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Research Article

**FORMULATION AND CHARACTERIZATION OF
GLICLAZIDE LOADED NANOGEL FOR TREATMENT OF
DIABETES MELLITUS TYPE-2****S. Mukhopadhyay*, Pragati Trivedi**

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Abstract:

Gliclazide is a weak acid compound with high lipophilicity and has pH-dependent solubility. The drug is insoluble under acidic condition in the stomach, when consumed orally causes several side effects namely heartburn, anorexia, nausea and ulcer. This leads to reduced patient compliance and in turn reduces drug efficacy. Topical drug delivery are potential routes for a variety of drugs with limited oral bioavailability. Nanogel formulations are efficient in enhancing the delivery of such drugs. Incorporating drug in the form of nanogel has potential in enhancing the poorly permeable drug for topical drug delivery. It showed promising results on delivering also showed a superiority based on its retention and adhesive properties for better absorption. In the report, a nanogel was developed and evaluated as a platform for topical drug delivery. We have prepared gliclazide nanogel at different drug polymer ratios. The particle size polydispersity retention viscosity were evaluated F2 and F4 showed higher releasing rate compared to F1. On the other hand, F1 showed higher skin permeation. Gliclazide nanogel formulation with ethanol as a penetration enhancer demonstrated a pronounced effect on enhancing Gliclazide skin permeability and content upon topical application. Based on these results, this study is further directed to choose a model for diabetes mellitus type 2 as a therapeutic tool.

Keywords: Nanogel, Nanotechnology, Gliclazide, topical drug delivery

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INTRODUCTION:

Type 2 diabetes is a chronic disease. It is characterized by high levels of sugar in the blood. Type 2 diabetes occurs when your body's cells resist the normal effect of insulin, which is to drive glucose in the blood into the inside of the cells. This condition is called insulin resistance. As a result, glucose starts to build up in the blood¹. Studies in different parts of India have demonstrated an escalating prevalence of diabetes not only in urban populations, but also in rural populations as a result of the urbanization of lifestyle parameters. The prevalence of prediabetes is also high. Recent studies have shown a rapid conversion of impaired glucose tolerance to diabetes in the southern states of India, where the prevalence of diabetes among adults has reached approximately 20% in urban populations and approximately 10% in rural populations. A recent study showed that total annual expenditure by patients on diabetes care was, on average, INR 10 000 (US\$227) in urban areas and INR 6260 (US\$142) in rural areas. According to the World Health Organization (WHO), India had 69.2 million people living with diabetes in 2015. In 2016, an estimated 1.6 million deaths were directly caused by diabetes. For treatment of diabetes mellitus type-2 several medications are available in market among them metformin is a choice of drug but there are patients in whom metformin is contra-indicated or not Tolerated². Sulphonylureas are considered in such cases the long-acting Sulphonylureas, chlorpropamide and glibenclamide are associated with a greater risk of hypoglycaemia can occasionally cause a disturbance in liver function. Gliclazide is a Sulphonylureas drug with an intermediate half-life of around 11 hours. It is extensively metabolised, and renal clearance accounts for only 4% of total drug clearance It specifically improves the abnormal first phase insulin release in type 2 diabetes, and also has an effect on the second phase This pattern of insulin release is thought to explain the lower incidence of hypoglycaemic episodes and weight gain compared with some other Sulphonylureas Gliclazide reduces platelet adhesion, aggregation and hyperactivity and increases fibrinolysis These actions, thought to be independent of its hypoglycaemic activity, may make gliclazide useful in halting the progression of diabetic microangiopathy³. Gliclazide has been reported to possess the properties of preventing the progression of diabetic retinopathy and of controlling blood glucose levels Thus, gliclazide seems to have additional properties compared with other sulfonylurea drugs⁴.

Though Gliclazide promises a great deal of choice over other Sulphonylureas yet there is certain limitation with the drug and its commercial dosage form such as Gliclazide is a weak acid compound with

high lipophilicity and has pH-dependent solubility drug is insoluble under acidic condition in the stomach also when consumed orally causes several side effects namely heartburn, anorexia, nausea and vomiting⁵. Along with this several research work has concluded that oral administration of drug produced rapid and significant lowering in the Blood Glucose level and effect terminated in just 6 hours. It has been reported that 40% of approved drugs and nearly 90% of the developmental pipeline drugs consist of poorly soluble molecules Conventional formulations of a poorly water-soluble drug are mostly accompanied with limited bioavailability⁶. To overcome this issue, several formulation approaches were reported such as mixing aqueous formulation with organic solvent (e.g. ethanol) for solubility enhancement, complex formation (e.g. cyclodextrin and its derivatives), solid dispersion, pH and salt forms alteration. However, these approaches showed limited success in respect to overall bioavailability improvement and even if there is some improvement was present the side effects associated with ulcer were still there.

To solve the above-mentioned limitations, we proposed formulation of Gliclazide based topical nanogel Gels are typically formed from a liquid phase that has been thickened with other components. The continuous liquid phase allows free diffusion of molecules through the polymers scaffold and hence release should be equivalent to that from a simple solution⁶. Due to their non-greasy properties, they can provide easily washable film on the skin and as they will not pass to git pathway ulcer, and other gastrointestinal disturbances can be overcome.

The therapeutic value of gliclazide is hampered by its poor permeability and aqueous solubility. To enhance skin permeability and deliver adequate amounts of the drug into the systemic circulation, formulation studies were conducted Gliclazide as a nanogel formulation based on a Carbopol gel matrix was effective in enhancing the drug permeability.

