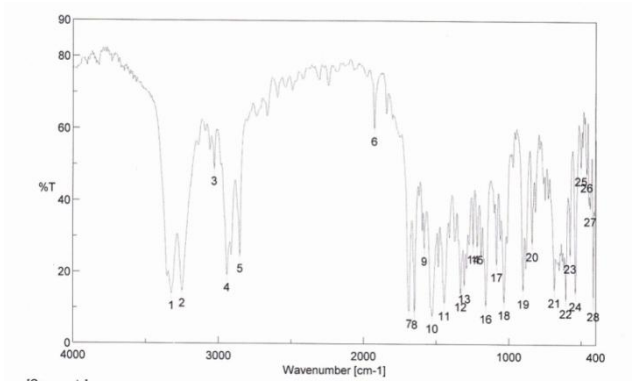
Statistical analysis of data

Data were expressed as mean±S.D. Statistical evaluation was performed by one-way analysis of variance (ANOVA) at a significance level of $p<0.05$ by Dunnett's multiple comparison test using GraphPad Prism software version 4.03.

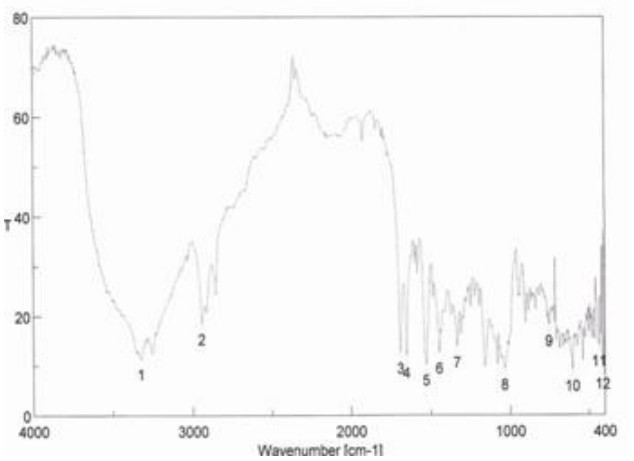
RESULTS

Compatibility studies

The FTIR spectra of the samples are shown in figure 1.



(A)



(B)

Figure 1: It shows the FTIR Spectrum of Glipizide (A), Formulation (B)

The principal peaks of the drug observed in all the samples showed no chemical interaction between the drug and the polymers. However, some additional peaks were observed due to the presence of polymers. The polymers employed are commonly used in matrix-type films and are compatible with a number of drugs. There were no changes in the major peaks of Glipizide in the presence of chitosan and β-CyD. So the drug and the excipients are compatible with each other.

Preparation and Physicochemical characterization of Glipizide transdermal films

Formulation F4 was the best formulation among the batch of films prepared without permeation enhancer. F4 was used as the control in our studies, with permeation enhancers. The film preparation method yielded translucent flexible films that did not become brittle over time. Chitosan 1.5% w/v with permeation enhancer Oleic acid: Ethanol (1:1.5) had the best drug content of 99.95%, shown in Table 3.

Table 3: It shows the physicochemical properties of Glipizide Transdermal films

Formulation Code	Percentage moisture content	Percentage moisture uptake	Percentage drug content
F1	2.89±0.745	1.42±0.005	86.60±15.39
F2	2.85±0.212	1.64±0.014	93.28±1.964
F3	3.18±0.008	2.96±0.128	94.82±0.754
F4	3.15±0.442	1.81±0.091	97.65±0.154
F5	4.20±0.637	3.14±0.725	96.08±0.529
F6	4.32±0.842	2.93±0.452	95.91±0.827
F7	3.56±0.174	1.56±0.908	97.93±1.081
F8	3.13±0.529	2.10±0.419	98.14±0.637
F9	3.40±0.263	1.76±0.529	97.65±0.418
F10	3.63±0.680	2.35±0.219	99.23±0.842
F11	4.28±0.938	2.08±0.349	98.02±0.547
F12	3.01±0.719	2.56±0.419	99.95±0.294
F13	4.56±0.963	1.93±0.716	98.54±0.108

Values are mean±S.D (n = 6)

The plasticizer propylene glycol was able to produce flexible films without any influence on drug release property. The thickness of the films was measured by using a screw gauge at five different positions. The average readings along with standard deviation are given in Table 4. The films prepared were thin, and flexible with almost uniform thickness. The weight variation was found to be in the range of 189.372±0.852 to 192.327±0.583.

