Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2013, 5 (3):278-286
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Development of matrix dispersion transdermal therapeutic system containing glipizide

Sundara Raj Behin[1*], Isaac Samraj Punitha[2] and Fels Saju[3]

[1]Department of Pharmaceutics, Shree Devi college of Pharmacy, Airport Road, Kenjar, Mangalore, Karnataka
[2]Department of Pharmacognosy, Shree Devi college of Pharmacy, Airport Road, Kenjar, Mangalore, Karnataka
[3]Department of Pharmaceutics, Nirmala College of Pharmacy, Muvattupuzha, Ernakulam, Kerala

---

ABSTRACT

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. 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 inorder to improve its therapeutic efficacy. In the preparation of films, chitosan was used as polymer. Inclusion complex of glipizide with β-Cyclodextrin was formed and compared with the control (F1).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. Films containing Chitosan (1.5% w/v) showed the highest drug content 97.65% and the drug release was 96% in a period of 24 hours. The values of thickness, weight variation, and folding endurance of the prepared formulations shows highest values as the polymer concentration increases.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 periods.The obtained results indicated the feasibility for transdermal delivery of Glipizide using Chitosan.

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

---

INTRODUCTION

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 [1].

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by high blood glucose level (hyperglycemia) caused due to insulin deficiency or insulin resistance [2]. Most of those diagnosed have type 2 Non Insulin Depedent 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 [3,4,5]. 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 [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 is to develop a transdermal delivery system for Glipizide. Chitosan is 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].

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 (0.5% 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: Formulae for the preparation of Glipizide TDDS

S. 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	Water	Upto 50ml	Upto 50ml	Upto 50ml	Upto 50ml	Upto 50ml	Upto 50ml

Preparation of the Glipizide - β -CyD Inclusion Complex [11]
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.

Preparation of TDDS Containing Glipizide - β -CyD Inclusion Complex [12]
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. The mixtures were then casted on glass moulds and dried in an incubator at 25℃ 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.

Characterization of Glipizide Transdermal films [13]
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.
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.

Percentage of Moisture Content
The films were weighed individually and kept in dessicators 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.

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

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 the formula

$$\% \text{ Elongation} = \frac{[\text{Final length} - \text{Initial length}] \times 100}{\text{Initial length}}$$

Weight variation

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 thus check the batch- to- batch variation.

***In vitro* drug release study** [14]

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. 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 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 [15]

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

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** [14,16]

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. 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 (F4) 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

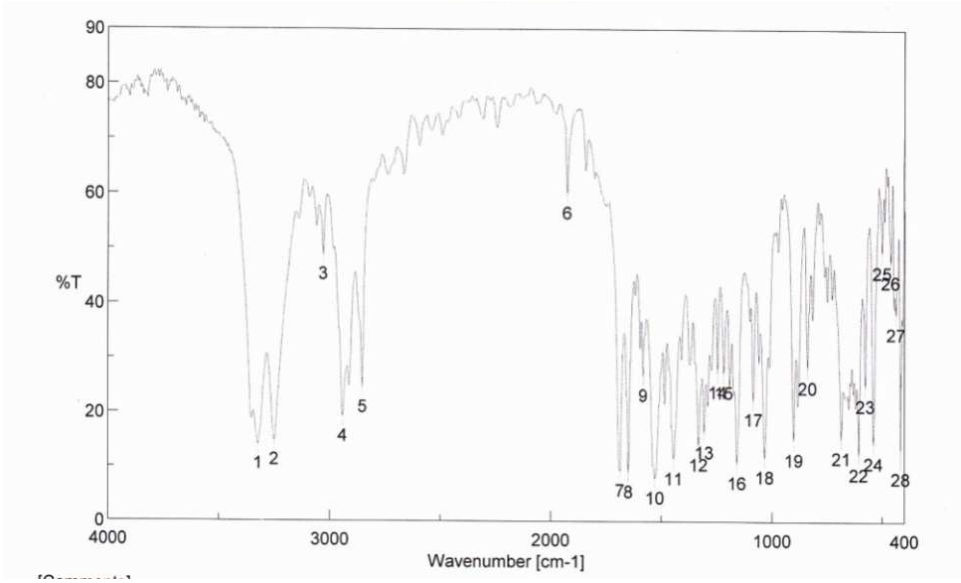
Data were expressed as mean±S.D. Statistical evaluation was performed by one-way analysis of variance (ANOVA) at a significance level of $p<0.05$ by Dunnett's multiple comparison test using GraphPad Prism software version 4.03.