MATERIALS AND METHODS:

Materials: Gliclazide was a gift sample from Ravian Life Science, Sidkul, Haridwar. Eudragit S-100 Carbopol 940, Tween 80 and Glycerol were obtained from chemical store of pharmaceuticals department at shri guru ram rai university Triethanolamine was purchased from Pharma Raw material, Roorkee

Method:**Preparation of Gliclazide loaded nanogel:**

Emulsion Solvent Diffusion Technique Aqueous phase containing Carbopol 940(5gm) dissolved in water with continue stirring and constant heat on

magnetic stirrer Drug containing phase i.e. Eudragit (0.25mg), tween 80(0.5ml), glycerol(5ml) and drug(100mg) is sonicated using Branson sonicator, Drug phase added dropwise into aqueous phase during homogenization (rate is controlled by optimizing a burette for 1ml/min). This results emulsion and the emulsion is further converted into nanodroplets by continue homogenization up to 1 hour 2 ml of Triethanolamine is added to form Gel with continue stirring, after stirring the system was ultrasonicated, and then the system under is cooled ice cooling plastic Glass vials of 18 mm in diameter were used for all nanogel storage. This standard procedure for the preparation of nanogels could be easily scaled for higher or lower amounts as long as the ratio of the reactants used is maintained.

CHARACTERIZATION OF THE FORMULATION:

1. Influence of Preparation Parameters: Sonication Time.

To assess the effect of sonication time variation two sets of experiments were performed where either one of the two times was kept constant at 60s, while to other was varied between 60s and 1500s⁷. For clarity of sample nomenclature, nanogels prepared with sonication time of 60s the following combination of parameters was examined for both sets 60s, 120s, 180s, 240s, 300s, 360s, 420s, 600s, 1500s.

2. Influence of Hydrophilic-Lipophilic Balance (HLB) of the Surfactants

The HLB value was tuned by the variation of the ratio of the surfactants span80, Tween 80 (Table 1). The dependence on nanogel diameter was investigated for four HLB values: 5, 6, 7 and 8. The experiments were performed at three different sonication times: 60s, 300s, 360s

TABLE 1: TWEEN 80 AND SPAN 80 COMPOSITION AT DIFFERENT HLB VALUES

HLB	Span 80 [mg]	Tween 80 [mg]
5	35.05	2.45
6	31.54	5.96
7	28.04	9.46
8	24.53	12.97

3. Influence of Polymer Concentration. To determine the effect of polymer concentration on the size of nanogels, nanogels were prepared as described with varying polymer concentrations of 40, 28 and 12 w/v % with respect to the aqueous phase at sonication time of 60s, 300s and 360s¹²

4. Physicochemical Properties of Formulations

Particle size and polydispersity index (PDI) were measured by suspending each sample in deionized water with appropriate dilution. The measurement was performed with Nicomp ZLS380 Nanosizer. The PDI reflects the particle size distribution.

5. In Vitro Release Study

Gliclazide release from the nanogel formulations was performed using Franz diffusion cells. The diffusion cell apparatus used in this study (PermeGear, Bethlehem, PA) holds up to 6 diffusion cells in series. The apparatus has a motor to rotate magnetic beads at 600 rpm. Regenerated cellulose dialysis membrane with a molecular weight cut off 12,000 Daltons was used in the drug release studies. The membrane (pre-soaked in a buffer for 2 h) was mounted horizontally between the donor and receptor halves of the diffusion cell. The surface area of the membrane exposed to the formulation in the donor chamber was 0.64 cm², and the receptor cell volume was 5 ml. Approximately 100 mg of the formulation was applied on the membrane facing the donor chamber. The receptor chamber was filled with PBS pH 7.4 to mimic the physiological condition. The temperature of the jacket was maintained at 37±0.5 Co. One millimetre of each sample was withdrawn from receptor cell at 0, 1, 2, 4, 6, 8, 12 and 24 hours and analysed for drug content by UV spectrophotometer.

6. Drug release kinetics Several drug release data on mathematical models can be obtained, hence drug release profile can be correlated with drug release kinetic models.

Zero order release kinetics According to the principles of pharmacokinetics, drug release from the dosage form can be represented by the below equation
 $C_0 - C_t = K_0t$ Eq.1
 $C_t = C_0 + K_0t$ Eq.2

C_t is the % amount of drug released at time t ,

C_0 is the % CR drug at time $t=0$

K_0 is the zero-order rate constant

Figure is plotted against % cumulative drug release vs. time.

First order release kinetics The release of drug which follows first order kinetics is given below, it is the first order process whose rate is directly proportional to the concentration of drug undergoing reaction
 $\log C = \log C_0 - K_1t/2.303$ Eq.3

K_1 is the first order rate equation expressed in time-1 or per hour.

C_0 is the initial concentration of drug C is the percent of drug remaining at time t Figure is obtained by log % of CR vs. Time.

Higuchi model Today it is considered as one of widely used and most well-known controlled release equation, which is represented below $Q = KH \times t^{1/2}$Eq.4

KH is the Higuchi constant

Figure is plotted as %CR vs. square root of time

Korsmeyer-Peppas Once it has been ascertained that the prime mechanism of drug release is diffusion controlled from Higuchi plot then it comes the release of drug follows which type of diffusion, to understand the dissolution mechanisms from the matrix the release data were fitted using the empirical equation. $F = (M_t / M) = K_m t^n$ Eq.5

F = Fraction of drug released at time, t^n M_t = Amount of drug released at time, t^n M = Total amount of drug in dosage form

