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The Pharmaceutical Application of Sulfoxy Amine Chitosan in Design, Development and Evaluation of Transdermal Drug Delivery of Gliclazide

Jadhav Rahul Laxman[1*], Ahire Pallavi[1], Yadav Adhikrao Vyankatrao[1], Gharge G. Varsha[1], Patil Manisha Vyankatrao[2] and Shaikh Siraj Nawaj[3]

[1]Department of Pharmaceutical Chemistry, Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara, Maharashtra, 415001, India.
[2]Department of Pharmaceutics, Adersh College of Pharmacy, Vita; Dist: Sangli, Maharashtra, 416416, India.
[3]Department of Pharmaceutics, Ali-Allana College of Pharmacy, Akkalkuwa, Nandurbar, Maharashtra, 425415, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author JRL designed the study. Author AP and all other authors performed the laboratory research work, wrote manuscript. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Objective: The aim & objectives of this research work was to explore applicability of our previously synthesized sulfoxy amine chitosan in design, development and evaluation of transdermal drug delivery of Gliclazide.
Methods: To determine the interaction between excipients used and to find out the nature of drug in the formulation, Fourier transforms infra-red spectroscopy (FTIR) and Differential Scanning Colorimetry (DSC) studies were performed. Gliclazide containing transdermal patch were formulated with help of Sulfoxy Amine Chitosan, HPMC, Penetration enhancer Dimethyl Sulfoxide and Glycerine by using solvent casting method.9 formulations prepared by using 3^2 full factorial designs the effect of formulation variable was studied on % Moisture Content, Folding endurance, % Cumulative drug release at 12 hrs.Formulated transdermal patches were evaluated for various parameters.

**Corresponding author: E-mail: rahuljadhav_25@rediffmail.com;*

Results: FTIR & DSC suggest study no drug & polymers interaction .All the prepared transdermal patches were found to be faint yellow in colored, flexible, uniform, smooth, and transparent. The weight of the transdermal patches for different type of formulations ranged between 12.00 ± 0.6 mg & 14.2 ± 0.52 mg. The thickness of the patches varied from 0.171 ± 0.0035 mm to 0.182 ± 0.0026 mm. The moisture content & water vapour transmission rate in the patches ranged from 2.33 to 4.55% & from 0.002246 to 0.003597 mg.cm/cm^2 24hrs.XRD diffractogram revealed pure Gliclazide exhibited characteristic high-intensity diffraction peaks & optimized formulation showed three peaks in 2θ= 20.6 28.7 and 38.95 with very weak intensities. Optimized batch F7 showed maximum drug release 98.41%. The folding endurance was lies in between 301 and 359. Optimization study was successfully conducted using 3^2 factorial designs.
Conclusion: We concluded that transdermal patches Gliclazide of was successfully formulated with synthesized Sulfoxy Amine Chitosan & evaluated.

Keywords: Sulfoxy amine chitosan; Gliclazide; transdermal patch; HPMC; penetration enhancer; optimization; % cumulative drug release.

1. INTRODUCTION

Diabetes mellitus is a heterogeneous group of metabolic disorder characterized by chronic hyperglycemia with disturbance of carbohydrate, protein and fat metabolism [1].Diabetes was first discovered in 1500 BCE and has been recognized as a calamitous and lethaldisease for about 2000 years. Diabetes affects more than 415 million people globally and is estimated to strike about 642 million people in 2040 [2]. Obesity and Diabetes mellitus are the most common metabolic disorders lead to morbidity and mortality [3]. The WHO reported that diabetes will become the seventh biggest cause of mortality in 2030. Almost 80% of the people die with diabetes in low and middle-income countries [4].

Insulin injection and oral hypoglycemic agents remain the primary treatments in diabetes management. These often present with poor patient compliance. However, over the last decade, transdermal systems in diabetes management have gained increasing attention and emerged as a potential hope in diabetes management owing to the advantages that they offer as compared to invasive injection and oral dosage forms [5].

Transdermal delivery system is innovative drug delivery systems intended for skin application to achieve a systemic effect [6]. It offers many advantages such as reduced side effects, less frequent administration to produce the desired constant plasma concentration associated with improved patient compliance [7].Transdermal medication avoids significant presystemic metabolism degradation in the gastrointestinal tract or by the liver and the need, therefore, for a lower daily dose of a drug. Drug levels can be maintained in the systemic circulation, within the therapeutic window, for a prolonged period of time. Reduced inter- and intra-patient variability and this is particularly true for those situations in which drug release from the transdermal patch is slower than drug diffusion across the stratum corneum [8,9].

Chemical modification of gums not only minimizes these drawbacks but also enables their use for specific drug delivery purposes but also alter their physicochemical properties [10].To improve their functional properties a number of physical and chemical modification approach have been employed [11].Among the polysaccharides Chitosan has prospective applications in Pharma field. In past few decades, to strengthen the functionality of Chitosan, developing its novel derivatives has become a new pursuit [12].

Drug gliclazide is the second generation sulfonylurea class of insulin secretagogues used in management of non-insulin dependent diabetes mellitus. The sulfonylurea acts by stimulating β-cells of pancreas to release insulin. It increases both basal insulin secretion and meal stimulated insulin release [13]. Gliclazide faces problems like its poor solubility, poor oral bioavailability with large individual variation and extensive metabolism [14].So our previously synthesized Sulfoxy Amine Chitosan used in this study in Transdermal Patch dosage forms.Therefore, The purpose of this investigation was to explore applicability of our previously modified sulfoxy amine chitosan in design, development and evaluation of transdermal drug delivery of Gliclazide.

2. MATERIALS AND METHODS

2.1 Materials

Gliclazide was received as gift sample from Dr. Reddy's Laboratory Ltd. Mumbai. HPMC received from Research Lab Fine-chem, Mumbai. Dimethyl sulfoxide & Glycerine obtained from SD Fine chem Mumbai. Sulfoxy Amine Chitosan Prepared in Laboratory of Department of Pharmaceutical Chemistry, Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara, Maharashtra, India. All other chemicals were used of analytical reagent grade.

2.2 Methods

2.2.1 Synthesis of polymer

Sulfoxy amine chitosan was synthesized per our previously described method & used in study of transdermal drug delivery [15].

2.2.2 Preformulation study

2.2.2.1 Preparation of stock solution

Accurately weighed 10 mg of Gliclazide was transferred to 100 ml volumetric flask and dissolved in pH 7.4 phosphate buffer and the volume was made up to 100 ml with pH 7.4 phosphate to get the final concentration of drug of 100 µg/ml[16].

2.2.2.2 Determination of λmax of gliclazide

The stock solution was 10 time diluted with Phosphate buffer pH 7.4 and measured maximum peak of curve by using Shimadzu UV/ Visible double beam spectrophotometer.

2.2.2.3 Preparation of calibration curve in phosphate buffer pH 7.4

Calibration curve of Gliclazide was developed in Phosphate buffer pH 7.4 at 226 nm wave length. From the stock solution, aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1 ml, 1.2 ml, 1.4 ml, 1.6 ml, 1.8 ml and 2 ml were pipette out into a series of 10 ml volumetric flask and volume was made up to 10 ml with Phosphate buffer pH 7.4 in order to get a concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 µg/ml respectively. Absorbance of each solution was measured by using Shimadzu UV-Vis double beam spectrophotometer at 226 nm using Phosphate buffer pH 7.4 as a reference standard. The experiment was performed in triplicate and based on average absorbance; the equation for the best line was generated [16].

