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Development and Evaluation of osmotically controlled drug delivery system of Gliclazide

Dr. Meenakshi Bharkatiya[a], Abhishek kumar[b]*, Dr. Chetan Singh Chauhan[a] and Dr. Komal Sharma[a]
[a] Faculty of pharmacy, B. N. Institute of Pharmaceutical Sciences, B.N. University, Rajasthan, Udaipur-313001
[b]Department of Pharmacy, Ashoka Institute of Technology and Management, Uttar Pradesh, Varanasi-221003

Corresponding address:
Corresponding author: Mr. Abhishek Kumar
Mailing address: Z/S, 8/48 Veernagar Colony, Shivpur Coat Varanasi-221003, India
Contact No: 09125671496
Email: abhishekaitm641@gmail.com

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Abstract

A controlled porosity osmotic pump of cellulose acetate for osmotic delivery of Gliclazide has been developed and influence of different pore forming agents and osmotic agents on *in vitro* drug release was investigated. The capsule membrane was prepared by the phase inversion technique. To ensure the osmotic delivery, two approaches were adopted: *(i)* PEG-400 was used in different concentrations as pore forming agent (*ii*) the drug was encapsulated with osmogent sodium chloride to increase the osmotic pressure. Formulations were evaluated for weight variation, thickness, void volume, tensile strength and *in-situ* pore formation. Dye test revealed *in-situ* pore formation in membrane.

A 3^2 factorial design was employed to optimize the concentration of pore forming agent (X_1) and osmogent (X_2) as independent variables.

Both the selected independent variables had a significant influence on the amount of drug released. The transformed values of the independent and dependent variables were subjected to multiple linear regression analysis to establish a full-model second-order polynomial equation.

The coefficient of independent variables suggests that osmogent Sodium chloride is the major contributing factor for the amount of drug released ($b_1 > b_2$). A contour plot is presented to represent the effect of independent variables on the amount of drug released. A checkpoint batch was also prepared to prove the validity of the mathematical model. Optimization studies showed asymmetric membrane capsule with 70% PEG as pore forming agent and 1.5% of sodium chloride as osmogent as the best formulation. The release kinetics reveal that optimized batch fits well with Zero order model.

Key words: cellulose acetate, sodium chloride, controlled porosity; Gliclazide, PEG-400

Introduction

Osmotically controlled drug delivery systems are innovative and highly versatile systems, utilizing principles of osmosis for controlled delivery of drugs. These systems release the drugs independent of GI physiological factors to a large extent[1]**.** The asymmetric membrane capsule is

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Subject::Science

also an example of a single core osmotic delivery system, consisting of a drug-containing core surrounded by an asymmetric membrane[2]. One of the advantages of an asymmetric membrane is the higher rate of water influx, allowing the release of drugs with low solubility[3]. The release rate from such system can be made independent of pH and rate of agitation by use of semipermeable membrane and osmotic excipients[4]. This system utilizes the principle of osmotic pressure and delivers drug dose in an optimized manner to maintain drug concentration within the therapeutic window and minimizes toxic effects. Controlled porosity osmotic pump contains drug, osmogens, excipients in core and a coating of semipermeable membrane with water soluble additives[5]. The asymmetric membrane capsule for osmotic delivery of drug consists of very thin; dense skin structure supported by a thicker, porous sub-structural layer[6-8]. The asymmetric membranes have high flux due to their porous nature and hence find their use in achieving higher release rate for poorly soluble drug [9]. Oral osmotic delivery systems have been used in a variety of therapeutic areas and have produced significant clinical benefits in the field of medicine[10].

Gliclazide is one of the most commonly prescribed drugs for the treatment of patients with type II diabetes mellitus. It is practically water-insoluble, but the absolute bioavailability is close to one. Thus, it belongs to class 2 of Biopharmaceutic Classification System. Gliclazide has a half-life of 6-8 hours, thereby requiring two to three times daily dosing in large number of patients, which often leads to non-compliance[11-12]. Thus, there is a strong clinical need and market potential for a dosage form that will deliver Gliclazide in a controlled manner thereby resulting in a better patient compliance.

