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Formulation and Evaluation of Asymmetric Membrane Capsule Osmotic Pump of Gliclazide

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ABSTRACT

The aim of this study was to demonstrate that the asymmetric membrane capsule can be used to deliver a poorly water soluble drug with a pH sensitive solubility such as gliclazide. In order to obtain the desired delivery duration, the drug was solubilized with the use of a pH-controlling excipient. The capsule wall membrane was made by a phase inversion process, in which asymmetric membrane was formed on glass mold pins by dipping the mold pins into a coating solution containing a polymeric material followed by dipping into a quench solution. This study evaluates the influence of coating formulation that was cellulose acetate (CA), ethyl cellulose (EC), and plasticizer (glycerin and PEG 600). Results show capsule that made by CA with glycerol and PEG 600(F8), which appear in asymmetric structure and are able to release gliclazide(GLZ) in significant percentage. Results show that sodium bicarbonate and D-mannitol is able to promote the release of GLZ from polymeric capsules prepared with CA with asymmetrical membrane. The addition of solubilizer, sodium lauryl sulphate (SLS) could enhance the release of GLZ by micelle formation of GLZ. Based on these results, influence of core formulation variables, including D-mannitol, sodium bicarbonate and the added amount of SLS were examined on the release of GLZ. It was found that HPMC 15cp was suitable to be a thickening agent and both added amount of HPMC and SLS showed a comparable and profoundly positive effect. *In vitro* release studies for all the prepared formulations were done (n=3). Statistical test (Dunnett's multiple comparison test) was applied for *in vitro* drug release at $P>0.05$. The best formulation closely corresponded to the marketed formulation by a similarity (f_2) value of 78.36 and difference (f_1) value of 4.49. The drug release was independent of pH but dependent on the osmotic pressure of the dissolution medium. The release kinetics followed the First order model and the mechanism of release was anomalous type.

KEYWORDS

Asymmetric membrane capsule, Osmotic pump, Antidiabetic agent, Gliclazide, Cellulose acetate, Ethyl cellulose.

INTRODUCTION

Drug delivery systems consisting of a drug-containing core which is coated with a semipermeable membrane, and with one or more delivery ports, have been previously developed and commercialized.

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The elementary osmotic pump[1] is an example of such a delivery system with a laser drilled delivery port. Other formulations of the osmotic coatings include those that consist of dense membranes containing a water-soluble ingredient which is leached out of the membrane to form the delivery ports *in situ*.[2,3,4]

Osmotic tablets with an asymmetric membrane coating which can achieve high water fluxes have also been described.[5] The drug delivery systems described above can release the drug only as an aqueous solution. On the other hand,

two-compartment osmotic tablets.[6,7] which contain an osmotic layer and an expandable layer are more complex but they can deliver either a solution or a suspension of drug.

One such modification is the utilization of asymmetric membrane capsules for osmotic drug delivery. The walls of an asymmetric membrane capsules (AMCs) are prepared by the phase inversion technique. As the name suggests, the membrane is asymmetric in nature, *i.e.,* it has a relatively thin dense region supported on a thicker porous region. Asymmetric membrane capsule consists of a cap and a body, which fit snugly. The wall of the asymmetric membrane capsule is made from a water-insoluble polymer like cellulose acetate(CA), ethyl cellulose (EC), cellulose acetate butyrate (CAB) or their mixture, thus the capsule shell of the asymmetric membrane, unlike the gelatin capsule, does not dissolve instantaneously and osmotically delivers the drug for a prolonged period of time, depending upon the core composition.[8] The porosity of asymmetric membrane can be easily controlled by the choice and variation in concentration of pore forming agent.[9,10,11,12] While in controlled porosity osmotic pump, using asymmetric membrane, the water soluble additives like glycerol, in contact with aqueous medium results in-situ formation of microporous membrane.[13,14]