2.2.3 Compatibility studies of drug & Polymers

2.2.3.1 Fourier Transforms Infra-red Spectroscopy (FTIR)

The potassium bromide (KBr) disks with Gliclazide alone & formulation blend were prepared manually by press method. About 1 mg of drug was triturated with about 10 mg of dry KBr and then pressed into the pallet manually [17].

2.2.3.2 Differential Scanning Calorimetry (DSC) studies

Possible interactions between the drug and the utilized polymers were analyzed from DSC thermograms of the pure drug Gliclazide and the formulation obtained. All the samples were sealed in flat-bottomed aluminum pans and heated over a temperature range of 25 to 300 °C at an increase rate of 5 °C/min[18].

2.2.3.3 X-ray Diffraction (XRD) studies

X-ray diffraction was used to investigate the crystallization of polymers and the model drugs as well as the effect of the plasticizer [18]. The samples for the XRD studies were prepared by cutting films to fit the square tiles of the holder, mounted on the sample.

2.2.4 Fabrication of transdermal patches of gliclazide

Gliclazide containing transdermal patch were formulated with help of Sulfoxy Amine Chitosan, HPMC, Penetration enhancer dimethyl sulfoxide(DMSO) and glycerine by using solvent casting method ,Polymer was accurately weighed keeping total polymer weight 300 mg, various ratios of polymer (Sulfoxy Amine Chitosan, HPMC) and dissolved in 20 ml of Distilled water and kept aside to form clear solution. To above polymeric mixture, added 30% w/w (on polymer basis) of glycerine and various percentages of DMSO as permeation enhancer in various formulations. Gliclazide (30 mg) was dispersed in above polymeric mixture. The solution was magnetically stirred for 2 h to get uniform dispersion. The solution of polymers was sonicated for 30 min to remove the air bubbles. Then, with the help of syringe, the 7 ml solution was poured into a Teflon mould of 15cm^2 Area. The solvent was allowed to evaporate for 24 at room temperature [19,20].

2.3 Experimental Design

Design of experiments technique was applied followed by response surface methodology to optimize formulation variables. The Ratio of polymer weight (Sulfoxy Amine Chitosan: HPMC) (X1) and Penetration enhancer Concentration of Dimethyl Sulfoxide (X2) were chosen as independent variables as shown in Table 1. Nine formulations were prepared according to the design; and the effect of formulation variable was studied on % Moisture Content, Folding endurance, % Cumulative drug release at 12 hrs drug release [21]. these are dependant variable by using Design Expert software latest version 12.

2.4 Characterization of Prepared Transdermal Patches

2.4.1 Visual inspection and appearance

The films were evaluated visually for its clarity, transparency and stickiness. Films that were satisfactory were evaluated further and if they were unsatisfactory they were discarded [21].

2.4.2 Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, patches from each batch were weighed individually and the average weight was calculated.

2.4.3 Thickness uniformity

Thicknesses of all membranes were measured by using screw gauze at five different points on each membrane and average reading was noted.

2.4.4 Surface PH

Surface pH of the patches was determined by the method described by Bottenberg et al. The patches were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1 hour in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute [21].

2.4.5 Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the center and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. 0% constriction is equivalent to 100% flatness [22].

2.4.6 Drug content analysis

An accurately cut patch of 1 cm 2 area was taken and added in to a 100 ml volumetric flask and dissolved in methanol and volume was made up with phosphate buffer pH 7.4. Subsequent dilutions were made and analyzed by UV spectrophotometer at 226.nm.

2.4.7 % Moisture content

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films were reweighed and determined the percentage moisture content from the below mentioned formula:

% Moisture Content= Initial weight – final weight / final weight×100

2.4.8 % Moisture uptake

The weighed films were kept in a desicator at room temperature for 24 h containing saturated

Table 1. Composition of Optimization batches

Formulation code	Gliclazide (mg)	Sulfoxy Amine Chitosan: HPMC)	Penetration enhancer(DMSO) (% w/w)	Glycerine (% w/w)
F1	100	1:1 (-1)	15% (-1)	*30*
F2	100	1:1 (-1)	20% (0)	30
F3	100	1:1 (-1)	25% (1)	30
F4	100	1:2 (0)	15% (-1)	30
F5	100	1:2 (0)	20% (0)	30
F6	100	1:2 (0)	25% (1)	30
F 7	100	2:1 (1)	15% (-1)	30
F8	100	2:1 (1)	20% (0)	30
F9	100	2:1 (1)	25% (1)	30

Factor level shown in bracket (-1) low, (0) medium (1) high while, Sulfoxy Amine Chitosan: HPMC (X1), Concentration of Dimethyl Sulfoxide (X2)

solution of potassium chloride in order to maintain 84% RH. After 24 h, the films were reweighed and determine the percentage moisture uptake from the below mentioned formula:

% Moisture uptake = Final wt−Initial wt. /Initial wt. ×*100*

2.4.9 Water Vapor Transmission (WVT) rate gm

1 gm. of fused calcium chloride as desiccant was taken in vials and polymeric patch fixed over vial by adhesive tape. The vial was weighed and kept in desiccators containing saturated solution of potassium chloride to provide relative humidity of 84%. The vial was taken out and weighed at every 24 hrs intervals for a period of 72 hrs. The water vapor transmission rate was calculated from the plots of amount of water vapor transmitted versus time [23].

2.4.10 X-ray Powder Diffractometry (XRD)

X-ray diffraction analysis was employed to detect the crystallinity of the pure drug and the formulation. Transdermal patchesand pure drug was subjected to p-XRD study using X-ray diffractometer.

2.4.11 Folding endurance

This was determined by repeatedly folding the film at the same place until it broke. The number of times the films could be folded at the same place without breaking/cracking gave the value of folding endurance.Folding endurance was determined by repeatedly folding a small strip of the film at the same place until it breaks. The number of times the film is folded at specific place without breaking gives the folding endurance.

2.4.12 *In* vitro permeation studies

For In vitro permeation studies of transdermal patch Franz diffusion cell was used. The receptor compartment of the diffusion cell was filled with 20.0 ml of phosphate buffer (pH7.4), and in vitro drug release studies were carried out using synthetic dialysis membrane. The prepared formulations were applied on to the membrane in the donor compartment and were uniformly spread onto the dialysis membrane. Temp. & RPM of Franz diffusion cell was kept at 37.0 ± 0.5°C at 50 RPM during the whole study period. Samples (0.5 ml aliquots) were then withdrawn at suitable time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h) and replenished with an amount of medium to maintain the receptor phase volume to 20 ml. The samples were analyzed Spectrophotometrically at 226 nm [23].

2.4.13 Mathematical modeling and release kinetics

The kinetics of Gliclazide release from patch was determined using the release kinetics method of drug release into various kinetic equations: zero order release kinetics, first order release kinetics, and Higuchi model**.** The release data was obtained was calculated using various parameters. The parameters 'n' and time component 'k', the release rate constant and 'R', the regression co-efficient were determined by korsmeyer-Peppas equation to understand the release mechanism [24].

3. RESULTS AND DISCUSSION

3.1 Determination of λ max

The prepared solutions of Gliclazide were scanned for UV absorption between 200-400 nm. The spectrum was recorded, which showed absorbance maxima (λ_{max}) at 226 nm for distilled water and Phosphate buffer pH 7.4 solutions.

