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Original Article

FORMULATION AND EVALUATION OF CARBOPOL 940 BASED GLIBENCLAMIDE TRANSDERMAL GEL

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ABSTRACT

Objective: To investigate the effectiveness of combination of permeation enhancers on the transdermal delivery of Glibenclamide.

Methods: The formulations were subjected to various physiochemical studies and in vitro permeation studies. The influence of β – cyclodextrin on the *in vitro* percutaneous absorption of Glibenclamide (GBM) and its combined effect with propylene glycol (PG) and oleic acid (OA) was studied using Franz-type diffusion cell using a cellophane membrane. The receiver solution was phosphate buffer (pH 7.4). The permeability study was carried out for 12 hours. To increase the aqueous solubility of GBM, it was incorporated as its inclusion complex with β – cyclodextrin. The inclusion complex was thoroughly characterized using techniques, including differential scanning calorimetry and scanning electron microscopy.

Results: The combination of these penetration enhancers synergistically enhanced percutaneous penetration of Glibenclamide gel. During release, data followed the korsmeyer peppas kinetic. It was found that highest flux was obtained by formulation containing 1:2 w/w β – cyclodextrin, 25% propylene glycol and 10% oleic acid during *in vitro* permeation studies.

Conclusion: Transdermal gel formulation containing Glibenclamide can be prepared by direct dispersion method, using Carbopol 940 as a carrier. Combination of penetration enhancers profoundly increases the drug flux to the desired extent. Comparing *in vitro* drug release data, formulation F10 showed better release pattern and physiochemical characteristics and no skin irritation reactions.

Keywords: Glibenclamide, β-cyclodextrin, Propylene glycol, Oleic acid, Skin permeability, Transdermal gel.

INTRODUCTION

Transdermal products are discrete dosage forms and deliver a drug through intact skin at a controlled rate into systemic circulation. Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. An essential prerequisite for the development of TDDS is that the drug must be capable of passing through skin at a sufficiently high rate to achieve therapeutically plasma concentrations. However the outermost layer of skin, stratum corneum (SC) forms a major barrier to most exogenous substances including drugs [1, 2].

The discovery of TDDS is a major breakthrough in the field of controlled drug delivery systems. The ability of TDDS to deliver drugs for systemic effect through intact skin while bypassing first pass hepatic metabolism has accelerated transdermal drug delivery research in pharmaceutics. Glibenclamide (GBM), a sulphonylurea class drug with potent hypoglycaemic action, is widely accepted in the treatment of diabetes mellitus. Until now, the percutaneous administration of GBM has been poorly studied although it seems to have many advantages over other administration routes. The biological properties of Glibenclamide, such as high first pass metabolism, wide blood level oscillations, gastric disturbances, low dose size, need for long term treatment make this drug an interesting candidate for transdermal administration [3]. The present work investigated the effectiveness of inclusion complex of drug with β – cyclodextrin (β – CD), both alone or in combination with propylene glycol (PG) and oleic acid (OA). Cyclodextrins are used in the pharmaceutical field to form inclusion complexes with drug molecules to increase their aqueous solubility or photostability, to mask unwanted characteristics or to reduce side effects [4]. Cyclodextrins are also reported to convey controlled-release properties to certain active ingredients.

OA is found to be an effective enhancer for many drugs. OA interact with stratum corneum (SC) and disrupt their structures, increasing their fluidity and consequently enhances the flux of drug from SC. It has been found that the major mechanism of enhancement of OA is an increase in permeation through the non-polar route, as it increases both diffusivity and partitioning. It also increases the partitioning of drug through polar route by increasing hydration of the stratum corneum [5].

PG was selected as a cosolvent not only to solubilise GBM in the vehicle, but also because it can alter the skin structure, thereby modifying the percutaneous absorption. PG readily permeates the skin and while doing so it may carry some drug molecules across the skin [6]. However, the use of PG in combination with an OA offer synergistic enhancement in drug flux.