K_m = Kinetic constant n = Diffusion or release exponent

t = Time in hours Figure is plotted log % CDR vs log time in hours

Hixson-Crowell model The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets. Hence, particles of regular area are proportional to cube root of its volume. The relationship between the time and drug release can be described as $W_0^{1/3} - W_t^{1/3} = K_H C t$ Eq.6. W_0 is initial amount of drug in pharmaceutical dosage form at time t $K_H C$ Hixson-Crowell constant Figure is plotted Cube root of %CDR vs Time^{8,9}

7. Drug Retention on Skin Layers

At the end of the skin permeation study, the residual drug remaining on the surface of the skin was removed by cotton swabs and by washing the surface with PBS pH 7.4. The skin surface was gently wiped with a cotton swab (Q-tips®), 200 μ l of the above buffer was added on the skin surface and the liquid was dabbed with a fresh (dry) cotton swab. This process of swabbing and dabbing was repeated 5 times. The active diffusion area was collected with a biopsy punch (George Tiemann & Co, Hauppauge, NY) and the skin was weighed and minced with a pair of sharp point dissecting scissors into a glass vial. To these glass vials, 1 ml of above buffer was added, sonicated for 15 min. and allowed to stand overnight. The samples were sonicated again for 30 min. The samples were filtered through 0.45 μ m membrane filter and the supernatants were diluted appropriately and analysed by UV¹¹.

8. Spreadability coefficient: It consists of a wooden block which is attached to a pulley at one end. Spreading coefficient is measured on the basis of "slip" and "drag" characteristics of nanogel. A ground glass slide is fixed on the wooden block. An excess of nanogel under study was placed on the glass slide. The nanogel formulation was sandwiched between the two slides having the same dimensions that of fixed ground slide. The weight of 100 grams was placed on the top of the two slides for few seconds to provide uniform film of nanogel between the two slides. A measured quantity of weight was placed in the pan attached to pulley with the help of hook. The time (in seconds) required by the top slide to cover a distance of 7 cm was noted. A shorter interval indicates better spreading coefficients¹⁰. Refer Table no 2

TABLE 2: SPREADABILITY OF NANOGEL FORMULATIONS

Formulation code	Spreadability (g.cm/s)
F1	28.10 (\pm 0.09)
F2	20.35 (\pm 0.05)
F3	15.49 (\pm 0.18)
F4	11.84 (\pm 0.06)

9. Viscosity Determination

The rheological properties were studied using Brookfield viscometer. The nanogel viscosity was determined via a viscometer (model DV-II₊, Brookfield, U.S.A.) using Spindle 51z. The reading was recorded in 30 seconds at various shearing stress values. The content and uniformity of gliclazide in the gel were determined by analysing three samples from each nanogel formulation (top, middle and bottom of the vial). The samples (0.5 gm) were dissolved in 5 ml of 0.01 NaOH then made to volume with PBS for quantification by UV- spectrometer ^[11,13]

RESULTS:

Sonication Time a variation of sonication showed strong influence on particle size in a first series of experiments, the sonication time was varied from 60 s up to 1500 s. **Table 3** presents and compares the diameter z-average as well as polydispersity index

(PDI) values obtained from dynamic light scattering (DLS) analysis.

The diameter z-average increased gradually up to the value of 500 nm for 420 s. Further increase of the sonication time led to the formation of visible large aggregates. These results suggest that long sonication times lead to destabilization of the emulsion which favours particle aggregation. In addition, despite of ice cooling, longer sonication can cause a certain bulk thermal heating caused by longer shear times. From the obtained results it can be concluded that nanogel size was relatively unaffected by sonication time. For the nanogels prepared, the slight change of the z-average is proportional to the sonication time, only at long sonication times or over sonication led to the formation of large aggregates. Based on these results all further experiments were performed by the sonication for 60 s after the system preparation.

TABLE 3: DIAMETER Z-AVERAGE AND POLYDISPERSITY INDEX (PDI)

Sonication time [s]	Z-average	PDI
60	350±13	0.410±0.010
120	400±20	0.334±0.012
180	400±15	0.392±0.012
240	400±22	0.318±0.014
300	420±20	0.301±0.002
360	420±16	0.344±0.004
420	500±23	0.375±0.006
600	-	0.334±0.012
1500	-	-

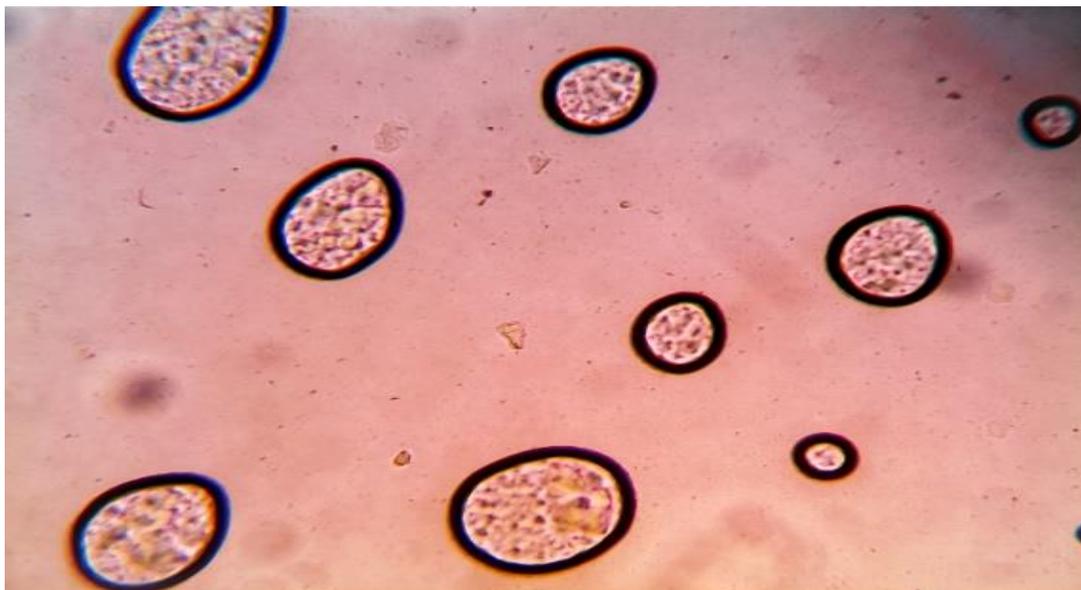


Figure 1: Micro Figure- magnification power is 100X

Influence of the Surfactants and the Hydrophilic-Lipophilic Balance (HLB)