The objective of the present investigation was to develop an asymmetric membrane capsule to deliver Gliclazide, based on osmotically controlled drug delivery system. The capsule contains two parts, Body and the Cap. The mixture of the drug and the osmotic agent was filled in the body of the capsule and the cap was snugly fitted to the body of the capsule.

Materials and Methods

CA was obtained from CDH. Ltd., India. PEG-6000, SLS, Mannitol and glycerol were obtained from S.D. Fine Chemicals Ltd Delhi; The Drug was a gift sample from FDC Pharmaceutical, Ltd Bombay India.

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Methods

Preparation of Asymmetric Membrane Capsules

The asymmetric membrane capsule was made by a phase inversion process. in which the membrane structure was precipitated on a stainless steel mold pin by dipping the mold pin in coating solution followed by quenching in an aqueous solution[13].

15% solution of CA was prepared in acetone/water (90/10 v/v) solvent system. Weighed quantity of CA was added to the solvent system and the resulting mixture was stirred in a well closed beaker until a homogenous solution was formed. While stirring PEG were added as pore forming agent in 50, 60 and 70% w/w of the cellulose acetate. The stainless steel mould pins were dipped in the coating solution of CA and glycerol for 2 minutes and removed carefully, so as to form a thin layer of solution on the mould. The pins were taken out and briefly air dried for 30 seconds followed by quenching in aqueous solution (10% w/v glycerol). This resulted in phase inversion and formation of asymmetric membrane. The resulting membrane was stripped off and trimmed to desired size and stored[14].

Filling and Sealing of asymmetric membrane capsules

The fabricated capsules were filled with the mixture of drug and osmogents respectively. The physical mixture of drug and Sodium chloride was prepared by mixing them in laboratory blender for 10 minutes and subsequently passing the mixture through sieve No. 80. The capsules were filled with mixture of drug and osmogents in the constant ratio of 1:0.5 in the body and the cap was snuggly fitted to the body. Body and cap of the filled capsule were finally sealed with a sealing solution of 16 % cellulose acetate. [15].

Evaluation of asymmetric membrane capsules

Weight variation

Twenty capsules were weighed individually. The average weight was calculated and was compared with the weight of each capsule.

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Thickness

Twenty capsules were randomly selected from each batch and individually measured the thickness of the wall and the effective surface area using the digital micrometer.

Void volume determination

The void volume of each of the asymmetric membrane as the function of the pore forming agents present at different levels was determined. The weight of the empty capsule (Wo) was obtained. The weighed capsule was put into a vial filled with distilled water and left overnight to effect complete quenching of the pore forming agent present in the wall of the capsule shell. The capsule was taken out of the vial, wiped with tissue paper and immediately weighed (Ww). The capsule was then placed into an oven at 50º C; it was periodically weighed until a constant weight was obtained (Wd). The volume of the pore forming agent (Vp) present in the capsule wall was measured by (Wo-Wd)/ρ, where, ρ = density of pore forming agent used.

The total volume of water (Vw) present in the dry film was measured by (Ww-Wd)/1 (density of water =1 g/cm3). The void volume of the polymer per unit weight of polymer was determined by[16-17]

(Vw-Vp)/Wd.

Tensile strength

A small strip of the membrane of the capsule was cut on a glass plate with a sharp blade. One end of the membrane was fixed between adhesive tapes to give support to the membrane when placed in the film holder. Another end of the membrane was fixed between the adhesive tape with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin where hook was inserted. A thread was tied to this hook, passed over the pulley and a small pin attached at the other end to hold this weight. A small pointer was attached to thread, which travelled over the graph paper affixed on the wooden plate. Weights were gradually added to the pan to increase the pulley force till the membrane

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November 2021
Impact Factor:5.7
Subject:Science

was broken. The weight required to break the membrane was noted as the break force. Tensile strength was calculated by using formula:

$$\% \text{ Tensile strength} = \left[\frac{\text{Break force}}{a \times b} \right] \left[1 + \frac{\Delta L}{L} \right]$$