3.2 Calibration Curve of Gliclazide in Phosphate Buffer pH 7.4

Calibration curve of the drug in Phosphate buffer pH 7.4 at λmax 226 nm was plotted by recording the absorbances of solutions depicted in Table no.2 of different concentrations (2-20 µg/ml). Absorbance data shown Table The Beers and Lamberts range was found to be in the range of 2-20 µg/ml.

Table 2. Absorbance data of Gliclazide in Phosphate buffer pH 7.4

Conc. (µg/ml)	Absorbance
0	0
2	0.101
4	0.174
6	0.24
8	0.315
10	0.393
12	0.468
14	0.518
16	0.61
18	0.705
20	0.768

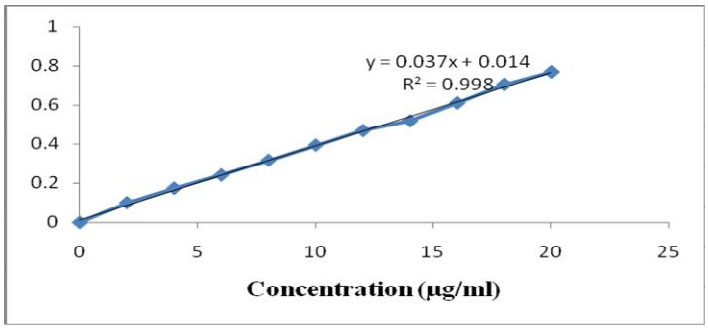

Fig. 1. Calibration curve of Gliclazide in Phosphate buffer pH 7.4

From the calibration curve equation is given as Y = 0.037x - 0.014. The value of Correlation Coefficient ($R^{2)}$ is 0.998. On the basis of obtained results shown in Fig. 1, it was concluded that Gliclazide obeys Beer–Lamberts law in the range of 2-20 µg/ml and shows λ_{max} at 226 nm in Phosphate buffer pH 7.4 Presented in Fig. 1 and Table 1.

3.3 Drug Polymer Compatibility Studies

The FTIR spectra of Gliclazide were determined. The prominent peaks in Gliclazide, physical mixture (Gliclazide, HPMC and modified chitosan) are as follows. Results are shown in Figs. 2 and 3 which confirms drug sample, polymer was authentic [14] and there was no interaction found between Gliclazide, HPMC and modified chitosan.

The thermograph of pure Gliclazide showed a melting endothermic peak at 170.16 ^{0} C. In the thermograph of the mixture peak was observed at 173.35^{0}C of Gliclazide.

The DSC thermograms of the mixture showed sharp distinct endothermic peaks for Gliclazide. This corresponds to the peaks of individual drug and polymer without exhibiting any modification which indicates that the drug did not interact with excipients [14,15] used in the patches. This confirmed that the presence of other excipients did not affect the drug stability shown in Fig. 4 & 5.

3.4 Characterization of Transdermal Patches

Prepared transdermal patches formulations were evaluated for various parameters given below. According to the design; and the effect of formulation variable was studied on % Moisture Content, Folding endurance, % Cumulative drug release at 12 hrs these are as a dependant variable