Particle size dependence at different HLB's in the range of 5 to 8 was investigated with three different sonication time parameters 60s, 300s and 360s (Table 4). A desired HLB value was obtained by changing the weight ratio of surfactant according to Equation 7. The weight ratios of emulsifier to reaction ingredients were always kept constant at 5 wt. %.

$$HLB = [4.3 \times x] + [15.0 \times (1-x)] \text{ Eq.7}$$

Where x is the weight fraction of Span 80. Values of 4.3 and 15 denote the HLB of Span 80 and Tween 80, respectively the influence of different combinations of commercially available non-ionic surfactants and co-surfactants at constant HLB = 7 was investigated. As oil soluble surfactants, Span 80 (HLB = 4.7) was used, next to Tween 80 (HLB = 9.7) were applied as water soluble co-surfactants. As seen from Table 3, nanogels prepared with surfactant/co-surfactant combination of

Span 60 / Tween 80 and Span 80 / Tween 80 showed narrow PDI with small particle size at sonication time of 300s whereas nanogels prepared with other surfactant combinations at this sonication time exhibited broader size distribution. This difference, is not immense; however, it demonstrates that a careful selection of the appropriate emulsifying system has an impact on the size and polydispersity of the particles. A possible explanation for this behaviour is a lower HLB making the interfacial film not closely-packed and thus mechanically weak and less stable in comparison to a better water-soluble Tween 80. Comparable results obtained with Span 60 and Span 80 is due to similarity in their molecular structure with only difference in the presence of a one double bond in a hydrophobic tail leading to a slightly better solubility of Span 80 in the oil phase. The yield of nanogels in all cases was between 85-90% with respect to the amount of polymer used was calculated by the dry mass of the nanogels after dialysis.

TABLE 4: INFLUENCE OF TYPE OF SURFACTANT AT HLB 7 ON NANOGEL SIZE

Surfactants	Sonication [s]	Z-average [nm]	PDI
Span 60 : Tween 80	60	300±15	0.308±0.008
	180	200±20	0.267±0.010
	300	200±21	0.211±0.010
	360	250±30	0.240±0.011
Span 80 : Tween 60	60	0.4110±0.010	0.410±0.010
	180	0.320±0.012	0.320±0.012
	300	0.175±0.013	0.175±0.013
	360	0.245±0.021	0.245±0.021
Span80:tween80	60	350±13	0.410±0.010
	180	350±09	0.320±0.012
	300	150±11	0.175±0.013
	360	250±11	0.245±0.021

Influence of Polymer Amount In all experiments described so far the polymer concentration was 40 w/v %. In this section, the influence of the amount of polymer on the particle size at two additional concentrations: 28 and 12 w/v % and at different sonication times is shown. From the data presented in Table 4 it can be clearly seen that a decrease in polymer concentration leads to an increase of nanogel size

TABLE 5: INFLUENCE OF POLYMER AMOUNT

Sonication time [s]	Polymer concentration [w/v %]	Z –average	PDI
60	40	350±13	0.410±0.010
60	28	450±13	0.400±0.009
60	12	480±14	0.375±0.006
300	40	150±11	0.175±0.013
300	28	250±14	0.125±0.008
300	12	275±15	0.123±0.018
360	40	250±11	0.245±0.021
360	28	300±16	0.290±0.011
360	12	375±16	0.310±0.008

DISCUSSION:

Since the sonication time, water oil ratio and the surfactant amount are kept constant, the size of the water droplets is most likely not affected by the polymer mass. However, by increasing the polymer amount the molar concentration of eudragit in each water droplet increases. Thus, a higher concentration of the polymer results in increased cross-linking density which decreases the relative swelling of nanogels and hence also the hydrodynamic radius in comparison with nanogels prepared using lower eudragit-polymer concentration. Gliclazide nanoparticle were produced by a top-down approach utilizing a ball mill technique. Using this method, we

were able to attain drug particles in the nanosize range for various batches. The mean particle diameter (d50) was in the range of 163-317 nm, and the PDI was within the acceptable limit of <0.5%. Gliclazide particle size (d50) for this formulation was 270 nm with a PDI of 0.3. The pH of this formulation was around 6, and the viscosity was 7177 (cP). The Gliclazide content of the gel was 99.6%, suggesting uniform drug distribution. Based on F1 composition we have slightly modified the formula composition to include selected skin penetration enhancers (F2, ethanol; F3, oleic acid and F4 propylene glycol) (Table 6).