Conformation of in situ pore formation

The in-situ pore formation in capsules should take place due to the virtue of leaching of the pore forming agent present in the asymmetric membrane into the release medium. To confirm this phenomenon dye-test was conducted. The capsule were filled with a water soluble amaranth dye (20 mg). The dye was filled in each of the capsule body manually and the cap was snugly fitted to the body and finally sealed with a sealing solution of cellulose acetate only (14% w/v). The capsules filled with dye were placed in 50 ml distilled water and observed for release of dye through the membrane. To demonstrate that the prepared system follows the osmotic principle to release its encapsulated contents, the capsules filled with amaranth dye were placed in a release medium of higher osmotic pressure (50 mL 10% w/v sodium chloride solution) and the capsules were visually observed for the release of dye[18].

Scanning Electron Microscopy

Asymmetric membranes obtained before and after dissolution of core contents were examined. Asymmetric membrane structures were dried at 50°C for 8 hours and stored between sheets of wax paper in dessicator before examination. Asymmetric membranes were sputter coated for 5 to 10 minutes with gold by using fine coat ion sputter at 50 mA and examined under SEM at suitable magnification.

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Factorial design

A 3^2 full factorial design was employed in the present study to optimize and evaluate the asymmetric membrane capsules of Gliclazide. Two factors are evaluated, each at three different levels and trials are performed at all 9 possible combinations.

The concentration of PEG-400 ($X_{1)}$ in the asymmetric membrane and the ratio of Sodium chloride (X_2) in the core of the formulation were considered as the independent variables. The maximum drug released at the end of the dissolution run was selected as dependent variable. The design was evaluated by quadratic model represented by the following equation:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2 \quad \text{- - - - - - - (1)}$$

Where Y is the response (dependent) variable, b_0 is the intercept, b_1, b_2, b_{11}, b_{22} and b_{12} represents the regression coefficient. X_1 and X_2 stands for the main effect, X_1 X_2 are the interaction terms and shows how the response changes when two factors are simultaneously changed. X_1^2 and X_2^2 are quadratic terms of independent variables to evaluate nonlinearity.

A check point analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken by designing two extra check points (C_1 and C_2) and determining the cum % release.

In vitro drug release study

In vitro release of Gliclazide from formulations was carried out by using USP type II apparatus (50 rpm, 37^o C) in 900 ml phosphate buffer (pH 7.4) at 50 rpm at 37°C. At appropriate time intervals, dissolution samples were withdrawn and filtered. Samples were analyzed at 223 nm by using UV-visible double beam spectrophotometer.

Result and discussion

The overall appearance and quality of asymmetric membrane capsules is a function of the formulation coating as well as variables in the capsules manufacturing process. The asymmetric membrane capsules were white to off white, opaque and glossy with no visible imperfections or blemishes.

ISSN: 2320-3714
Volume:4 Issue: 2
November 2021
Impact Factor:5.7
Subject::Science

Weight variations and their dimensions were demonstrated to be consistent with little variation. However the weight of the capsule increased as the concentration of pore forming agent was increased. This corresponds with the fact that concentration of polymer has more pronounced effect on the weight of the AMCs. Separate lengths of caps and bodies were found to be consistent within the capsules from each batch. This confirms that the process of producing these AMCs was reproducible and robust.

Membrane thickness and surface area was found to be almost same for all the capsules with slight variation. This confirms the uniformity as well as robustness of the process employed in their fabrication. The tensile strength and void volume was found to increase with increase in concentration of pore forming agent. The average physical parameters of the asymmetric membrane capsules are shown in Table No.2 respectively.

In situ pore formation in asymmetric membrane wall for releasing drug was proven by filling the capsule with water soluble dye, amaranth. A stream of coloured dye was observed to be diffusing from capsule wall when suspended in water after a lag time. This indicates in-situ pore formation of delivery orifice due to leaching of pore forming agent present in the asymmetric membrane.