The critical difference between the asymmetric membrane osmotic dosage form and other osmotic devices is a higher rate of water influx due to the micro porous nature of the asymmetric membrane. It aids in delivery of a drug with lower osmotic pressure and solubility. For drugs of poor solubility, high water influx is desirable, which can be easily achieved with the asymmetric membrane by proper choice and concentration of the pore forming agent. Further, the solubility of the poorly water-soluble drug inside the core can be increased by encapsulating the drug with osmogents or solubilizing agent to ensure its osmotic delivery.[15]

Gliclazide (GLZ) [1-(Hexahydrocyclopenta(c) pyrrol-2(1H)-yl)-3-(p-tolylsulfonyl)urea][16,17] is an important second generation antidiabetic agent, effectively used in the treatment of type-2 diabetes mellitus. Because of its less aqueous solubility of GLZ, it is difficult to develop oral sustained-release formulations of this drug. So it is highly desirable to develop such sustained release formulation in order to achieve improved therapeutic efficacy and patient compliance.

The aims of this work were (1) to develop and evaluate asymmetric membrane capsules (AMCs) to deliver drugs with varying solubility, GLZ, in a controlled manner, and (2) to evaluate the influence of variables like the effect of polymer diffusibility and different osmotic pressure on the drug release from the prepared AMCs. Because the drug solubility was expected to be a decisive factor for the success of AMC, the drug release mechanism from AMC was further studied by examining the influence of sodium bicarbonate, considered to be a solubility enhancer for the drug.

MATERIALS AND METHODS

Gliclazide were obtained from Intas Pharmaceuticals Ltd. (Ahmedabad, India). Cellulose acetate was supplied from Alembic Pharma (Vadodara, India). Gift sample of Ethyl cellulose was kindly provided by Colorcon Asia Pvt. Ltd. (Ahmedabad, India). Other ingredients used were of analytical grade.

DRUG – EXCIPIENTS COMPATIBILITY STUDY

FTIR Study

Fourier-transform infrared **(**FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The samples (Gliclazide and Excipients) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample:KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

DSC Study

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The samples (drug and excipients) were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.

PREPARATION OF ASYMMETRIC MEMBRANE CAPSULES

The asymmetric membrane capsules were prepared by using a phase inversion process in which the membrane structure was precipitated on a stainless steel mold pin by dipping the mold pin in a coating solution followed by quenching in an aqueous solution. Glass mold pin was dipped in coating solution contained 10% w/v of Cellulose acetate or Ethyl cellulose and proportions of glycerol (10%w/v) and PEG 600 (10%w/v) dissolved in acetone and ethanol, and air-dried for 15 Sec. Then it was immersed in a water quench bath for 3 min. Immersion of the coated mold pin in the water quench bath allowed exchange of the polymer solvent that cause generation of asymmetric membrane structure. After removal from the water quench bath, the capsules were air-dried under ambient conditions for at least 12h. Gliclazide (30 mg) and other excipients as shown in table 2, were accurately weighed, mixed and filled in the capsules by hand. D-mannitol was used as osmotic agent and Sodium bicarbonate ($NaHCO_3$) provides basic pH within the capsule to increase the solubility of Gliclazide. The ingredients of different capsular systems are listed in table 1. The filled capsules were sealed.

EVALUATION OF ASYMMETRIC MEMBRANE CAPSULE

***In vitro* Drug Release**

In vitro cumulative drug release from the prepared formulations (n=6) was studied by using USP type-II (paddle) apparatus (rotating speed 75 rpm at 37˚C ± 0.5˚C). The dissolution medium was 0.1N HCl with 0.25%SLS as simulated gastric fluid (SGF) (900 ml, pH 1.2) for the first 2 hours, followed by phosphate buffer as simulated intestinal fluid (SIF) (900 ml, pH 7.4) for the rest of the experiment. Five milliliter of the sample was withdrawn at specified time intervals and suitably diluted by fresh dissolution medium and analyzed at 227.8 nm. The amount of drug released at each time point was calculated and summed to give cumulative amount.