MATERIAL AND METHODS

Materials

Glibenclamide (GBM) was kindly provided by USV Pharmaceuticals, Baddi (H.P., India). Carbopol 940 (Loba Chemie Pvt. Ltd. Mumbai), propylene glycol (Hi Media Laboratories Pvt. Ltd., Mumbai) and oleic acid extra pure was purchased from S.D. Fine Chem. Ltd., Mumbai. All other reagents were of commercial purity grade. Distilled water was used throughout the study.

Drug excipients interaction study

While preparing a formulation for the development of final drug dosage form, it is mandatory to confirm about the compatibility between drug, polymer and β - cyclodextrin to be used and to ensure that the drug is not interacting with them. The Fourier Transform Infra – Red (FT- IR) analysis were carried out for qualitative compound identification using Perkin Elmer 1600.

The pellets were prepared on KBr – press (Spectra Lab., India). The spectra were scanned over wave number range of 4000 cm^{-1} – 400 cm^{-1}. Since FT-IR is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds. FT-IR is helpful to confirm the identity of the drug and to detect the interaction of the drug with excipients.

Inclusion Complex formation of Glibenclamide with β – cyclodextrin (β - CD)

As the drug is very slightly soluble in water, its complex was formed with β - CD in weight ratio 1:1, 1:2, 1:3 respectively by kneading method as reported by Rawat S et al [7]. In this method, β - CD was added in mortar, and a small quantity of 50% v/v ethanol was added, while triturating to get slurry like consistency.

Then slowly the drug was incorporated into slurry and trituration was continued further for 1 hr at 75ºC. After that it was dried at 50ºC for one day, crushed and sieved.

Preparation of Glibenclamide gel

The 100 g gel was prepared by direct dispersion method. In this firstly, propyl paraben was dissolved in water at 80ºC and then accurately weighed quantity of carbopol 940 was dispersed in water at 40ºC with constant stirring for 30 min [8]. Accurately weighed quantity of drug for formulation F1 was dissolved in minimum quantity of ethanol and then incorporated in the above prepared solution of carbopol with continuous stirring. In formulations F2-F4 the complex of drug and β – CD in different concentrations was incorporated after dissolving in ethanol. The pH of all gel formulations were adjusted to pH 6, using triethanolamine and stirred slowly until a gel was obtained. From batches F2 – F4, the batch F3 was showing good cumulative release as compared to F2 and F4. So we have selected F3 for further incorporation of different concentrations of propylene glycol.

Finally from above batches F5-F8, batch F7 was selected for further addition of different concentrations of oleic acid as it was showing better cumulative release among other batches in order to get required and satisfactory release of drug.

Table 1: Composition of GBM gel without any permeation enhancer

Formulation Code	F1
Drug	460 mg
Carbopol 940	0.5 % w/w
Propyl paraben	0.01 % w/w
Ethanol	10 ml
Triethanolamine	q.s.
Water	q.s.

Table 2: Composition of GBM gels containing different concentrations of β - cyclodextrin

Formulation Code	F2	F3	F4
Drug: β - cyclodextrin	1: 1 w/w	1: 2 w/w	1: 3 w/w
Carbopol 940	0.5% w/w	0.5% w/w	0.5% w/w
Propyl paraben	0.01%w/w	0.01 % w/w	0.01 % w/w
Ethanol	10 ml	10 ml	10 ml
Triethanolamine	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.

Table 3: Composition of GBM gels containing different concentrations of propylene glycol

Formulations Code	F5	F6	F7	F8
Drug: β - cyclodextrin	1: 2 w/w	1: 2 w/w	1: 2 w/w	1: 2 w/w
Carbopol 940	0.5 % w/w	0.5 % w/w	0.5 % w/w	0.5 % w/w
Propyl paraben	0.01 % w/w	0.01 % w/w	0.01 % w/w	0.01 % w/w
Propylene Glycol	15 % w/w	20 % w/w	25 % w/w	30 % w/w
Ethanol	10 ml	10 ml	10 ml	10 ml
Triethanolamine	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.