The morphology of the asymmetric membrane capsule was studied by scanning electron microscopy. Fig. 1 shows the dense thin layer on the outside and a thicker highly porous layer on the inside of the shell.

In-Vitro Release Studies

The *in vitro* release of Gliclazide from the capsules for all formulations were studied. The *in-vitro* release was performed using 900 ml of phosphate buffer (pH 7.4) for 9 hours. Variable release profile of Gliclazide from different osmotic pump was observed.

It was found that the amount of drug release increased as the concentration of pore forming agent was increased from 50% to 70%. When the pore forming agent was at a higher concentration, the release was higher probably owing to increased pore formation on the membrane during dissolution. Thus, the membrane with higher porosity would lead to early solubilization of the drug, causing its higher release.

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Impact Factor:5.7
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In spite of the increase in the porosity in the membrane, the amount of drug released by the virtue of its own osmotic pressure would be slow due to low aqueous solubility of drug causing small pressure gradient. Thus to increase the osmotic pressure gradient the drug was encapsulated with sodium chloride as osmotic agent. The release of Gliclazide from the osmotic pump was determined and results shows that the osmogent sodium chloride in core formulation had a marked influence on drug release. The results of *in-vitro* drug release of Gliclazide from capsules are shown in table 3. The data revealed that the release pattern of the formulations was best fitted for zero order kinetics since its coefficient of correlation values predominates over first order and higuchi kinetics.

A 3^2 full factorial design was employed to systematically study the effect of pore forming agent (X_1) and osmotic agent (X_2) on cumulative drug release at 540min (%Y540) (Table 3). In this design, 2 factors are evaluated, each at 3 levels and experimental trails were performed at all 9 possible combinations. The quadratic model generated by the design is of the form:

$$\mathbf{Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2} \quad \text{- - - - - (1)}$$

Where, Y is the dependent variable, βo is the arithmetic mean response of the nine runs, and βi is the estimated coefficient for the factor Xi. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_{12} and X_{22}) are included to investigate nonlinearity. A mathematical relationship in the form of quadratic equations for % CDR is as follows:

$$\mathbf{Y = 59.99 + 10.70X_1 + 17.03X_2 - 3.47X_1^2 - 2.93X_2^2 + 7.04X_1X_2} \quad \text{- - - - - (2)}$$

The amount of drug released at the end of dissolution run for all the 9 batches (F1 to F9) showed wide variation (33.568 mg to 87.32 mg). This variation indicates that the amount of drug released strongly depends on the selected independent variables. This is also reflected by the coefficient of the terms of equation (2). The results of in-vitro drug release are subjected to multiple linear regression analysis. Results of regression analysis are presented in Table 4.

The value of the correlation coefficient (r^2) of equation was found to be 0.9972, indicating good fit. The significance of each coefficient was determined by student's t-test and P value. The

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Peer Reviewed
Multidisciplinary
International
ISSN: 2320-3714
Volume:4 Issue: 2
November 2021
Impact Factor:5.7
Subject::Science

larger the magnitude of the t-value and smaller the p-value, the more significant is the corresponding coefficient. This suggests that the main effect of PEG - 400 ($X_{1)}$ and sodium chloride (X_2) are significant ($P<0.05$). The second order main effect of PEG-400 and sodium chloride are also significant ($P<0.05$). The interaction between X_1X_2 was found to be significant. ($P<0.05$). The result of ANOVA of full model is shown in table 5.

As the calculated value F is greater than the tabulated value ($F = 9.013455$; $\alpha = 0.05$, $df = 2, 3$), it was concluded that the selected independent variables contribute significantly in the amount of drug released from the controlled porosity osmotic pump. A higher value of correlation coefficients (0.9972 for full model) signifies an excellent correlation between the independent variables. The result of multiple linear regressions suggests that the release rate of drug from the prepared osmotic system increases with the increase in both the amount of PEG 400 in the asymmetric membrane and the ratio of sodium chloride present in the core of formulation, as the coefficient for both these factors (b_1, b_2) and their interaction coefficient (b_{12}) bears a positive sign. However the amount of sodium chloride (osmotic agent) in the core of the formulation was found to be major contributing factor compared to the proportion of PEG 400 (pore forming agent) in asymmetric membrane, because the value of coefficient b_1 (10.70) was found to be less than coefficient b_2 (17.03). This leads to the conclusion that the osmotic pressure of the core of the formulation is an important factor to affect the osmotic delivery of the poorly water soluble drug.