Table: 1 Composition of Asymmetric Membrane Capsules

Component	Coating solution (AMC 1)	Coating solution (AMC 2)	Quenching solution (AMC 1)	Quenching solution (AMC 2)	Sealing Solution (AMC 1)	Sealing Solution (AMC 2)
Ethyl cellulose (%w/v)	10	-	-	-	10	-
Cellulose acetate (%w/v)	-	10	-	-	-	10
Glycerol (%w/v)	10	10	10	10	-	-
PEG 600 (%w/v)	10	10	10	10	-	-
Acetone:Ethanol (2:1)	Up to 100ml	Up to 100ml	-	-	Up to 100ml	Up to 100ml
Dist. Water	-	-	Up to 100ml	Up to 100ml	-	-

Table: 2 Compositions of Core Ingredients in Asymmetric Membrane Capsules

Batch code	Drug (mg)	Capsule	D-mannitol (mg)	Sodium bicarbonate (mg)	Sodium Lauryl Sulphate (mg)	HPMC 15cp (mg)
F1	30	AMC 1	100	50	10	20
F2	30	AMC 2	100	50	10	20
F3	30	AMC 1	120	50	10	20
F4	30	AMC 2	120	50	10	20
F5	30	AMC 1	100	70	10	20
F6	30	AMC 2	100	70	10	20
F7	30	AMC 1	120	70	10	20
F8	30	AMC 2	120	70	10	20

Physical Characterization of Prepared AMCs

Physical characterization of AMCs is done by measuring the following parameters: Physical appearance, Thickness of capsule membrane and Dimensions of capsule (Length, Diameter, Thickness).

Scanning Electron Microscopy

Asymmetric membranes obtained after complete dissolution of core contents were examined for their porous structure using Scanning electron microscope. After dissolution, asymmetric membrane structures were dried at 50°C for 8 hours and stored in dessicator before examination. Asymmetric membranes were sputter coated for 5 to 10 minutes with gold by using fine coat ion sputter and examined under SEM [JEOL JSM-5600, Tokyo, Japan].

Content Uniformity (%)

The powder blends containing 30 mg of Gliclazide was dissolved in 100 ml of PBS pH 7.4. The solution was passed through a whatmann filter and analyzed spectrophotometrically at 227.8 nm after sufficient dilution with PBS pH 7.4.

Kinetic of Drug Release

The cumulative amount of drugs released from the systems at different time intervals was fitted to different kinetic model of Zero order, First order, Higuchi model, Hixson-Crowell model and Korsmeyer-Peppas model to find out whether the drug release from the systems provides a constant drug release pattern. The correlation coefficient (R^2), Sum of square (SSQ) and Release constant also calculated to find the fitness of the data to different kinetic models. Similarity factor (f_2) and Difference factor (f_1) were also obtained by comparing drug release of AMCs with Marketed product (Dianorm-OD-30).

Statistical Analysis

The release rate profiles of GLZ from all formulations (n=3) in dissolution medium were statistically compared with release rate profile of respective drugs from Marketed preparation. The statistical significance was tested by using Dunnett's multiple comparison test (Graphpad-Instat software, Graphpad, CA, USA) and a value of $P < 0.05$ was considered statistically significant.

Stability Testing

Stability studies were carried out at 25ºC/60%RH and 40ºC/75%RH for the selected formulation for the period of 1 month. The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 25ºC/60%RH and 40ºC/75%RH for 1 month and evaluated for their physical appearance, drug content, Drug release and drug excipients compatibility.

RESULT AND DISCUSSION

Interpretation of FTIR spectra

Fourier transform infrared spectroscopy was used to characterize possible interactions between the drug and excipients. The IR spectra of pure Gliclazide and drug-excipients mixture are compared with the each other figure 1 to 7. The IR spectrum of Gliclazide was characterized by the absorption of carbonyl (C=O) sulfonyl urea group and N-H group at 1709.59 cm^{-1} and 3273.57 cm^{-1}, respectively. In the spectra of drug and drug-excipients mixture, these peaks shows no remarkable change which indicate no well-defined interaction in between Gliclazide and excipients. This indicates that the drug is compatible with the formulation components.