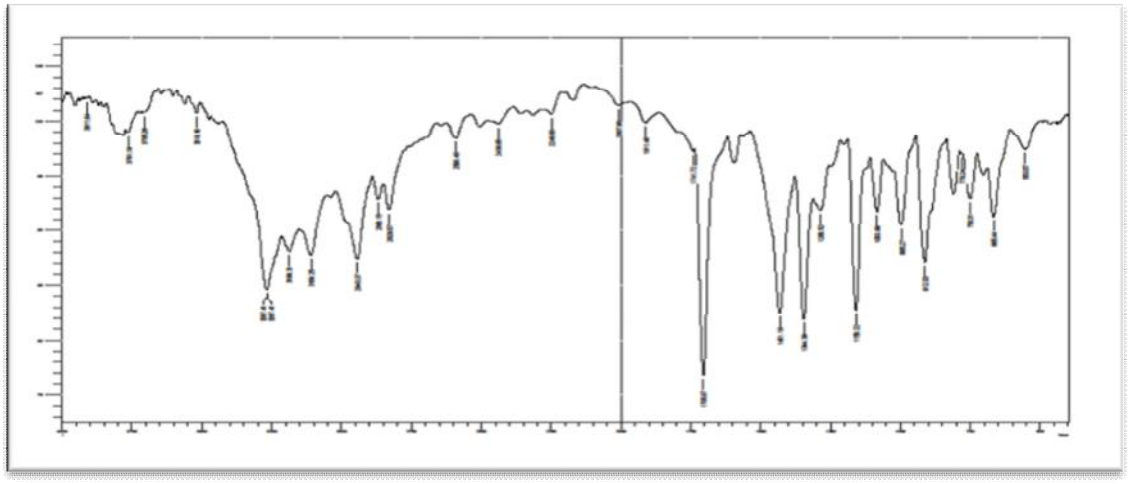

Fig. 2. FTIR Spectra of Gliclazide

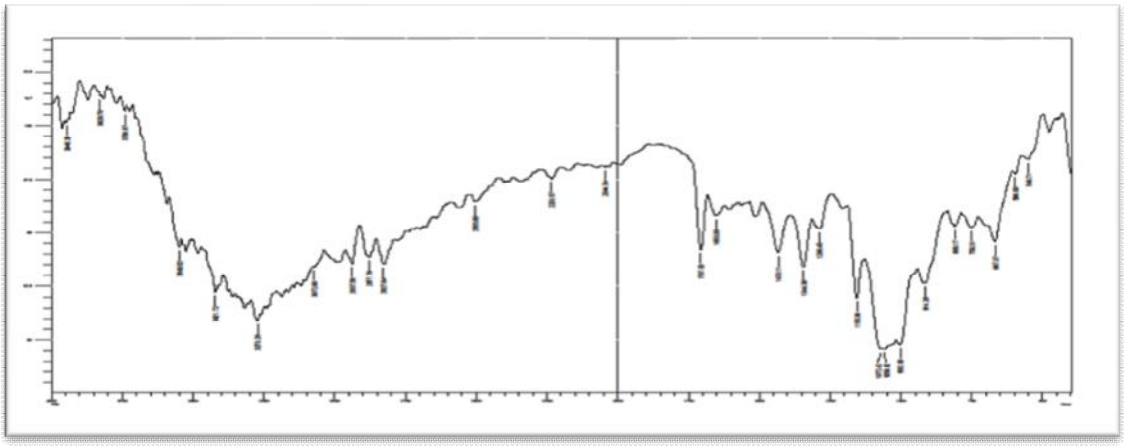

Fig. 3. FTIR Spectra of Mixture of Gliclazide, HPMC and Modified chitosan

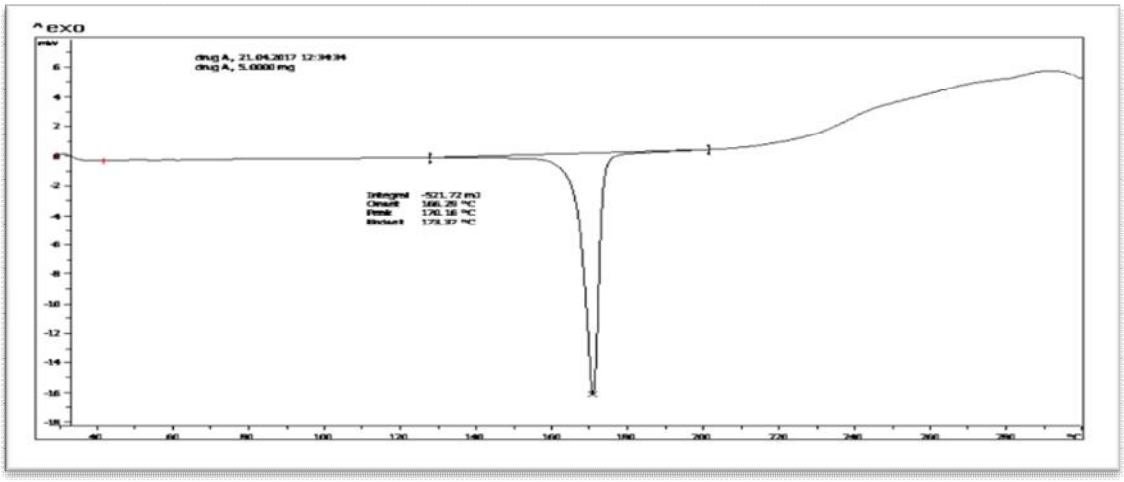

Fig. 4. DSC Thermogram of Gliclazide

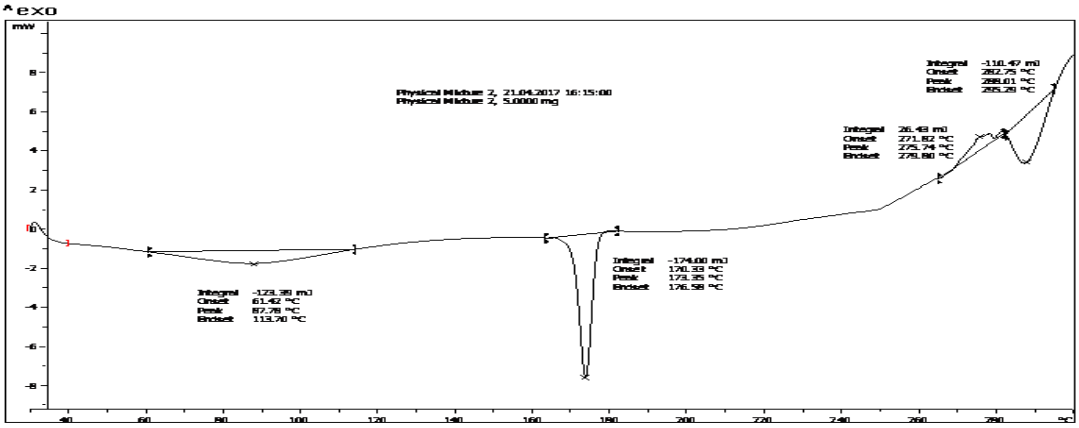

Fig. 5. DSC Thermogram of Mixture of Gliclazide, HPMC and Modified chitosan

Table 3. Evaluations of Optimization Batches

Batch code	Weight variation (mg)	Thickness (mm)	Surface pH	Flatness	% Drug content
F1	12.60±0.6	0.175±0.004	5.7	100	98.33±0.59
F2	12.27±0.61	0.172±0.0075	5.8	100	95.75±0.38
F3	13.87±0.65	0.182±0.002	6	100	97.3±0.38
F4	12.90±0.61	0.179±0.0015	5.9	100	97.94±0.22
F5	12.2±0.65	0.171±0.0035	5.8	100	96.39±0.45
F6	13.07±0.75	0.182±0.0026	5.8	100	97.94±0.59
F7	12.77±0.71	0.175±0.0025	5.6	100	96.14±0.38
F8	12.00±0.6	0.174±0.002	5.7	100	97.17±0.58
F9	14.2±0.52	0.181±0.002	5.6	100	97.29±0.6

*All values are expressed as mean of n=3±standard deviation (SD) ** p>0.005*

3.5 Visual Inspection and Appearance

All the formulations were visually transparent, faint yellow colored, thin, Uniform and smooth. The films which are formed with good appearance and smooth are used for further evaluations.

3.6 Weight Variation

As per Table 3 for each formulation, three randomly selected patches were used. For weight variation test, 3 patches from each batch were weighed individually [15] and the average weight was calculated.

Such determination was carried out for each formulation. The test ensures the uniformity of the formed film.

The weight of the prepared transdermal patches for different type of formulations ranged between 12.00 ± 0.6 mg and 14.2 ± 0.52 m.

3.7 Thickness Uniformity

The thickness of the patches varied from 0.171 ± 0.0035 mm to 0.182 ± 0.0026 mm. Low standard deviation values in the film thickness measurements ensured uniformity of the patches.

3.8 Surface pH

The surface pH value of all patches (5.6 to 6) was close to human skin pH (6.4) which means that there will be no skin irritation and therefore the patches will have good patient compliance[16,17] as the patch was intended for once-a-day application. A very high and low pH value can be harmful to the skin.

3.9 Flatness

As per Table 3 the flatness study showed that all the films had the same strip length before and after their cuts, indicating 100% flatness. Thus, no amount of constriction was observed which shows that all patches had smooth flat surface which would be maintained when the patches are applied to the skin.

3.10 Drug Content

The drug content uniformity of all the formulations was determined. The results of the drug content in all the formulations were found to be in the range 96.27 to 99.87%. A near uniform drug content was noted for the prepared transdermal films ranging from This suggests that the process employed to prepare the films was capable of affording uniform drug content and minimum variability these findings are similar to reference.

3.11 Moisture Content

As per Table 3 & Figs. 6 and 7 it is an important parameter which is very necessary in case if the patches are meant to be applied over the surface of the wound. This phenomenon is utilized to assess the capability of film to absorb wound exudates. The moisture content of the prepared transdermal film was low, which helps to remain stable and maintains suppleness, thus preventing drying and brittleness. Batches containing with high ratio of Sulfoxy Amine Chitosan shows low moisture uptake, so it may be concluded that patches having high ratio of Sulfoxy Amine Chitosan have greater stability [20,21].

The moisture content in the patches ranged from 2.33 to 4.55%. The moisture content in the

formulations was found to be increased by increase in the concentration of HPMC. The prepared film had tendency to absorb moisture effectively.

3.12 Moisture Uptake Studies

The moisture uptake in the patches ranged from 3.17 to 5.69%.The moisture uptake was found to be higher in batches F1, F4, and F7, which might be due to HPMC .Developed transdermal patches with Glycerine had significantly lower moisture loss indicating that the plasticizer will help the formulation remain stable and will also make it less brittle during long-term storage particularly [20,21] under dry conditions. Low moisture uptake protects the material from microbial contamination and bulkiness.