The data transformation simplifies the calculations for model development. To demonstrate graphically the effect of X1 and X2, and to find an optimized formulation within the factorial space, the contour and response surface plots were generated for the dependent variables.

The contour plot (Fig. 2) and Response Surface Plot (Fig. 3) demonstrates that dependent variables are strongly dependent on the independent variables. As the amount of osmotic agent increased, % CDR increased; this is because of its osmotic property it creates osmotic pressure and that will be helpful to increase % CDR. Similarly, as the concentration of pore forming agent increased, % CDR increased. However, the effect of sodium chloride seems to be more pronounced at lower level as compared to PEG - 400.

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Peer Reviewed
Multidisciplinary
International
ISSN: 2320-3714
Volume:4 Issue: 2
November 2021
Impact Factor:5.7
Subject::Science

Check – Point analysis

A check point analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken by designing two extra check points (C_1 and C_2) and determining the cumulative % release. The theoretical values of % cumulative drug release were calculated by substituting the values in the polynomial equation.

The cumulative % release from the full model was found to be 55.09 and 51.43 respectively for C_1 and C_2, where as those observed experimentally are 56.34 and 52.71 respectively. Results indicated that the measured % CDR values matched well with expected % CDR. The closeness of the predicted and experimental values for C_1 and C_2 indicates that the mathematical model is valid. The results of Checkpoint batches with predicted and measured % CDR are shown in Table 6.

Table 1 Variables and their levels in 3^2 Full Factorial Design

Batch	Variable level in coded form	
	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Independent	Levels

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ISSN: 2320-3714
Volume:4 Issue: 2
November 2021
Impact Factor:5.7
Subject:Science

Variables	Low	Medium	High
X_1 = Concentration of PEG-400	50 %	60 %	70 %
X_2 = Amount of Osmotic agent (NaCl)	50 mg	100 mg	150 mg
Transformed (Coded) Value	-1	0	+1
Dependent variable = Y_{540}	Y_{540} = % Cumulative Drug Release at 540 minutes		

*X_1 indicate PEG-400 and X_2 indicate Sodium chloride, F1 to F9 are factorial batches, C1 and C2 are check point batches.

Table 2 Average physical characteristics of the asymmetric membrane capsules (PEG – 400)

Capsule shell code	**PEG – 50%**	**PEG – 60%**	**PEG – 70%**
Capsule shell weight (mg)	104.53 ± 0.042	106.86 ± 0.060	118.58 ± 0.557
Length(mm) Body	19.73 ± 0.025	19.91 ± 0.015	18.71 ± 0.390
Length(mm) Cap	12.81 ± 0.012	12.85 ± 0.026	12.81 ± 0.012
Membrane thickness (cm)	0.210 ± 0.002	0.218 ± 0.003	0.241 ± 0.003
Surface area (mm^2)	596.52 ± 1.01	604.02 ± 1.95	603.88 ± 1.78
Void volume (cm^3/g)	1.661 ± 0.004	1.707 ± 0.001	1.850 ± 0.008
Tensile strength (kg/cm^2)	0.132 ± 0.001	0.148 ± 0.005	0.186 ± 0.004

Table 3: Variables and their levels in 3^2 Full Factorial Design

Batch	**Variable level in coded form**		**Q_9 (mg)**
	X_1	X_2	
F1	-1	-1	33.56 ± 0.426

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F2	-1	0	45.89 ± 0.984
F3	-1	+1	52.16 ± 0.684
F4	0	-1	39.05 ± 0.612
F5	0	0	59.21 ± 0.470
F6	0	+1	75.87 ± 0.548
F7	+1	-1	40.55 ± 0.520
F8	+1	0	67.95 ± 0.630
F9	+1	+1	87.32 ± 0.611
C1	-0.5	0.1	56.34 ± 0.212
C2	0.1	-0.5	52.71 ± 0.334