RESULTS

Compatibility studies

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

A



B

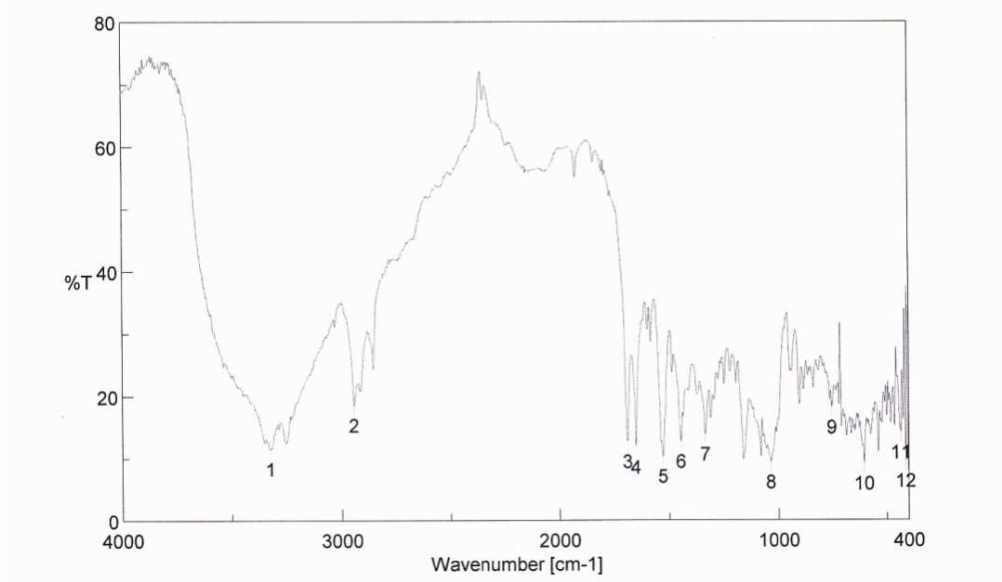


Figure 1: FTIR Spectrum of Glipizide (A), Fomulation (B)

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.

Preparation and Physicochemical characterization of Glipizide transdermal films

The film preparation method yielded translucent flexible films that did not become brittle over time. Chitosan at 1.5% w/v had the best drug content of 97.65% (table 2).

Table 2: 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

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 3.

Table 3: 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

Values are mean±S.D (n = 6)

The films prepared were thin, and flexible with almost uniform thickness. The weight variation was found to be in the range of 181.813±0.041 to 195.247±0.104. Folding endurance test results indicated that the films would not break and would maintain their integrity with general skin folding when applied.

In vitro Drug Release Studies

Results of *in vitro* release are shown in table 4.

Table 4: *In Vitro* Drug Release Studies of Formulations F2 to F6

Time in Hour	% 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

Release studies were performed in formulations F2 to F6 and formulation F1 had only Glipizide which is insoluble in water, hence it was not selected for the study. F2 had 99% release at the end of 11 hours, which relates to the low content of chitosan (0.5 % w/v). F4 had the best control release of 96.17% over a period of 24 hours, which had the optimum content of chitosan (1.5% w/v). Further increase in polymer had affected the release property of the drug in F5 and F6 (figure 2).