Table 4: Composition of GBM gels containing different concentrations of oleic acid

Formulations Code	F9	F10	F11
Drug: β - cyclodextrin	1: 2 w/w	1: 2 w/w	1: 2 w/w
Carbopol 940	0.5 % w/w	0.5 % w/w	0.5 % w/w
Propyl paraben	0.01 % w/w	0.01 % w/w	0.01 % w/w
Propylene Glycol	25 % w/w	25 % w/w	25 % w/w
Oleic acid	5 % w/w	10 % w/w	15 % w/w
Ethanol	10 ml	10 ml	10 ml
Triethanolamine	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.

Physiological evaluation

The pH of gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated.

The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 20 using spindle no. 64 and the corresponding dial reading was noted.

One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load, lesser the time taken for separation of two slides, better the spreadability [9].

Drug Content

The drug content uniformity was determined for all the formulations by UV spectrophotometric method. A 500 mg of Glibenclamide gel was taken and dissolved in 50 ml of methanol. The volumetric flask were kept for 2 hours and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered. The drug content was measured spectrophotometrically at 300 nm against methanol as blank.

Differential scanning calorimetry (DSC)

Prior to DSC analysis, a baseline was obtained which was used as a background. Samples (3–4 mg) were accurately weighed and sealed in aluminium pans and heated at a rate of 5 °C/min. The measurements were performed at a heating range of 40–400°C under a nitrogen purge. A nitrogen flow rate of 20 ml/min was used for DSC run. DSC analyses were performed on GBM, β – CD and on GBM: β – CD complex samples in order to ensure the formation of inclusion complex

In vitro permeation studies

A modified Kehshary-Chein diffusion cell was used for *in-vitro* permeation study. Commercially semi permeable membrane was employed in the study as permeation barrier. The diffusion cell was fabricated from borosilicate glass and consists of two compartments, receptor and donor, which it has a diffusional surface area of 1.76 cm^2. 0.5 g of the gel was placed on the membrane surface in the donor compartment while the receptor was filled with 5 ml of phosphate buffer (pH 7.4). During the experiments, the receptor solution was stirred at 600 rpm and kept at 37±1 ºC [10, 11].

The amount of drug permeated into the receptor solution was determined by removing 1ml of sample at hourly for 12 hours. The withdrawn volume was replaced with an equal volume of buffer solution. The cumulative amount of drug released as a function of time was determined by spectrophotometrically assaying its concentration in the receptor compartment at fixed intervals. Each experiment was performed at least three times and the results were averaged.

Analysis of permeation data

The kinetics of drug release from Glibenclamide gel formulations during permeation study in phosphate buffer pH 7.4 was determined using zero-order [12], first-order [13], and Higuchi equation [14]. The diffusion data were also fitted to the well-known exponential equation (Korsmeyer–Peppas equation), which is often used to describe the drug release behaviour from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved [15].

To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer Peppas model.

$M_t / M_n = Kt^n$ Eq. 1

Where,

- M_t / M_n is a fraction of drug released at time t
- K is the release rate constant

The n is used to characterize different release for cylindrical shaped matrices.

In this model, the value of n characterizes the release mechanism of drug as described in Table 4.6. For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, n = 0.89 to Case II (relaxational) transport, and $n > 0.89$ to super case II transport. To find out the exponent of relese constant (n), the portion of the release curve, where $M_t / M_\infty < 0.6$ was used. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release [16].