Independent Variables	Levels		
	Low	Medium	High
X_1 = Concentration of PEG-400	50 %	60 %	70 %
X_2 = Amount of Osmotic agent (NaCl)	50 mg	100 mg	150 mg
Transformed (Coded) Value	-1	0	+1
Dependent variable = Q_9	Q_9 = % Cumulative Drug Release at 9 hour		

*X_1 indicate PEG-400 and X_2 indicate Sodium chloride, F1 to F9 are factorial batches, C1 and C2 are check point batches, Q_9 amount of drug released after 9 hours.

Table 4 Model Coefficients Estimated By Multiple Regression Analysis.

Factor	**Coefficients**	**Computed *t*-values**	**P-value**

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Intercept	59.99 (b_0)	51.18644	1.64E-05
X_1	10.70 (b_1)	16.66904	0.00047
X_2	17.03 (b_2)	26.52872	0.000118
X_1^2	-3.47 (b_{11})	-3.12203	0.052389
X_2^2	-2.93 (b_{22})	-2.63641	0.0770895
X_1 X_2	7.04 (b_{12})	8.956541	0.002937

* b_0, b_1, b_2, b_{11}, b_{22} and b_{12} represents the regression coefficient. X_1 and X_2 are main effect, X_1 X_2 are the interaction terms and X_1^2 and X_2^2 are quadratic terms of independent variables to evaluate nonlinearity.

Table 5: ANALYSIS OF VARIANCE (ANOVA) OF FULL MODEL

		DF	SS	MS	F	R^2
Regression	FM	5	2667.302	533.4603	215.7094	0.9951

Table 6: Checkpoint batches with predicted and measured %CDR

Batch Code	Amount of Pore forming agent (X_1)	Amount of Osmotic agent (X_2)	% CDR (at 540 mins)	
			Measured	Predicted
C_1	-0.5	0.1	56.34	55.09
C_2	0.1	-0.5	52.71	51.43

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Impact Factor:5.7
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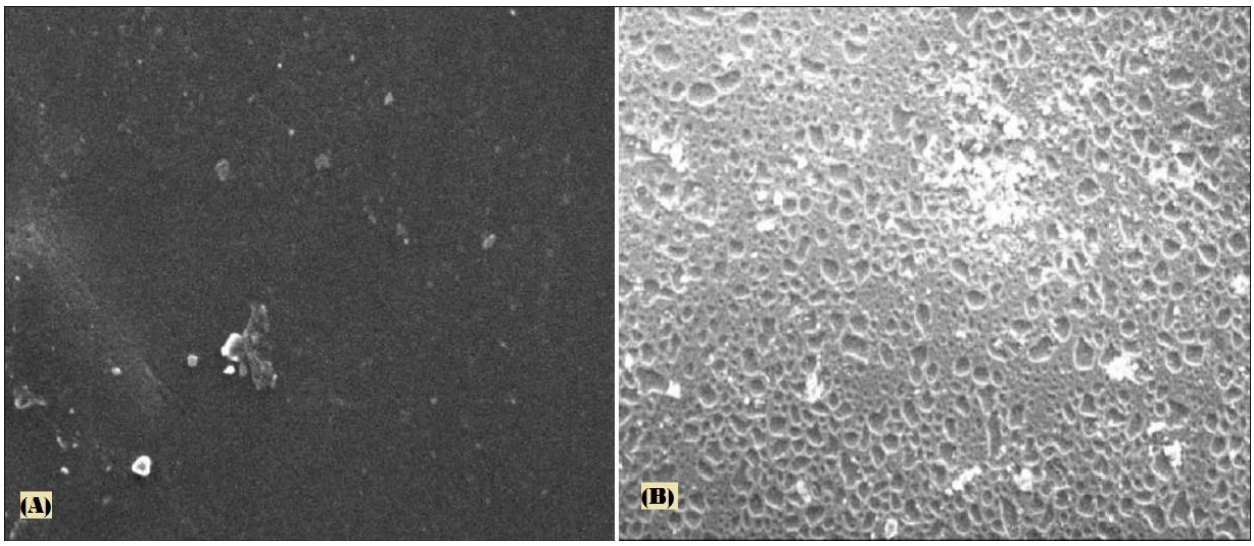