Table 4: It shows the physicochemical properties of Glipizide Transdermal Films

Formulation	Thickness (mm)	Weight variation (mg)	Folding Endurance (No's)	Tensile strength (MPa)	% elongation
F1	0.291±0.008	184.341±0.572	231.663±3.528	8.24±0.034	68.02±0.571
F2	0.286±0.014	181.813±0.041	228.051±2.729	7.19±0.087	63.91±0.416
F3	0.349±0.011	185.674±0.964	330.342±5.333	9.42±0.017	71.28±0.284
F4	0.424±0.047	190.517±0.128	432.715±1.527	11.82±0.051	83.14±0.639
F5	0.481±0.092	192.135±0.291	451.284±3.366	14.08±0.182	94.03±0.253
F6	0.521±0.038	195.247±0.104	480.552±1.928	15.27±0.069	96.52±0.962
F7	0.421±0.025	189.372±0.852	429.721±6.228	12.08±0.027	87.29±0.413
F8	0.437±0.061	191.254±0.638	430.527±5.281	11.47±0.073	86.31±0.851
F9	0.428±0.020	190.309±0.462	417.857±3.842	11.93±0.056	86.96±172
F10	0.441±0.271	192.327±0.583	425.364±2.851	12.62±0.024	89.39±0.738
F11	0.402±0.097	191.591±0.171	411.439±6.813	13.93±0.009	90.36±0.164
F12	0.412±0.072	190.937±0.634	420.651±2.843	12.52±0.146	88.67±0.172
F13	0.432±0.022	189.538±0.395	415.865±5.492	13.61±0.085	89.96±0.114

Values are mean±S.D (n = 6)

Folding endurance test results indicated that the films would not break and would maintain their integrity with general skin folding when applied.

Table 5: It shows the *In Vitro* Drug Release Studies of Formulations F2 to F6

Time in Hours	% CDR				
	F2	F3	F4	F5	F6
0	0	0	0	0	0
1	9.85±0.410	7.56±0.163	6.52±0.177	5.39±0.481	4.12±0.253
2	18.29±0.523	13.18±0.212	11.96±0.452	9.63±0.023	8.59±0.173
3	26.34±0.429	21.81±0.121	18.72±0.646	14.27±0.185	11.92±0.429
4	36.29±0.312	26.42±0.293	25.02±0.124	21.38±0.096	17.63±0.391
5	45.84±0.152	33.29±0.350	30.87±0.372	26.26±0.281	22.15±0.276
6	53.36±0.509	40.71±0.641	36.41±0.363	30.03±0.185	27.48±0.384
7	64.19±0.284	48.64±0.521	41.29±0.129	36.33±0.471	32.66±0.246
8	73.81±0.221	55.43±0.120	48.27±0.279	40.57±0.074	37.71±0.560
9	81.53±0.535	62.09±0.414	54.63±0.272	46.01±0.174	43.05±0.293
10	91.96±0.480	69.91±0.342	61.14±0.312	52.16±0.141	48.27±0.297
11	99.38±0.172	76.83±0.574	66.91±0.153	58.59±0.264	52.39±0.529
12		83.94±0.351	72.38±0.472	64.29±0.359	56.56±0.193
24		99.85±0.221	96.17±0.396	89.08±0.419	77.25±0.281

The values are expressed in mean ± S.D. No significant difference was observed at $p<0.05$, one way ANOVA followed by Dunnett's multiple comparison test.

Table 6: It shows the In *vitro* Drug Release Studies of Formulations F7 to F13

Time in hours	% CDR						
	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0
1	6.91±0.128	7.24±0.245	6.52±0.174	8.13±0.185	7.19±0.193	8.56±0.228	7.90±0.367
2	12.39±0.159	13.19±0.462	11.99±0.142	15.58±0.196	12.82±0.732	16.18±0.428	13.72±0.328
3	19.24±0.128	20.53±0.195	19.11±0.196	22.39±0.140	19.39±0.163	22.90±0.429	21.63±0.142
4	25.69±0132	26.30±0.185	25.23±0.196	26.89±0.553	25.40±0.543	26.31±0.192	25.39±0.527
5	31.29±0.126	31.78±0.428	31.25±0.328	33.59±0.729	30.52±0.429	34.93±0.452	32.52±0.274
6	35.28±0.852	36.93±0.193	36.91±0.196	37.42±0.742	35.63±0.729	38.15±0.197	36.71±0.021
7	42.08±0.952	43.87±0.145	41.59±0.254	44.96±1.352	43.93±0.963	42.39±0.284	44.57±0.085
8	49.36±0.147	50.61±0.125	49.07±0.196	50.59±0.296	50.09±0.833	50.72±0.096	49.67±0.282
9	54.96±0.123	55.91±0.198	53.93±0.296	56.27±0.139	55.61±0.963	57.11±0.285	55.14±0.180
10	62.58±0.363	63.09±0.543	61.51±0.428	63.91±0.824	61.11±0.572	63.29±0.741	63.04±0.394
11	67.75±0.182	68.39±0.458	67.01±0.196	70.13±0.192	66.29±0.273	71.85±0.652	69.37±0.630
12	72.91±0.174	73.10±0.182	72.88±0.732	75.22±0.429	72.17±0.429	77.41±0.639	73.29±0.149
24	97.35±0.429	98.41±0.124	97.22±0.193	98.97±0.182	97.23±0.719	99.39±0.125	98.59±0.277

The values are expressed in mean ± S.D. No significant difference was observed at $p<0.05$, one way ANOVA followed by Dunnett's multiple comparison test.