Table 5: Interpretation of Diffusion Release Mechanism from Polymeric Films

Release Exponent (n)	Drug Release Mechanism	Rate as a Function of Time
0.5	Fickian Diffusion	$t^{-0.5}$
0.5 < n > 1.0	Anomalous Transport	t^{n-1}
1.0	Case II Transport	Zero order release
Higher than 1.0	Super Case II Transport	t^{n-1}

Scanning electron microscopy (SEM)

The morphology of samples was determined using scanning electron microscope (SEM) (HITACHI S-3000N, Japan), operated at an accelerating voltage of 20 kV (filament current of 1.75 µA, beam current of 30–40 mA and probe current of 250 pA). Samples were prepared by mounting ~0.5 mg of powder onto a 5 mm × 5 mm silicon wafer affixed via graphite tape to an aluminum stub. The powder was then sputter-coated for 40 s at beam current of 38–42 mA with a 200 Å layer of gold/palladium alloy.

Stability studies

The stability study consists of a series of tests in order to obtain an assurance of stability of a drug product. The optimized gel formulation was stored in well closed stoppard glass container and then stored at 5°C ± 3°C and at 30°C ± 2°C. Physical appearance, content uniformity and drug permeation study data was determined at regular time intervals for 3 months.

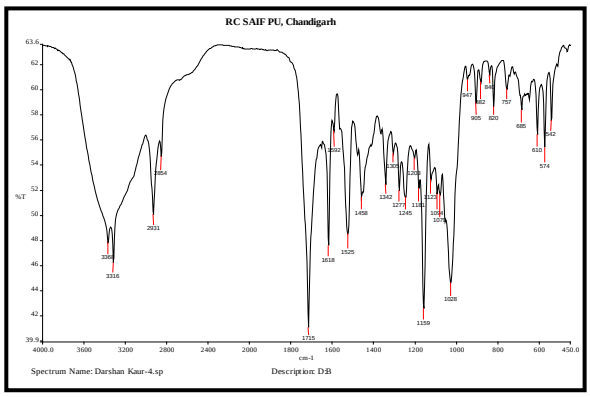

Fig. 1: FT-IR spectra of physical mixture of Glibenclamide, carbopol 940 and β – cyclodextrin

RESULTS AND DISCUSSION

Drug excipients interactions study

The physical mixture of drug containing polymer and β – CD was shown to have peaks at 3316 due to N-H stretching, 2931 due to C-H (aromatic) stretching, 1525 due to C=C stretching, 1715 due to C=O stretching, 1159 due to S=O stretching, 1342 due to C-N (amines) stretching, 1028 due to C-O stretching and at 685 die to C-Cl stretching which are characteristics of Glibenclamide (fig 1).

Physiological evaluation

β - CD and propylene glycol as penetration enhancers have more viscosity than other gel formulations that we have prepared, but it is a satisfactory viscosity which a gel should possess. As we increase the concentration of β – cyclodextrin and propylene glycol in gel formulations the viscosity of gel starts increasing. The spreadability plays an important role in patient compliance and helps in uniform application of gel on the skin. A good gel takes a less time to spread and a gel with high spreadability cant't spread uniformly. The data of pH, viscosity and spreadability is shown in table 6.

Table 6: Physiological data of all batches (n=3)

Formulations	pH	Viscosity (cps)	Spreadability (gm.cm/sec)
F1	7.0 ± 0.10	45695 ± 31.59	13.45 ± 0.34
F2	7.2 ± 0.10	46835 ± 11.32	13.67 ± 0.64
F3	6.9 ± 0.15	47278 ± 7.760	13.28 ± 0.48
F4	6.6 ± 0.15	47879 ± 46.80	12.62 ± 0.57
F5	7.0 ± 0.10	47942 ± 11.06	13.09 ± 0.66
F6	6.9 ± 0.20	48563 ± 39.96	12.76 ± 0.46
F7	6.9 ± 0.15	49028 ± 63.26	12.26 ± 0.38
F8	7.0 ± 0.17	50659 ± 9.500	11.72 ± 0.27
F9	6.9 ± 0.05	48345 ± 28.02	12.43 ± 0.42
F10	7.1 ± 0.10	48682 ± 23.96	12.65 ± 0.32
F11	7.0 ± 0.05	48734 ± 23.18	12.89 ± 0.41

Drug Content

The result of drug content varies between as shown in table 7. The results indicated that process employed to prepare gel formulations in this study was capable of producing gel formulation with uniform drug content and minimal variability. The drug was dispersed uniformly throughout the gel.