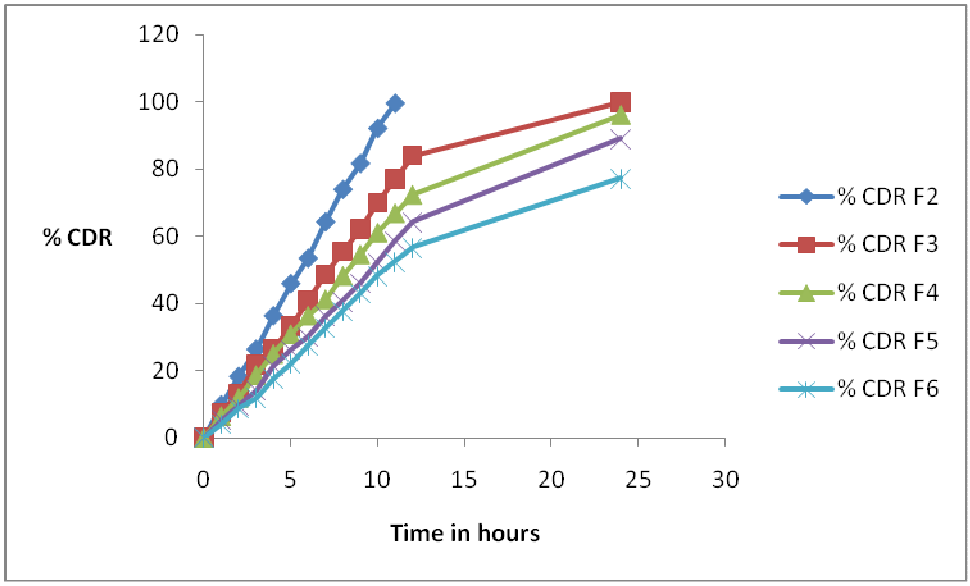


Figure 2: *In vitro* drug release of Glipizide transdermal films F2-F6. The values are expressed in mean ± S.D. No significant difference was observed at p>0.05, one way ANOVA followed by Dunnett's multiple comparison test.

Ex vivo permeation and Irritation studies

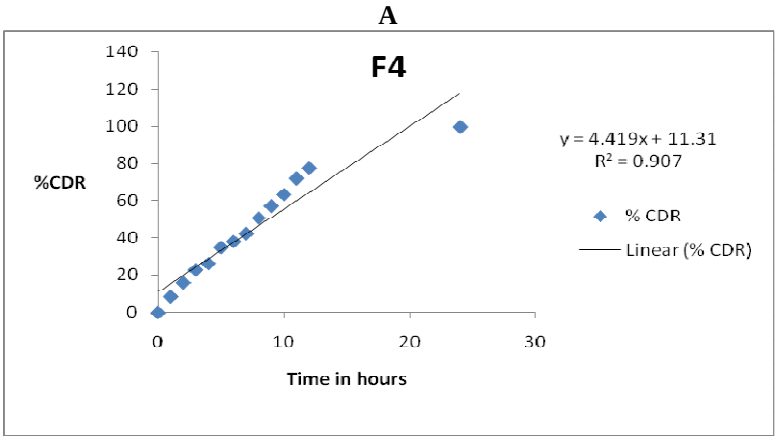
Permeation was studied for the best formulation F4. In 24 hours of study 53.12% of drug permeated the rat membrane. Best formulation F4 was subjected to skin irritation test in six healthy rats and plain polymer film was used as the control. The films were removed after 24 hours and the skin had no symptoms of erythema and oedema (table 5).

Table 5: Skin Irritation Studies of F4

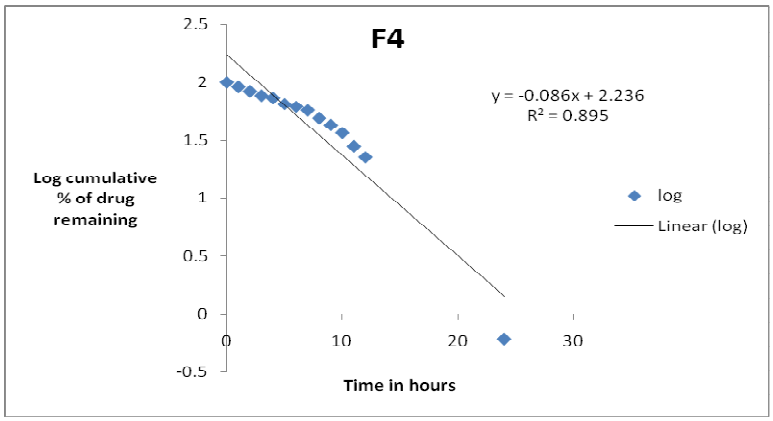
Category	Condition	Score obtained (n=6)
Control	Erythema	0
	Oedema	0
Test	Erythema	0
	Oedema	0

Kinetic Analysis

The mechanism of drug release closely followed Higuchi Model, data obtained were plotted as cumulative percentage drug release versus square root of time and the mechanism of drug release was diffusion (figure 3).