Fig. 1: Scanning electron microphotographs of asymmetric membrane osmotic capsule: (A) Outer layer of capsule shell (original magnification×1000); (B) Inner layer of capsule shell (original magnification×1000)

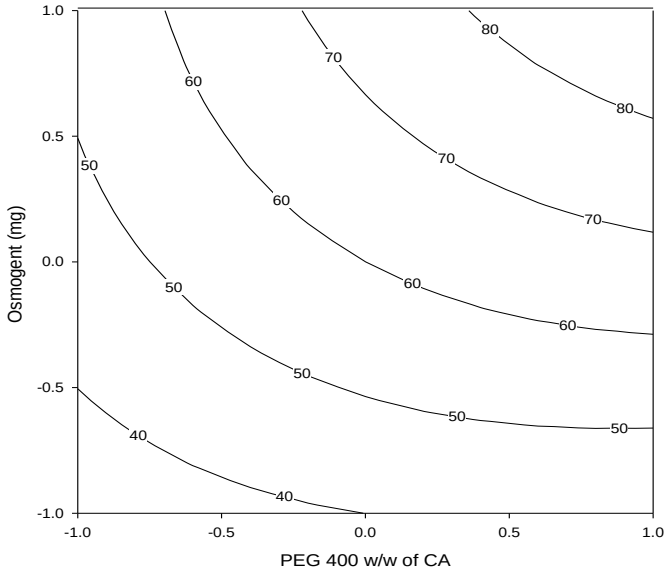

Fig. 2: Contour plot showing effect of level of PEG-400 (X_1) and Sodium chloride (X_2) on the amount of release of Gliclazide from the system.

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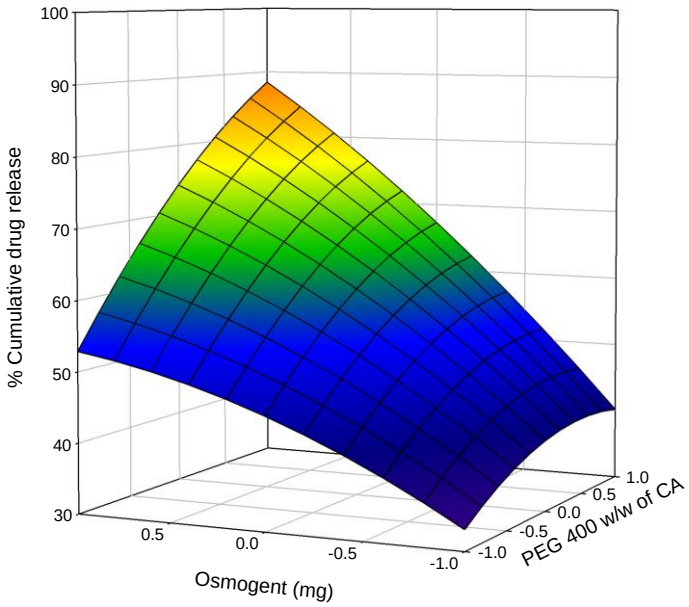

Fig. 3: Response surface plot showing effect of level of PEG-400 (X_1) and Sodium chloride (X_2) on the % CDR.

CONCLUSION

The present study demonstrates that asymmetric membrane capsules were successfully prepared and evaluated using dip coating process for delivery of Gliclazide. The release of Gliclazide increases remarkably with increase in the % of pore forming agent and level of osmotic agent in the core. The system was found to deliver Gliclazide at a zero order rate for 9 hours. The study concluded that asymmetric membrane capsules containing a pore forming agent and osmogent can successfully deliver Gliclazide in a controlled manner.

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