Table 4. Other parameters Evaluations of optimization batches

Batch code	% Moisture content	% Moisture Uptake	WVTR (mg.cm/ cm^2. 24hrs)	Folding endurance	Q12 (%)
F1	2.33	3.17	0.002374	355±7	76.88
F2	3.23	4.03	0.002246	328±4	74.35
F3	4.32	5.04	0.002447	301±4	72.49
F4	2.38	3.20	0.002922	354±5	88.12
F5	3.57	4.96	0.002940	334±6	86.73
F6	4.55	5.69	0.002976	303±6	85.15
F7	2.56	4.48	0.003561	359±6	98.54
F8	3.28	5.00	0.003542	329±3	96.92
F9	4.29	5.56	0.003615	303±2	93.65

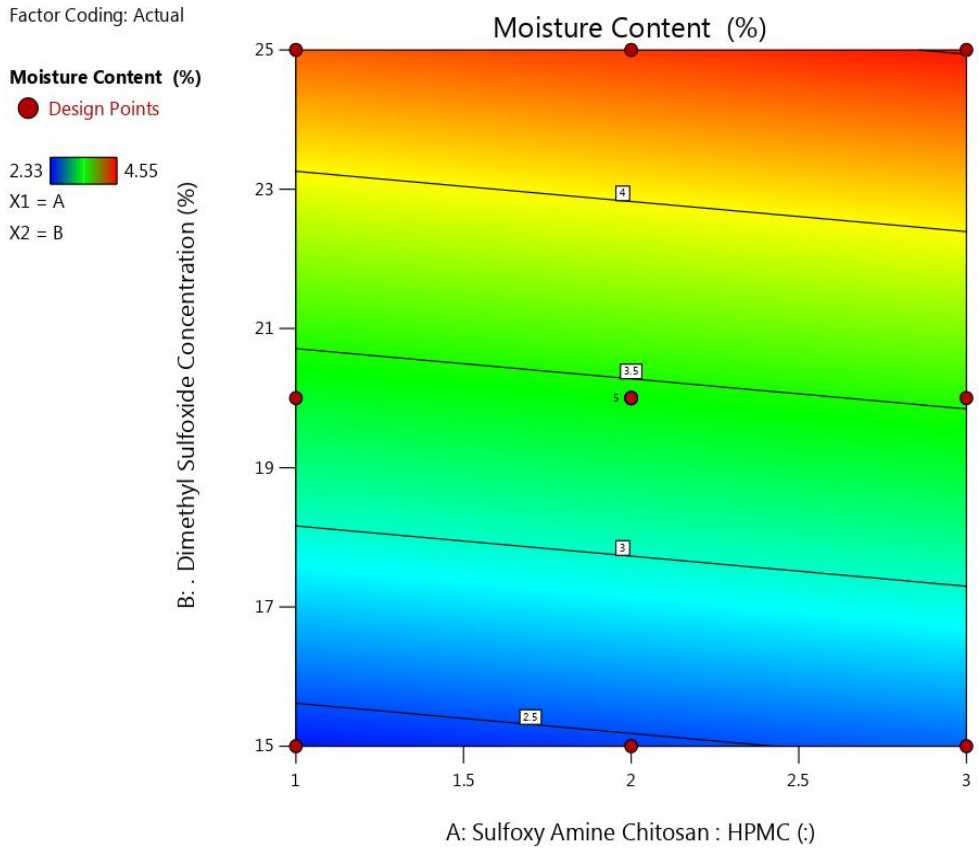

Fig. 6. Contour Plot presenting the effects of Sulfoxy Amine Chitosan:HPMC (X1) and Dimethyl Sulfoxide Concentration (X2) on the % Moisture Content

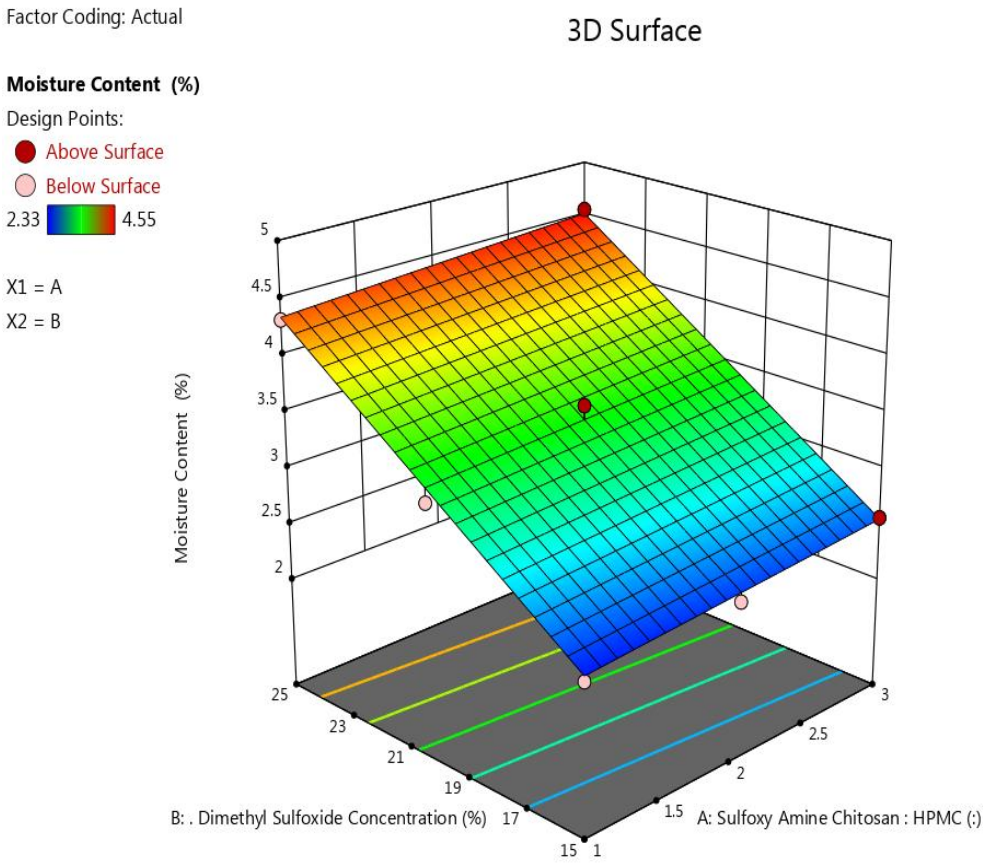

Fig. 7. Repose surface Plot presenting the effects of Sulfoxy Amine Chitosan:HPMC (X1) and Dimethyl Sulfoxide Concentration (X2) on the % Moisture Content

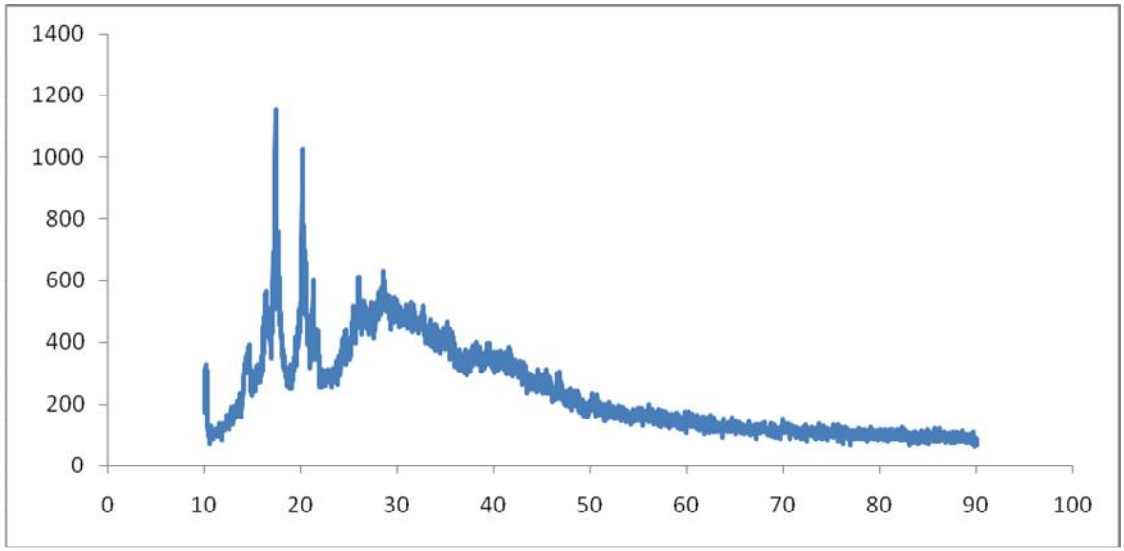

Fig. 8. X-ray powder diffractometry n of Gliclazide

3.13 Water Vapor Transmission Studies

Water vapour transmission studies were carried out to determine the permeability characteristics of the transdermal patches. The water vapour transmission rate for the prepared patches ranged from 0.002246 to 0.003597 mg.cm/cm^2 24h indicating that all the formulations were permeable to water vapour as shown in Table 3.