F12 had 99.39% release at the end of 24 hours, in a controlled manner. Oleic acid: Ethanol (1:1.5) ratio was used in the formulation F12, proving to be the best permeation enhancer in our studies. In order to find out the mechanism of drug release, the *in vitro* drug release data was fit into different equations and kinetic models to explain the release kinetics of Glipizide from transdermal patch. The kinetic models used were zero order equation, first order equation and Higuchi model. The release profiles of drug seemed to follow Higuchi model as it was evidenced by correlation coefficients ($r^2 = 0.950$) better than zero order ($r^2 = 0.907$) and first order ($r^2 = 0.895$) given in Figure 2.

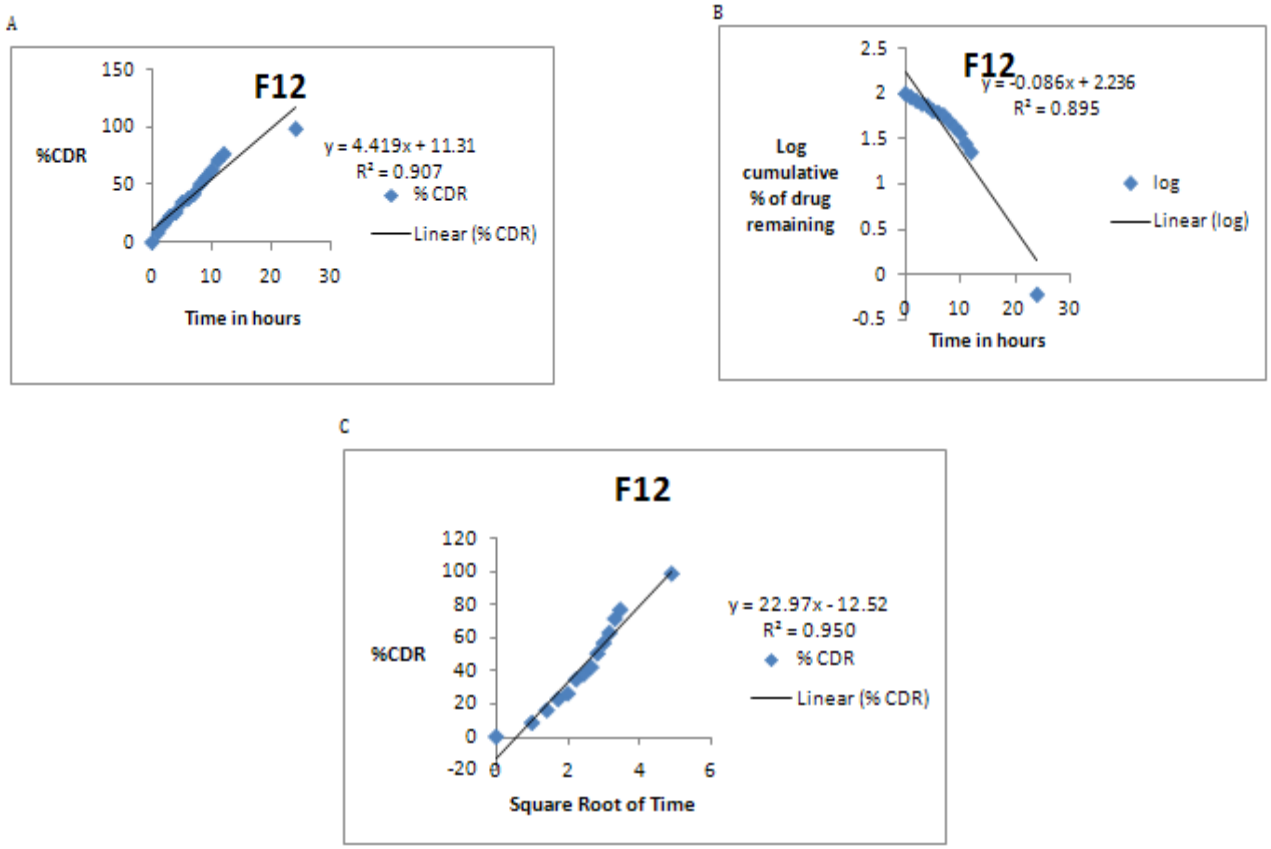


Figure 2: It shows graphical representation of Kinetic models for the best formulation (F12) based on *in vitro* release profile (A) Zero order (B) First order (C) Higuchi plot

Ex vivo permeation and Irritation studies

In 24 hours of study 87.36% of drug permeated the rat membrane. Formulation F4 which had no permeation enhancer resulted in 53.12% permeation. This clearly demonstrates the need for permeation enhancers to achieve better permeation. The effect of permeation enhancers is shown in Table 7.