Table 7: Drug Content data (n=3)

Formulations	Drug Content (%)
F1	98.49 ± 0.85
F2	99.00 ± 0.31
F3	99.03 ± 0.72
F4	97.76 ± 0.46
F5	98.00 ± 0.54
F6	98.89 ± 0.30
F7	99.27 ± 0.31
F8	99.62 ± 0.80
F9	98.90 ± 0.54
F10	99.27 ± 0.62
F11	98.83 ± 0.66

Differential scanning calorimetry

Fig 2 shows pure crystalline single, sharp melting endotherm at 178.09°C of GBM in DSC. Fig 3 shows a DSC thermogram of β – cyclodextrin (β – CD). β - CD does not have a definite melting point and above 200ºC it starts to decompose. The β - CD thermogram displayed a very broad endothermic effect with a maximum around 115.47°C, which was attributed to liberation of crystal water of this β - CD. The other endothermic peak at 318.99°C observed in the DSC profile of β - CD was due to the decomposition of β – CD.

Fig 4 show a DSC thermogram of GBM: β – CD in 1:1 w/w prepared by kneading method. Some reduction of area, broadening and small downshift of the peak temperature of GBM melting endotherm (173.43°C) was observed in the kneaded product. GBM endothermic peak was partially reduced, the presence of this peak indicates that a true inclusion complex was not achieved.

When guest molecules are incorporated in the β - CD cavity their melting points generally shift to a different temperature or disappear within the temperature range where the β - CD lattice is decomposed.

Absence of GBM sharp endothermic peak at 178.09°C in fig 4 indicated the existence of interactions between the drug and β - CD in the solid state and may be considered as a strong indication for the formation of real inclusion complex. This indicates that the drug penetrated into the β - CD cavity, replacing some water molecules.

***In-vitro* permeation studies**

The data from the *in vitro* study was fitted to various kinetic models to determine kinetics of drug release as tabulated in table 8 for formulations F1-F3. The correlation coefficient of each of these models was calculated.

Up to 12 hr, cumulative % of drug permeated through the membrane into the *in vitro* fluid of all gel formulations is tabulated in table 8. From regression coefficient (R^2) it is clear that there is a zero order drug release from all of the gel formulations, because the dispersed drug matrixes ensured constant concentration. The regression coefficient (R^2) of formulations F1-F11 is tabulated in table 9. The flux (mg cm^{-2} hr^{-1}) of Glibenclamide was calculated from the slope of the plot of the cumulative amount of Glibenclamide permeated per $cm^2$of membrane at steady state against the time using linear regression analysis and is tabulated in table 10.

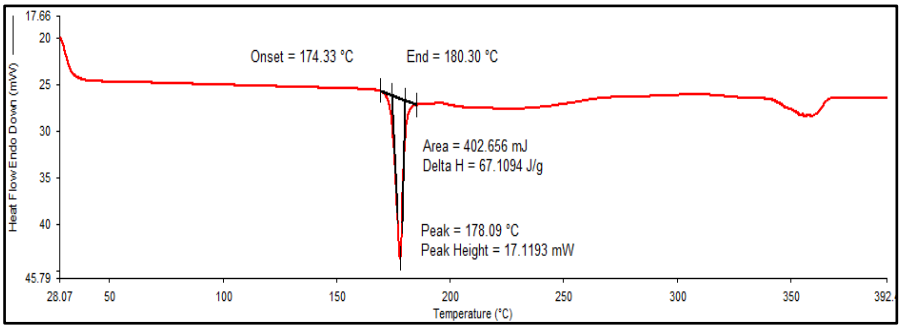

Fig. 2: DSC thermogram of Glibenclamide (GBM)