Figure2. formulations of Nanogel

TABLE 6: COMPOSITION OF NANOGEL FORMULATION

Ingredient %	F1	F2	F3	F4
Gliclazide	5.00	5.00	5.00	5.00
Carbopol 940	0.50	0.50	0.50	0.50
Polysorbate 80	5.00	5.00	5.00	5.00
Triethanolamine	0.35	0.35	0.35	0.35
Ethanol	-	10.00	10.00	-
Oleic acid	-	-	5.00	-
PG	-	-	-	10.00
Water	89.15	79.15	74.15	79.15

TABLE 7: PHYSICAL PROPERTIES OF NANOGEL FORMULATIONS

Formula	F1	F2	F3	F4
Particle size (nm)	270	317	314	163
Particle Size distribution (PI)	0.321	0.284	0.235	0.140
pH	6.03	6.50	6.40	6.09
Viscosity (cP)	7177	7477	6535	9362
Drug Content %	99.6	100.5	101.0	100.8

The formulations F2, F3 and F4 provided satisfactory results on particle size, polydispersity index, pH, viscosity and drug content. Oleic acid (F3) was chosen because of its potent effect on skin penetration as it increases the fluidity of the lipid component of SC and enhances the permeation across skin layers. The physicochemical characterization of the formulation exhibited comparable properties with respect to particle size, polydispersity index, drug content and pH. However, F3 showed the lowest viscosity (6535 cP at 5 RPM) among all prepared formulations with the same percentage of the gelling agent. The lower viscosity might be a result of the oily nature of oleic acid which interacts with Carbopol and weakens its ability to form a gel. Formulations F2, F3 and F4 showed similar particle size, polydispersity index, viscosity, drug content and pH value (Table 7).

Drug release studies were conducted on various formulations as the gel matrix plays a role in drug retention. It is also essential to determine if the gel is able to release the incorporated drug for percutaneous absorption. Figure 3 describes the drug release from

various formulations. All formulations showed a similar biphasic drug release pattern; an initial fast release up to 8 hours (F1, F3) or up to 12 hours (F2 and F4) followed by a slower release up to 24 hours. The lowest release of F3 may be due to the affinity of Gliclazide to oleic acid. F2 and F4 showed higher releasing rate compared to F1. The higher release by F2 and F4 compared to F3 can be explained by the use of polar solvents (ethanol, and propylene glycol, respectively) which do not interfere with the release of drug from the formulations as with oleic acid. Figure 8 describes the drug release from various formulations. All formulations showed a similar biphasic drug release pattern; an initial fast release up to 8 hours (F1, F3) or up to 12 hours (F2 and F4) followed by a slower release up to 24 hours. The lowest release of F3 may be due to the affinity of Gliclazide to oleic acid. F2 and F4 showed higher releasing rate compared to F1. The higher release by F2 and F4 compared to F3 can be explained by the use of polar solvents (ethanol, and propylene glycol, respectively) which do not interfere with the release of drug from the formulations as with oleic acid.

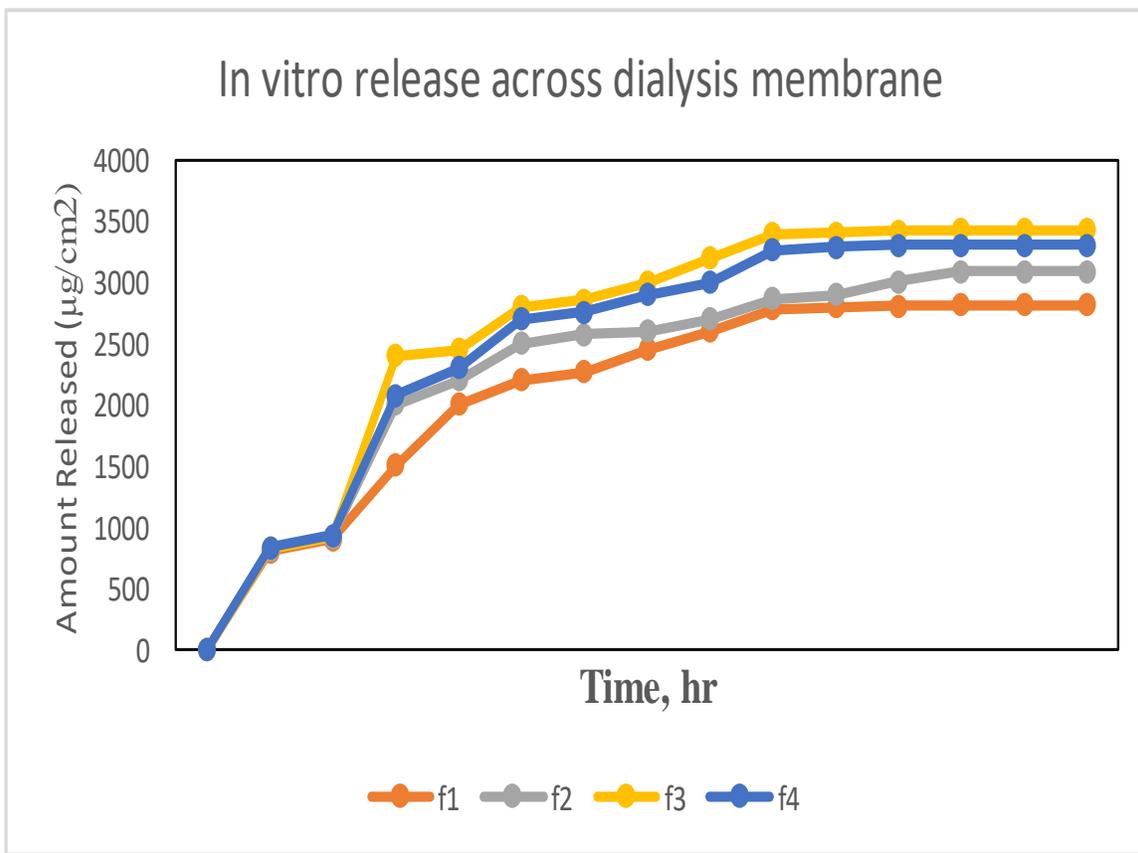
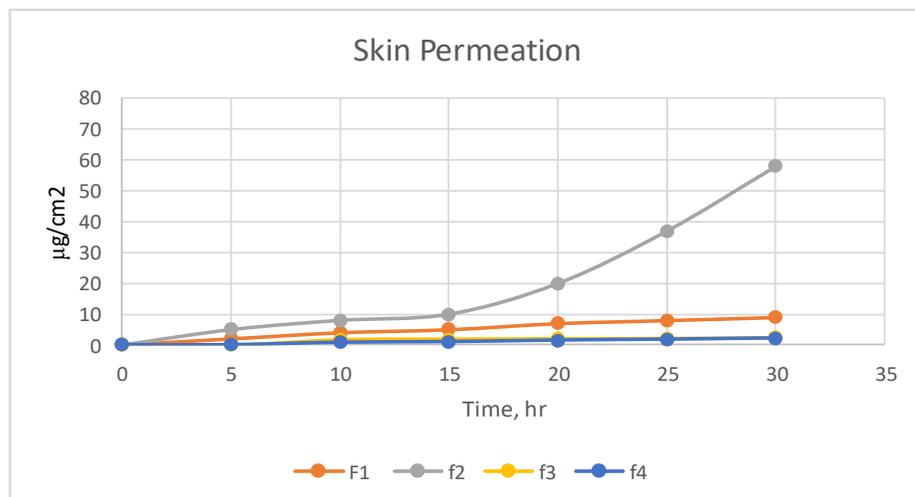
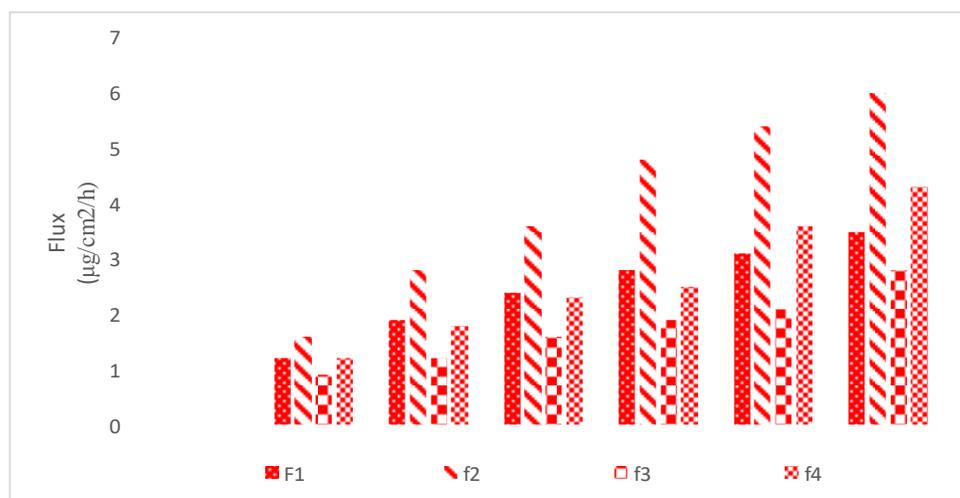