Table 7: It shows enhancing effects of different permeation enhancers

Time (Hrs)	% drug permeated							
	F4	F7	F8	F9	F10	F11	F12	F13
0	0		0		0	0	0	0
1	3.69±0.855		5.13±0.852		5.24±0.753	3.16±0.213	6.53±0.963	5.85±0.252
2	6.51±0.155		9.41±0.743		10.72±0.951	6.52±0.185	11.30±0.240	10.48±0.234
3	10.72±0.984		14.28±0.951		14.70±0.369	11.29±0.147	15.92±0.285	14.19±0.213
4	13.64±724		19.29±0.360		19.52±0.347	15.18±0.258	20.23±0.128	19.31±0.125
5	17.02±373		23.71±0.286		24.85±0.1659	20.39±0.136	25.39±0.142	23.99±0.185
6	20.61±0.481		29.95±0.174		30.87±0.257	27.15±0.145	31.85±0.125	26.67±0.174
7	24.52±0.515		35.12±0.396		35.93±0.353	32.82±0.258	37.17±0.112	35.63±0.852
8	28.71±0.651		41.25±0.197		41.74±0.275	38.19±0.295	43.38±0.124	42.10±0.752
9	32.08±0.182		46.32±0.285		47.29±0.196	42.13±0.157	49.53±0.369	48.47±0.174
10	36.43±0.449		50.18±0.147		52.81±0.352	45.61±0.324	54.08±0.185	53.39±0.746
11	40.19±0.187		55.17±0.196		58.43±0.315	49.20±0.152	59.62±0.301	58.61±0.585
12	45.28±0.856		60.39±0.254		64.09±0.296	53.61±0.129	66.63±0.247	60.36±0.529
24	53.12±0.720		73.65±0.147		80.62±0.215	75.08±0.132	87.36±0.239	78.91±0.288

Best formulation F12 was subjected to skin irritation test in six healthy rats and plain polymer film was used as the control. The films were removed after 24 hours and the skin had no symptoms of erythema and oedema. The results of skin irritation studies indicated that neither the blank patch nor the drug incorporated patch caused any noticeable irritation on the rat skin throughout the study.

DISCUSSION

There were no changes in the major peaks of Glipizide in the presence of chitosan and β-CyD. So the drug and the excipients are compatible with each other. Prepared films were thin, flexible, smooth, and transparent. From the physicochemical evaluation data of the films, it is evident that there was no physical change like appearance, colour, and flexibility when the films were stored at room temperature. F1 shows large variation in the percentage drug content. This is because F1 contains only Glipizide which is insoluble in water. Due to this large variation, in the further formulations Glipizide was used with β-CyD as inclusion complex. So the other formulation (F2 to F13) does not show large variations in the drug content. From the graphical study F4 was selected as the best formulation and so the remaining studies (effect of penetration enhancers) was proceeded with the same formulation, by adding different penetration enhancers.

F10 which contains oleic acid in the ratio 1:1 showed highest release rate as compared to the other formulations. So to optimize this formula again three formulations were prepared by varying the ratio of oleic acid and ethanol (1:0.5, 1:1.5, 1:2 for F11, F12, F13) respectively. Among these formulations, F12 showed the highest release rate compared to F11 and F13. The increased release rate is due to the presence of ethanol.

Use of penetration enhancers characteristically increases the permeation rate of the drug through stratum corneum. F12 showed high flux (0.083±0.024) due to the mutual effect of oleic acid and ethanol. The results of skin irritation studies indicated that neither the blank patch nor the drug incorporated patch caused any noticeable irritation on the rat skin throughout the study. Hence, the transdermal patches were free of skin irritation.

Based on the results of our study, it can be concluded that a well-controlled release and effective skin permeation of the drug was achieved by the film F12. The order of permeation enhancement of Glipizide through stratum corneum was found to be Oleic acid:ethanol (1:1.5) > Oleic acid:ethanol (1:1) Oleic acid:ethanol(1:2) > Oleic acid:ethanol (1:0.5) > DMSO > SLS > Urea. However, to establish the therapeutic efficacy of this formulation, pharmacokinetic studies in humans need to be conducted.

ACKNOWLEDGEMENT

The authors are grateful to Shree Devi Education Trust, Mangalore, India for providing the necessary facilities to carry out the Research work.

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