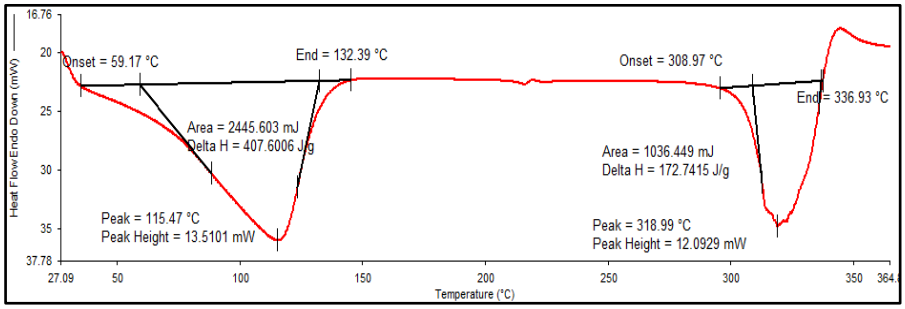

Fig. 3: DSC thermogram of β – cyclodextrin (β-CD)

The process of drug release in most controlled release formulations including transdermal gels is governed by diffusion and polymer matrix has a strong influence on the diffusivity as the motion of a small molecule is restricted by three dimensional networks of polymer chains. The controlled release behaviour of a drug from polymer matrices was characterized by Korsmeyer – Peppas Power Law equation $M_t / M_\infty = Kt^n$. The value of release exponent (n) represented from slope of ln M_t / M_∞ Vs ln t is indicating of the operating release mechanism. The (n) value shown in table 10, obtained by this equation indicated that the amount of drug released from all the gel formulations follow anomalous transport (0.5<n<1). In the anomalous process of drug release, fickian diffusion through the hydrated layers of the matrix and polymer chain relaxation/erosion is both involves. The contribution of these two mechanisms to the overall release are considered to be additive. From the formulations F2-F4, the formulation F3 was showing

maximum cumulative % drug permeation. The increase in permeation was due to the formation of water-soluble inclusion complexes with β - CD. The water molecules in the cavities of β - CD are in an energetically unfavoured state because of the apolar nature of the cavity. The replacement of high-energy water molecules with a hydrophobic guest in the cavity is therefore favoured. The removal of the high-energy molecule out of the cavity by displacement is the driving force for the formation of an inclusion complex in an aqueous solution. The guest molecule is associated with β - CD by noncovalent and weak intermolecular forces. The interactions between the hydrophobic part of the guest and the apolar cavity causes dehydration of the hydrophobic guest molecule and its transfer into the cavity, thereby increasing the affinity toward water and hence increasing the permeation of drug.

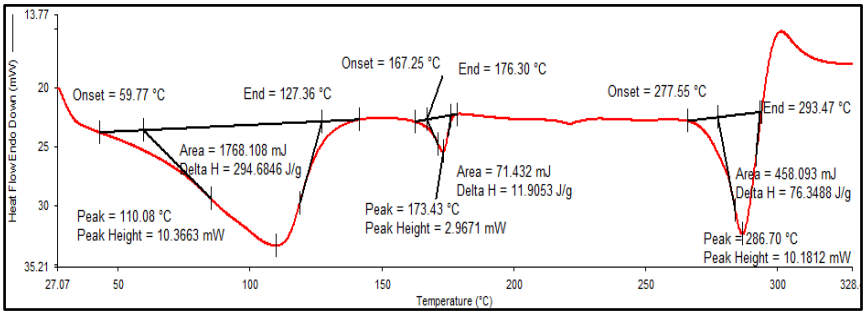

Fig. 4: DSC thermogram of GBM:β – CD (Kneaded in 1: 1 w/w)

That's why we had selected formulation F3 for further incorporation of different concentrations of propylene glycol as the formulations F2 and F4 decreased the cumulative % drug permeation because in Formulation F2, there was no formation of inclusion complex and in formulation F4, excess β – cyclodextrin reduced the apparent partition coefficient of the drug from the aqueous exterior to the lipophilic membrane. Thus, excess cyclodextrin lowered the permeation of drug.