3.14 X-ray Powder Diffractometry

X-ray diffraction analysis was employed to detect the crystalline nature of the pure drug and the formulation. Transdermal patches and pure drug was subjected to p-XRD study using X-ray diffractometer.

The diffraction pattern of pure optimized formulation of transdermal patch is shown in Figs. 8 and 9. XRD diffractograms revealed that pure gliclazide showed distinctive peaks in 2θ=14., 17.3, 20.1, 25.8 and 28.4 which indicate the crystalline nature of pure Gliclazide [22]. The XRD patterns of pure drug, polymers, and physical mixture of drug and polymers are represented in Figs. 8.10-8.13. The diffractograms of pure gliclazide and patch exhibited a series of intense peaks, which are indicative of their crystallinity. XRD diffractogram revealed that optimized formulation patch showed three peaks in 2θ= 20.6 28.7 and 38.95 with very weak intensities. The crystalline structure of Gliclazide was destroyed in patch which was evident from decrease in number and intensity of peaks. This indicates the amorphous dispersion of the drug after incorporation into patches. In other words these findings suggest that the Gliclazide crystals might have converted to amorphous form in patch formulation which was considered to be mainly responsible for the dissolution enhancement [23]. In the case of a Physical mixture; the total number of peaks is reduced due to use of hydrophilic polymers Modified chitosan and HPMC as constituents of film. In this case, the dilution of drug due to excipient has reduced the intensity of peaks.

3.15 Folding Endurance

Folding endurance represents the mechanical property of the property of the film to withstand the conditions during blinking of eye [24]. The Folding Endurance of ocular insert of all formulations was shown in Table 4. Folding endurance was determined by repeatedly folding a small strip of the film at the same place until it break as shown in Figs. 10 and 11. This test was performed to evaluate the flexibility of the films; the films were analyzed by folding endurance studies. The values were in the range of 301 and 359 as seen in the formulation. It was found to be high in patches containing higher amount of HPMC. However, out of these five formulations F7 was shown a highest folding endurance 359±6 for that concentration.

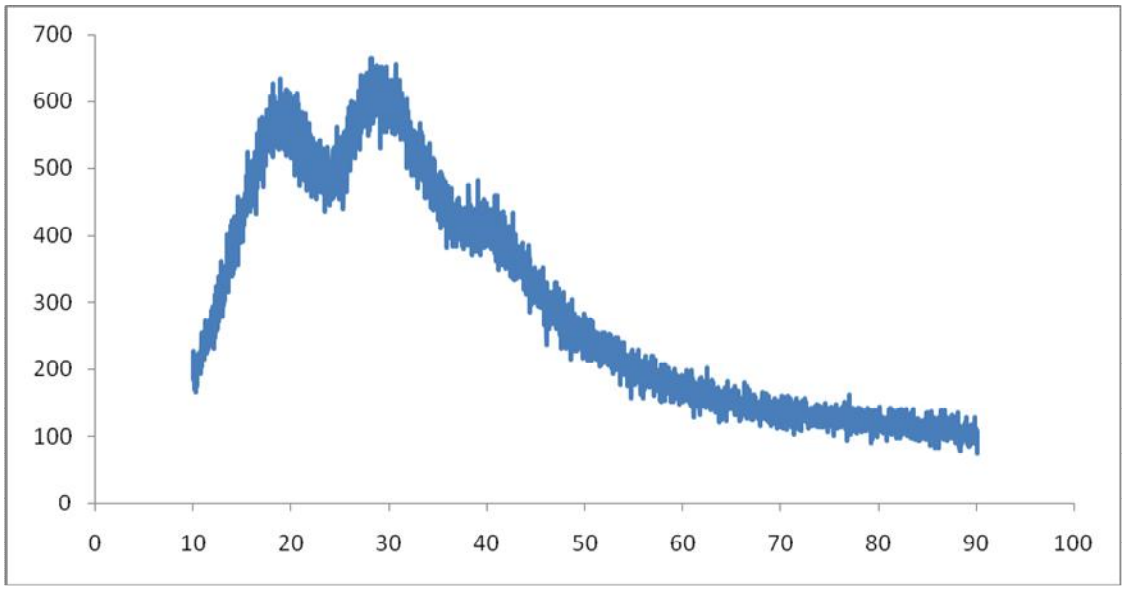

Fig. 9. X-ray powder diffractometry of Mixture of Gliclazide, Modified chitosan and HPMC

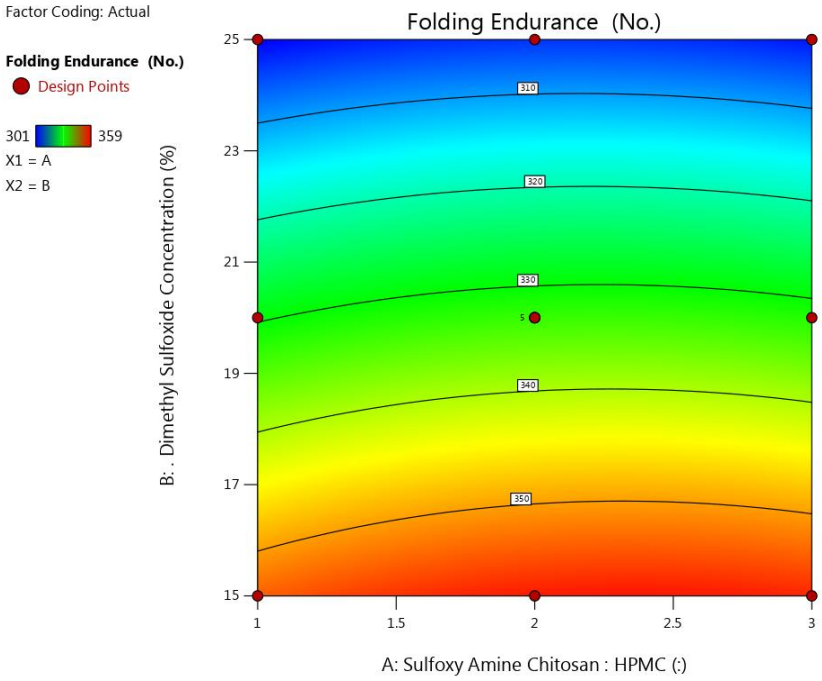

Fig. 10. Contour Plot presenting the effects of Sulfoxy Amine Chitosan:HPMC (X1) and Dimethyl Sulfoxide Concentration (X2) on the Folding Endurance