B



C

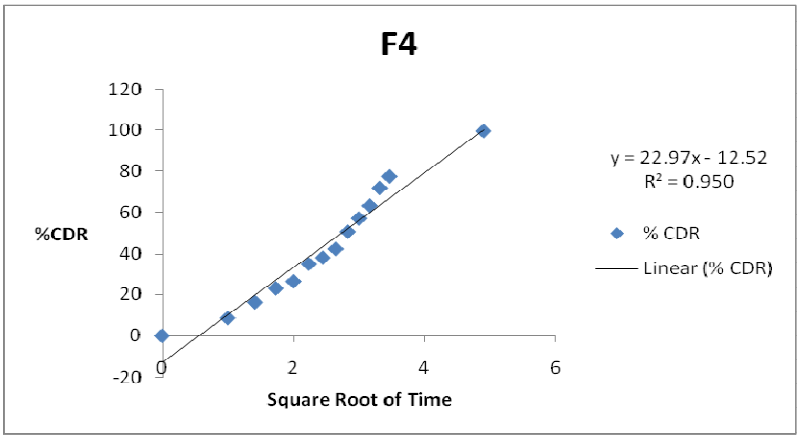


Figure 3: Graphical representation of Kinetic models for the best formulation (F4) based on *in vitro* release profile (A) Zero order (B) First order (C) Higuchi plot

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. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage. Similarly the moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduce bulkiness.

The study revealed that the percentage drug released from the chitosan film comprising Glipizide was inadequate. The release rate values revealed that complexation of the drug within β-CyD increases the release rate from the formulations. F2 shows 99.38% drug release at 11hr. All the other formulations show controlled release of drug. F6 shows the least drug release because of the increased amount of chitosan. In order to find out the mechanism of drug release, the *in vitro* drug release data was graphically treated according to Higuchi's equation. Correlation value of Higuchi's plot revealed that the mechanism of drug release is diffusion. The results of skin irritation studies indicated that neither the blank patch nor the drug incorporated patch caused any noticeable irritation on the rabbit skin throughout the study.

CONCLUSION

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 F4 (Chitosan 1.5%w/v) for extended periods of time. However, to establish the therapeutic efficacy of this formulation, pharmacokinetic studies in humans needs to be conducted.

Acknowledgement
The authors are thankful to Principal, Management and Staff of Shree Devi College of Pharmacy, Mangalore, Karnataka for providing the facilities.

REFERENCES

[1] Sankar. V, Benito Johnson D, Sivanand V, Ravichandran V, Raghuraman V, Rajasekhar S. *Ind J Pharma Sci*., **2003**, 65(5),510-5.
[2] Diabetes mellitus: diabetes.co.in. [cited **2011** Nov 29].
[3] Type 2 Diabetes mellitus treatment and management: emedicine.medscape.com/article/117853-treatment [cited **2011** Nov 29].
[4] Tripathi KD. Essentials of medical pharmacology. Jaypee Brothers Medical Publishers., **2010**, 254-55, 62-63, 70-72.
[5] Diabetesmellitus: en.wikipedia.org/wiki/Diabetes_mellitus [cited **2011** Sept 16].
[6] Shankar. S.J, Varalakshmi C, Patel R, Manoj K. *IJPRD*., **2011**, 3(4), 131 – 138.
[7] Brunton. LL, Lazo. J, Parker. K.L. Goodman & Gilman's the pharmacological basis of therapeutics. **2006**,1619-37.
[8] Mutalik. S, Udupa. N, Kumar. S, Agarwal. S. *Life Sci*., **2006**, 79,1568-77.
[9] Abdul Ahad. H, Sreeramulu. J, Hima Bindu. V, Chitta Suresh Kumar, Kumar. K, Reddy B, et al.. *J Pharm Res.*, **2010**,3(7),1583-86.
[10] Vaseeha Banu. T.S, Som. S, Khaleel. M, Nirmal. Havannavar T, *Res J Pharm Bio Chem Sci*, **2010**,412-21.
[11] Bhosale. A.V, Hardikar. S, Jagtap. R.S, Patil, N.B, Sushant. S, Dhawale. S.S.. *Int J Pharm Res*., **2009**, 1(3), 773-8.
[12] Ammar. H.O, Salama, Ghorab. M, Nahas E, Elmotase. H. *Curr Drug Del*., **2006**, 3:333-41.
[13] Bangale. G.S, Rathinaraj.S, Rajesh. K.S, Gajanan. V, Shinde, Deepak. G. *J Chem Pharm Res.*, **2010**, 2(3),593-604.
[14] Ammar. H.O, Salama, Ghorab. M, Nahas. E, Elmotase. H. *Curr Drug Del.*, **2008**, 5(4),290-98.
[15] Bharkatiya. M, Nerma. R.K, Gupta. G.D, Guara. R.S.. *The Pharma Review*., **2005**,3(16),113-14.
[16] Jayachandran. D.L, Krishnamoorthy. M, Jeganath. S, Ashlin V. Sheeja Devi K. *IAJPR*., **2011**,1(4),289-304.