As we increased the concentration of propylene glycol, the cumulative % drug permeated also increased. Propylene glycol acts as a cosolvent to solubilise the drug in the vehicle. But the formulation F8 didn't exhibited any significant increase in cumulative % drug permeation, because of increased viscosity of the formulation due to high concentration of propylene glycol. Therefore we had selected formulation F7 for the incorporation of different concentrations of oleic acid to increase the permeation of Glibenclamide, as it was showing maximum permeation from formulations F5-F8.

Propylene glycol exhibits a synergetic effect in permeation enhancement with oleic acid. Oleic acid enhanced the permeation of drug due to the hydration of the skin. As we increased the concentration of oleic acid in formulation, the cumulative % drug permeation starts increasing. But the formulation F11 containing highest concentration of oleic acid showed decrease in cumulative % drug permeation. This could be due to the fact that the β – cyclodextrin (β - CD) could decrease the amount of free fatty acid present in the gels as a result of oleic acid – β - CD complex formation and decreases the cumulative % drug permeation. Therefore based on the physiochemical observations and release rate kinetics, the formulation F10 gave the best results and came out to be as an optimized formulation.

Table 8: Cumulative percent of drug permeated from formulations F1-F11 after 12 hours (n=3)

Formulation code	Cumulative % drug permeated
F1	32.2691 ± 0.05
F2	36.7412 ± 0.07
F3	46.1759 ± 0.61
F4	42.7764 ± 0.09
F5	52.5051 ± 0.14
F6	58.7577 ± 0.04
F7	66.9519 ± 0.03
F8	64.9049 ± 0.05
F9	74.6583 ± 0.06
F10	87.2711 ± 0.08
F11	79.2762 ± 0.05

Table 9: Correlation coefficients (R^2) and release constants (n) of formulations F1-F11

Formulation	Correlation coefficient (R^2)			Korsmeyer - peppas	
Code	Zero order	First order	Higuchi	Release exponent (n)	R^2
F1	0.997	0.912	0.922	0.902	0.995
F2	0.998	0.989	0.973	0.863	0.997
F3	0.996	0.991	0.923	0.941	0.994
F4	0.998	0.992	0.921	0.915	0.995
F5	0.997	0.960	0.924	0.995	0.989
F6	0.997	0.936	0.937	0.961	0.969
F7	0.994	0.986	0.954	0.811	0.997
F8	0.998	0.974	0.938	0.896	0.999
F9	0.998	0.964	0.921	0.937	0.995
F10	0.998	0.937	0.932	0.914	0.997
F11	0.997	0.964	0.940	0.866	0.998

Scanning electron microscopy

The scanning electron microscopy (SEM) images of Glibenclamide (GBM), β – cyclodextrin (β – CD) and optimized gel formulation F10 are shown in fig 6 – fig 8 respectively. The SEM images of drug GBM represented in irregular shaped crystals and β – CD represented in planer structure with large crystals. The SEM image of gel showed that the complex is uniformly dispersed in gel.

The kneading technique yielded products of amorphous appearance, with the presence of particles, of a typical spherical shape and a smooth surface.

Table 10: Kinetics of drug release, drug transport mechanism and flux of gel formulations

Formulation code	Kinetics of Drug Release	Drug Transport Mechanism	Flux (mg/cm²/hr)
F1	Zero Order	Anomalous Transport	0.997 ± 0.34
F2	Zero Order	Anomalous Transport	2.89 ± 0.52
F3	Zero Order	Anomalous Transport	1.56 ± 0.7
F4	Zero Order	Anomalous Transport	5.98 ± 0.67
F5	Zero Order	Anomalous Transport	7.72 ± 0.43
F6	Zero Order	Anomalous Transport	10.73 ± 0.31
F7	Zero Order	Anomalous Transport	14.39 ± 0.25
F8	Zero Order	Anomalous Transport	12.78 ± 0.16
F9	Zero Order	Anomalous Transport	14.78 ± 0.4
F10	Zero Order	Anomalous Transport	17.45 ± 0.32
F11	Zero Order	Anomalous Transport	13.89 ± 0.21