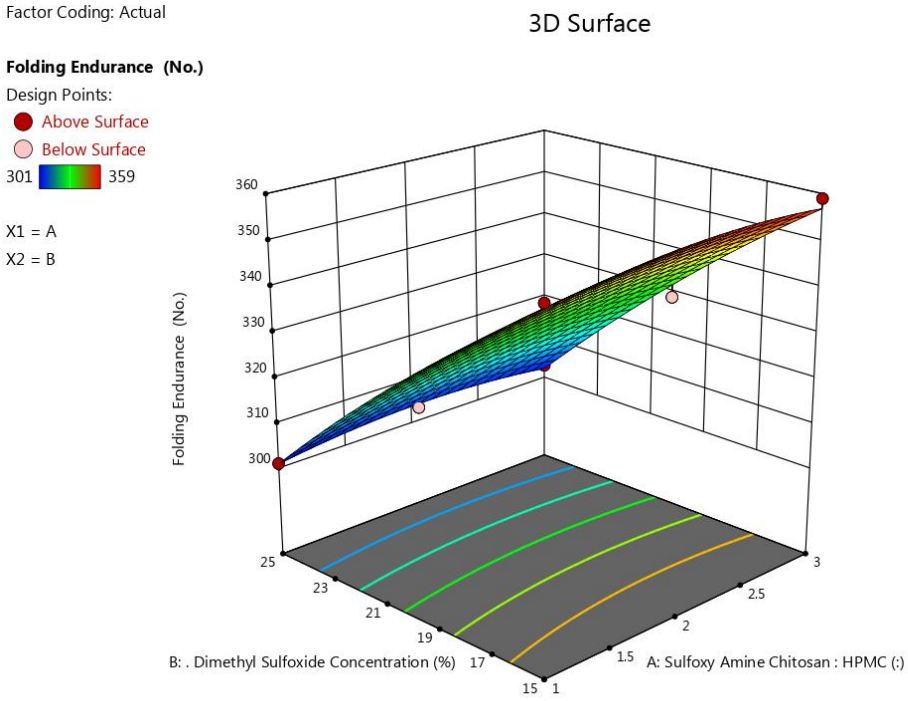

Fig. 11. Repose surface Plot presenting the effects of Sulfoxy Amine Chitosan:HPMC (X1) and Dimethyl Sulfoxide Concentration (X2) on the Folding Endurance

3.16 *In vitro* Permeation Studies

The diffusion studies were conducted to get an idea of permeation of drug through barrier from the transdermal system using. The Franz horizontal diffusion cells with a receptor compartment were utilized. The drug release profile of all formulations is presented in Fig. 12 and 13. In The order of in-vitro drug Release of the formulations were F3<F2<F1<F6<F5<F4<F9<F8<F7. Initial burst release is higher in matrix film formulated using low viscosity grade HPMC, compared to polymer with high viscosity modified chitosan From the Fig. 14, it can be concluded that the drug release appeared to increase more with an increasing amount of the DMSO and also HPMC. Batch containing high proportion of HPMC shows greater release than batch containing high proportion of Modified chitosan, due to sustaining property of chitosan. shows fast release of drug from patch due to its more hydrophilic nature than HPMC [24-27]. The batch F7 shows high drug release at 12 hrs 98.54%, as this batch contain high proportion of DMSO and HPMC .kinetics study, the results of all formulations were treated by different kinetic method as shown in Figs. 11 and 12 [28].

Responses observed for nine formulations were fitted to Design Expert software latest version 12 outcome of ANOVA is as shown in Table 4. Statistical analysis data suggested that Linear model for % Moisture Content, Quadratic model for folding endurance variables & Model Linear for % CDR variables [25-26]. All the polynomial equations were found to be statistically significant (P < 0.01), as determined using analysis of variance (ANOVA) shown in Table 5.

The equation in terms of coded factors can be used to make predictions about the response [27,28]. for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

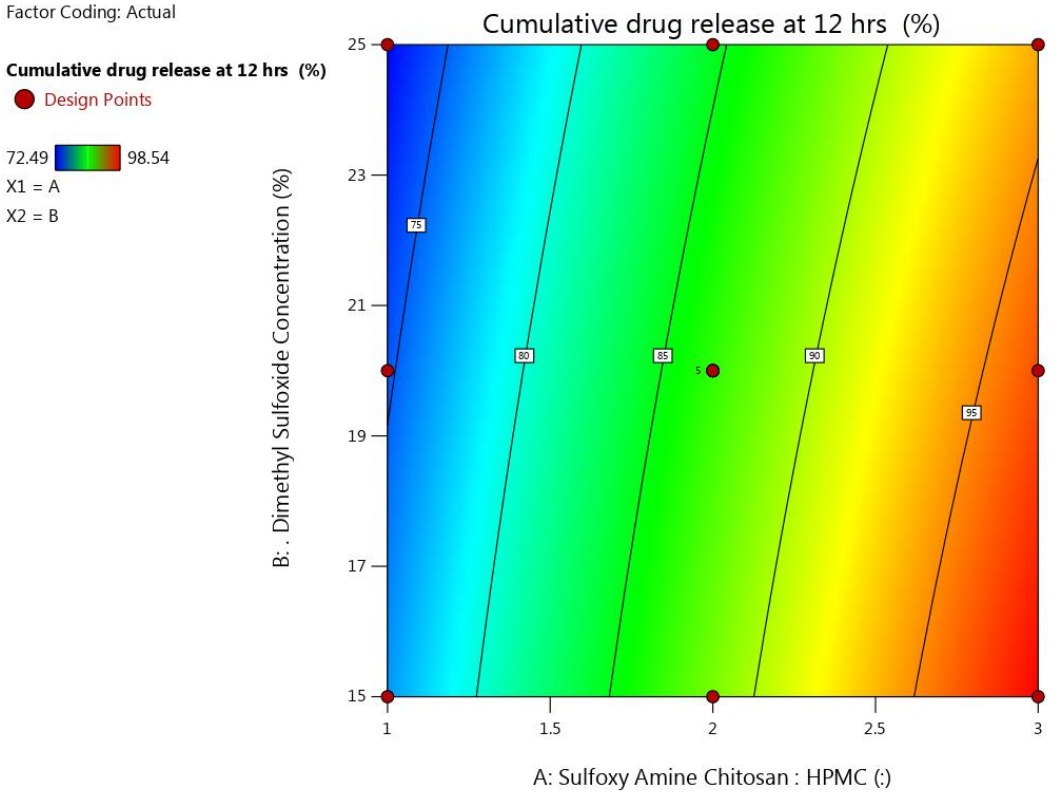

Fig. 12. Contour Plot presenting the effects of Sulfoxy Amine Chitosan:HPMC (X1) and Dimethyl Sulfoxide Concentration (X2) on the % CDR