Figure.3. In vitro release across dialysis membrane. Each study was performed in triplicates (n=3)

Figure 4 illustrates permeation profiles of various Gliclazide nanogel formulations. F1 showed higher skin permeation with a flux of $0.22 \mu\text{g}/\text{cm}^2/\text{hr}$. Ethanol (F2) provided a dramatic increase in skin permeation ($2.68 \mu\text{g}/\text{cm}^2/\text{hr}$). F2 showed profound enhancement effect in comparison to F1, F3, F4 and ($P < 0.01$). The formulations F3 and F4 did not show a significant increase in skin permeation relative to or F1. The enhancement effect of F2 formulation can be due to fluidization of lipid structure of the SC particularly via interaction with a polar head group of the lipids. This leads to enhance a drug transportation and accumulation across skin layers since the main barrier is the stratum corneum. The formulation F2 (ethanol as enhancer) showed 1.8-fold higher skin levels than F1 (no enhancer). Also from the above drug release kinetics it was found that it follows Hixon-Crowell model of drug release kinetics as the value of R_2 was found to be near 1 that is 0.953.



[A]



[B]

Figure 4: Passive skin permeation: A. Passive skin permeation: A. Skin permeation for F1, F2, F3, F4. B. Flux of F1, F2, F3, F4. Each formula was evaluated in triplicate (N=3).

Overall, the nanogel formulation greatly facilitates the accumulation of the drug in the skin, this formulation should provide improved therapeutic value for Gliclazide as a topical anti diabetic agent

TABLE 8: DRUG RELEASE MODELS

Model Name	Slope	Intercept	R2
Zero order release	7.2909	5.8909	0.9424
First order release	0.0973	0.6459	0.3397
Higuchi model	0.74	29.511	0.9483
Korsmeyer Peppas	1.6647	0.5003	0.4478
Hixon-Crowell	8999.7	9325.6	0.9538