Values are presented as mean ± SD (n=3)

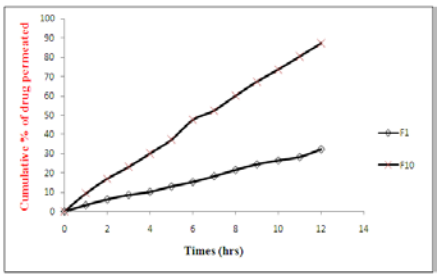

Fig. 5: Comparison of cumulative % of drug permeated from formulation F1 having no permeation enhancer and optimized formulation F10.

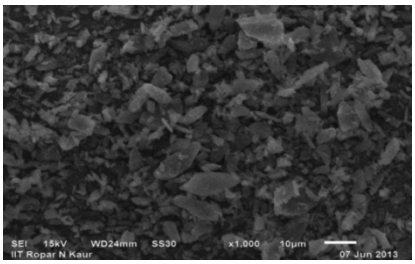

Fig. 6: Scanning Electron Photomicrograph of GBM

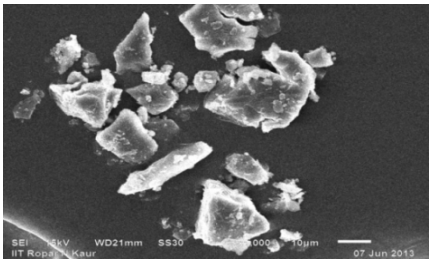

Fig. 7: Scanning electron photomicrograph of β – CD

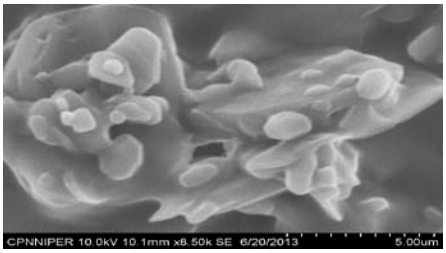

Fig. 8: Scanning Electron Photomicrograph of optimized Gel Formulation F10

Stability studies

The physical appearance of optimized formulation F10 was found to be unchanged after 3 months at all the conditions to which it was exposed. Also the drug content was found to be good even after 3 months. The cumulative % of drug permeated after 12 hour at 5°C ± 3°C and at 30°C ± 2°C was found to be 86.48 ± 0.29 and 86.23 ± 0.91 respectively after 3 months. There was no significant decrease in cumulative % of drug permeation from zero months which was 87.27 ± 0.08.

CONCLUSION

The delivery of drugs through the skin provides several important advantages over traditional oral and intravenous delivery routes. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through the skin at predetermined rate with minimal inter and intra patient variability. Glibenclamide is an oral potassium channel inhibitor used as an antidiabetic drug. Although it is absorbed from the gastrointestinal tract, its bioavailability is low, due to first pass effect. The aim of the present study is to formulate, design and evaluate Glibenclamide transdermal therapeutic system that would provide continuous dosing of Glibenclamide at constant and controlled rate up to predetermined period. From the experimental findings, it can be concluded that transdermal gel formulation containing Glibenclamide can be prepared by direct dispersion method, using carbopol 940. Addition of penetration enhancers profoundly increases the drug flux to the desired extent. Formulation containing 10% oleic acid, 25% propylene glycol and drug with its inclusion complex with β – cyclodextrin in 1:2 w/w exhibited highest permeation rates. Comparing *in vitro* drug release data, formulation F10 has showed better release pattern and physiochemical characteristics. The mechanism of drug release from the formulations was found to be swelling controlled drug release and compiled with zero order kinetics.

CONFLICT OF INTERESTS

Declared None

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