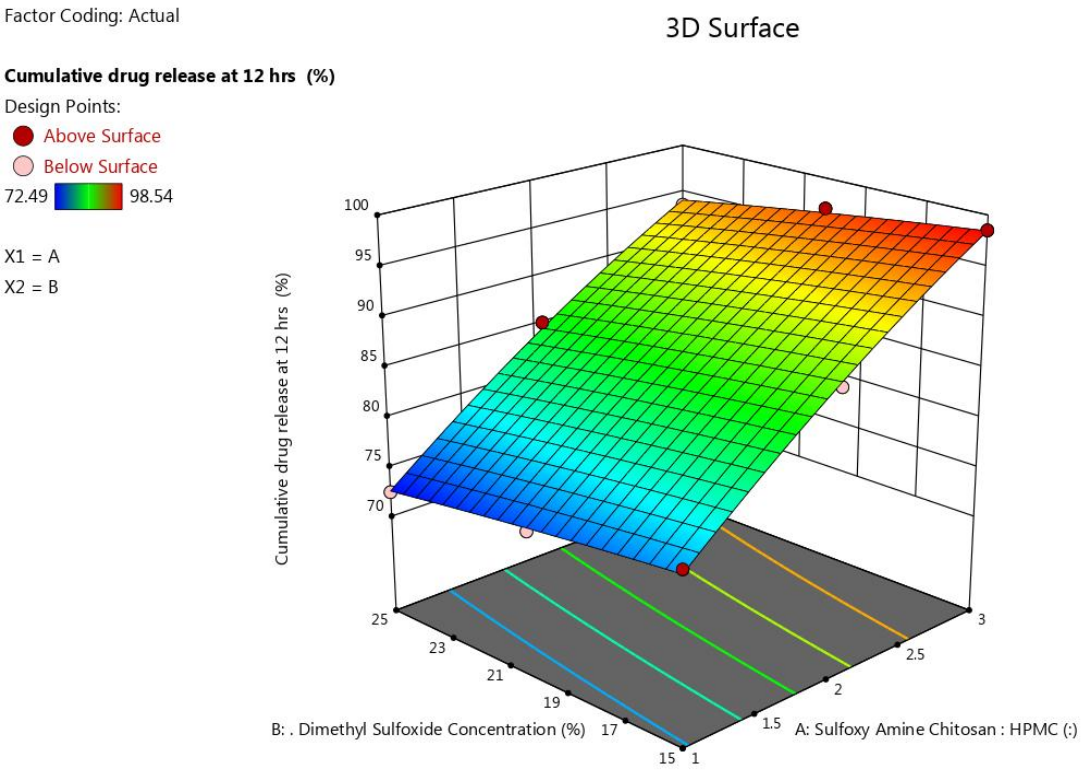

Fig. 13. Repose surface Plot presenting the effects of the effects of Sulfoxy Amine Chitosan:HPMC (X1) and Dimethyl Sulfoxide Concentration (X2) on the % CDR

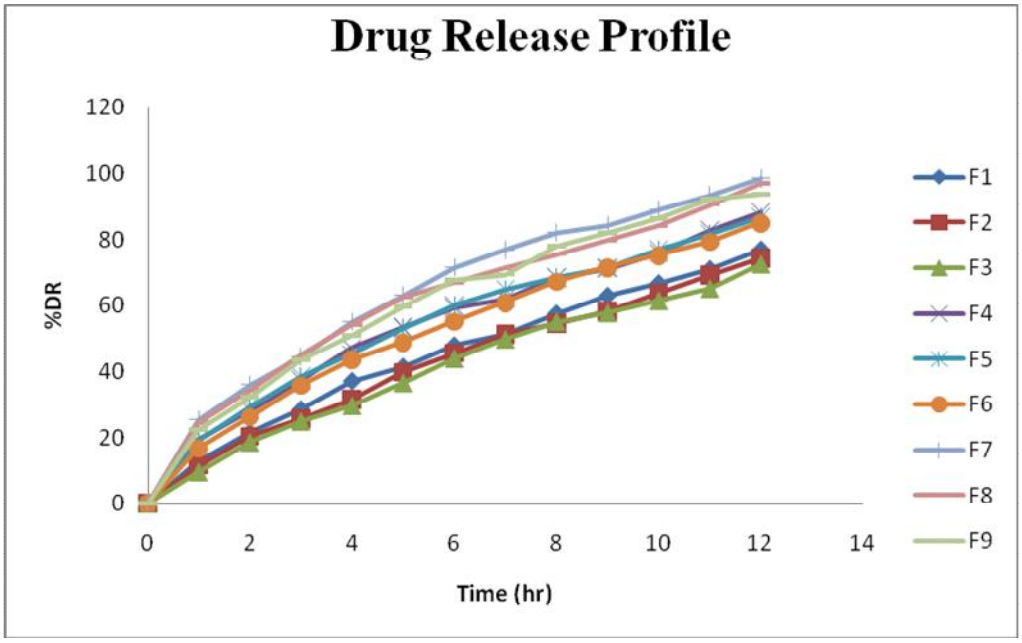

Fig. 14. *In Vitro* Drug permeation profile for batch F1 to F9

Table 5. Result of ANOVA

Response Model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Ade. Precision	CV %
% Moisture Content	6.01	12	2.92	155.30	Significant	0.9626	32.42	3.97
Folding Endurance	4414.9	12	891.23	171.23	Significant	0.9861	36.89	0.68
% CDR	744.08	12	148.69	148.73	Significant	0.9968	85.37	0.51

Table 6. Release Mechanism of Optimized Formulation

Batch code	Zero order	First Order	Higuchi Model	Koresmeyer- Peppas	
	R^2	R^2	R^2	R^2	*n*
F7	0.962	0.866	0.994	0.995	0.556

Mathematical relationship in the form of polynomial equation for the measured response % folding endurance

% Moisture Content = +3.45+0.0850 A+0.9817 B

Mathematical relationship in the form of polynomial equation for the measured response % folding endurance

Folding Endurance = +333.10+1.17A-26.83B-0.5000AB-2.36A^2 – 2.36 B^2

Mathematical relationship in the form of polynomial equation for the measured response % CDR

% CDR = +86.75+10.90A-2.04B*--0.1250*AB--1.17*A^2 +-0.1674B^2

3.17 Mathematical Modeling and Release Kinetics

As per Table 6 the results were suggested that, the value of of R^2 (Regression coefficient) was obtained linear in case of Higuchi Kinetics as compared to zero order and first order kinetics for all formulations .Hence, to confirm the exact mechanism of drug permeation from these patches, the data were fitted to the Korsmeyer-Peppas model. In the present study, the coefficient of determination (*R2* =0.995) was found to be much closer to 1 and the release exponent 'n' value vary between 0.556 , which explained that drug released from the films occurs by Non- fickian type of diffusion [29]. Overall results of kinetic modeling suggest that diffusion is dominant mechanism for drug release following Non-Fickian type of diffusion.

4. CONCLUSION

As per aim & objectives of the study Transdermal patches of Gliclazide have been successfully formulated by solvent casing method with the help of Sulfoxy Amine Chitosan, HPMC, Penetration enhancer DMSO and Glycerine. The Ratio of polymer weight (Sulfoxy Amine Chitosan: HPMC) (X1) and Penetration enhancer Concentration of Dimethyl Sulfoxide (X2) were chosen as independent variables. Nine formulations were prepared according to the design; and the effect of formulation variable was studied on % Moisture Content, Folding endurance, % Cumulative drug release at 12 hrs these are as a dependant variable. Drug excipient compatibility shows that the drug and excipients were compatible with each other. The films were evaluated for various parameters. The weight of the transdermal patches for different type of formulations ranged between 12.00 ± 0.6 mg & 14.2 ± 0.52 mg. The thickness of the patches varied from 0.171 ± 0.0035 mm to 0.182 ± 0.0026 mm. The moisture content & water vapour transmission rate in the patches ranged from 2.33 to 4.55% & from 0.002246 to 0.003597 mg.cm/cm^2 24hrs. XRD diffractogram revealed pure Gliclazide exhibited characteristic high-intensity diffraction peaks & the Gliclazide crystals might have converted to amorphous form in patch formulation. Optimized batch F7 showed maximum drug release 98.41%. The folding endurance was measured manually and it lies in between 301 and 359 . Thus, the design of experiment with response surface method is an efficient tool to determine and optimize formulation conditions within experimental conditions. On basis of research finding it was concluded that we concluded that transdermal patches of Gliclazide of was successfully

formulated with synthesized Sulfoxy Amine Chitosan & evaluated & synthesized Sulfoxy Amine Chitosan can be used as a polymer for designing various dosage forms of other drugs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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