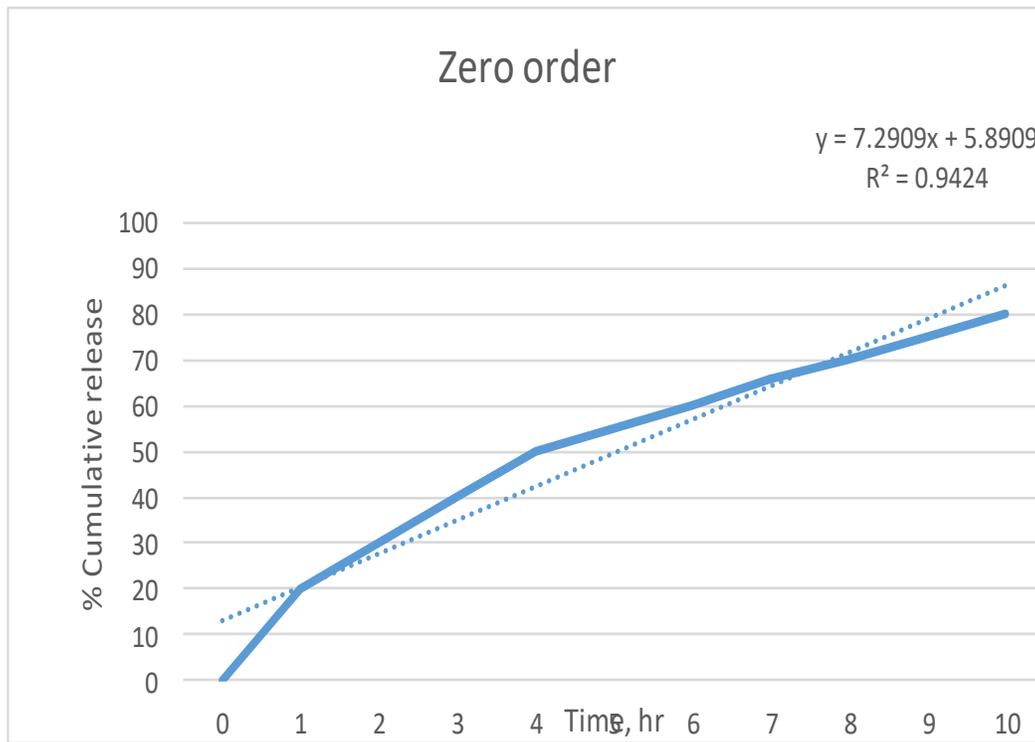


Figure5: Zero order release kinetics

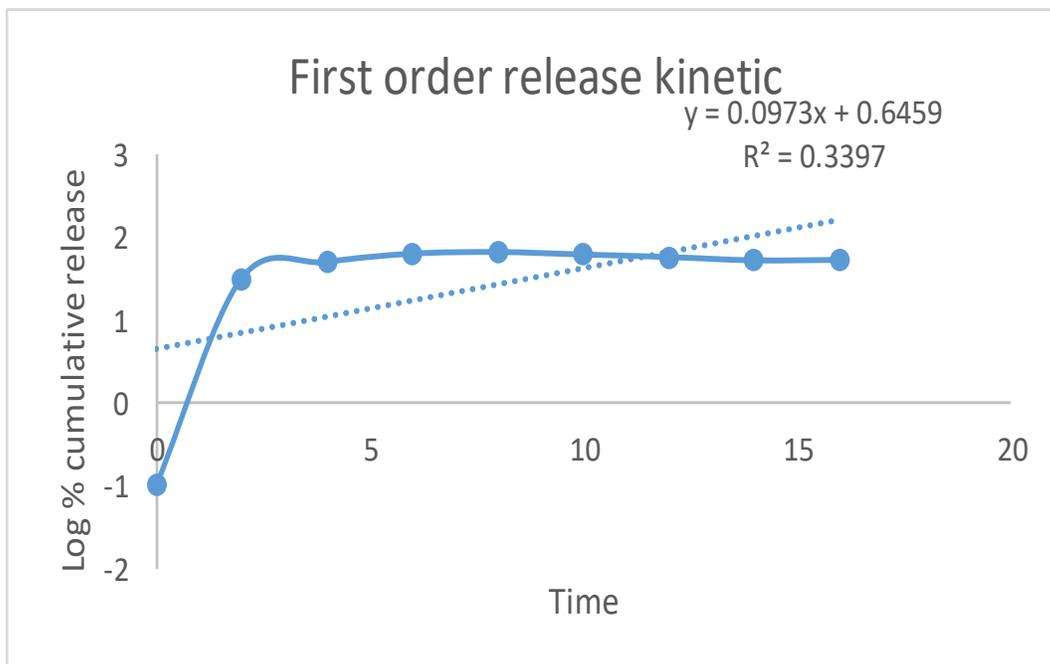


Figure 6: First order release kinetics

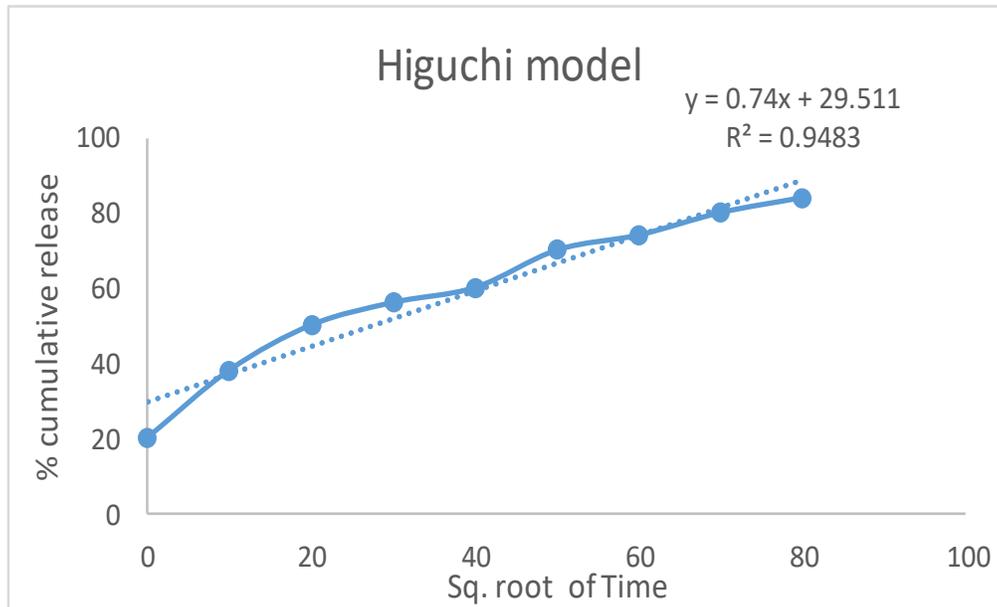


Figure 7: Higuchi Model

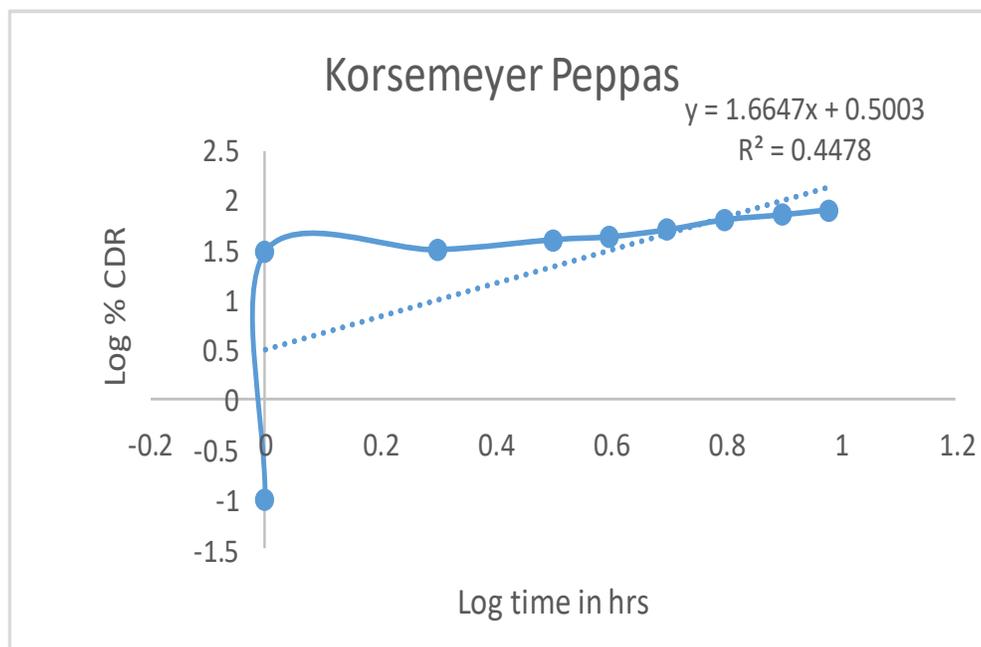


Figure 8: Korsmeyer Peppas

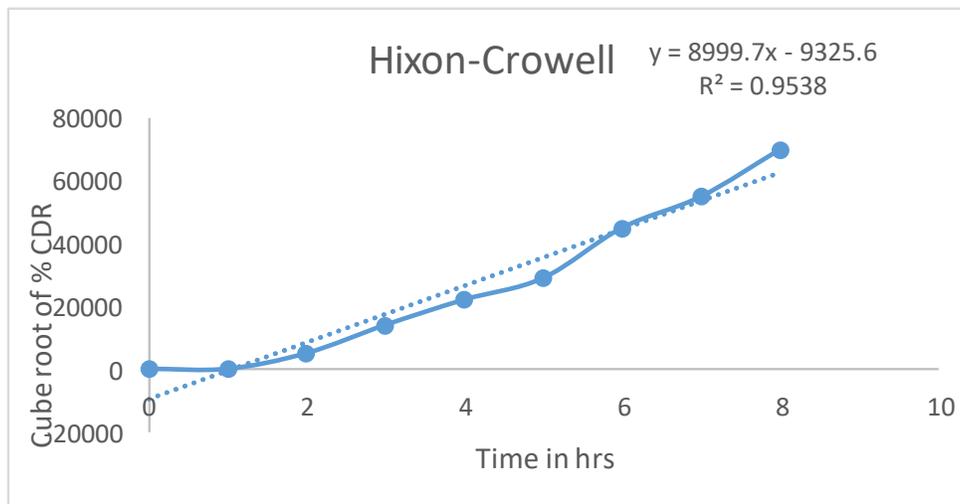


Figure 9: Hixon-Crowell

CONCLUSION:

The therapeutic value of gliclazide is hampered by its poor permeability and aqueous solubility. To enhance skin permeability and deliver adequate amounts of the drug into the systemic circulation, formulation studies were conducted Gliclazide as a nanogel formulation based on a Carbopol gel matrix was effective in enhancing the drug permeability. Ethanol was very effective as a skin penetration enhancer for Gliclazide. The above results agree with studies on nanogel for enhancing the delivery of topically applied drugs. Hence the hypothesis with which we've started the study has been succeeded.

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LIST OF ABBREVIATIONS

SC: Stratum Corneum
 FA: Ferulic acid
 UV: Ultraviolet-visible
 HPMC: Hydroxypropyl methylcellulose

CMC: Na Sodium carboxymethyl cellulose
 PEG: Polyethylene glycol PG Propylene glycol
 AUC: Area under the curve
 Cmax: Peak concentration
 Tmax: Time to observed peak concentration
 Wp: white powder
 PEG: Poly ethylene Glycol,
 glz: gliclazide
 TEA: Triethanolamine
 t1/2: Plasma half-life
 HP β CD: Hydroxypropyl- β -cyclodextrin
 MRM: Multiple reaction monitoring

DISCLOSURES

The authors state no conflict of interest.

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