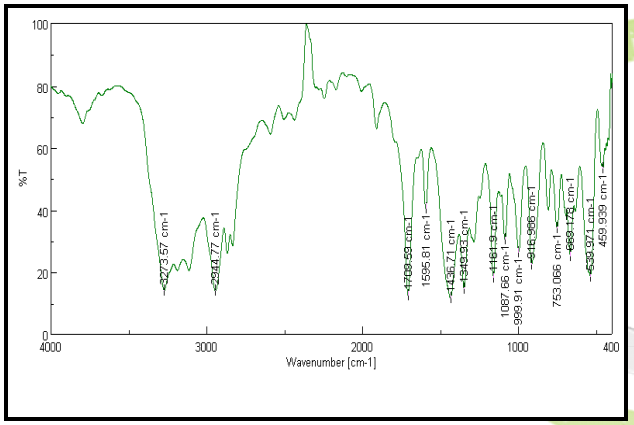


Figure: 1 FT-IR Spectrum of Pure Gliclazide

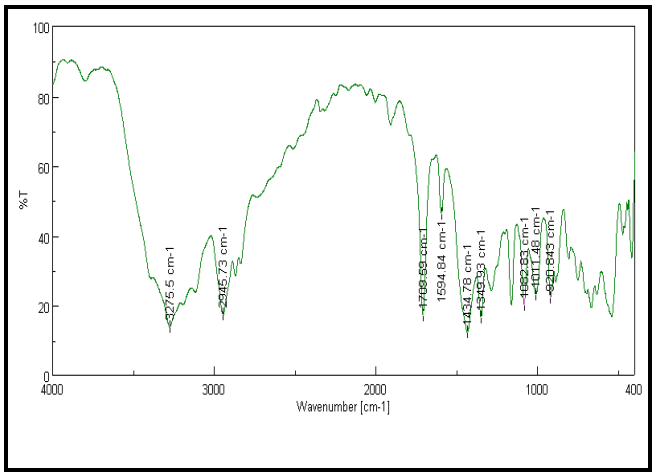


Figure: 2 FTIR Spectrum of Gliclazide and Ethyl Cellulose

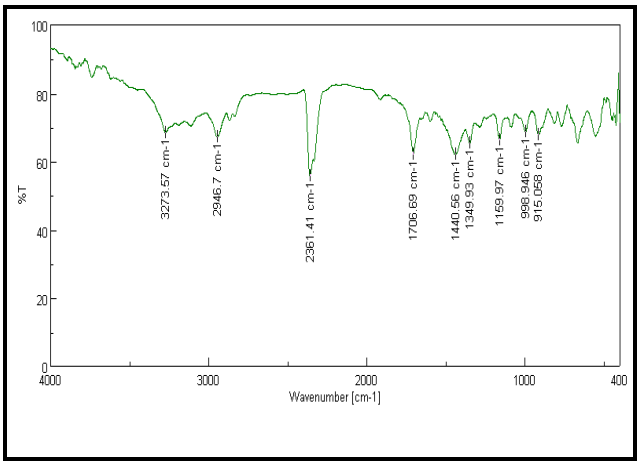


Figure: 3 FTIR Spectrum of Gliclazide and Cellulose Acetate

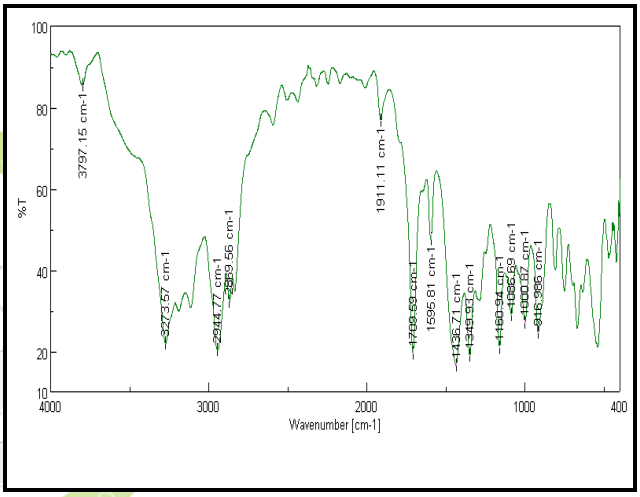


Figure: 4 FTIR Spectrum of Gliclazide and D-mannitol

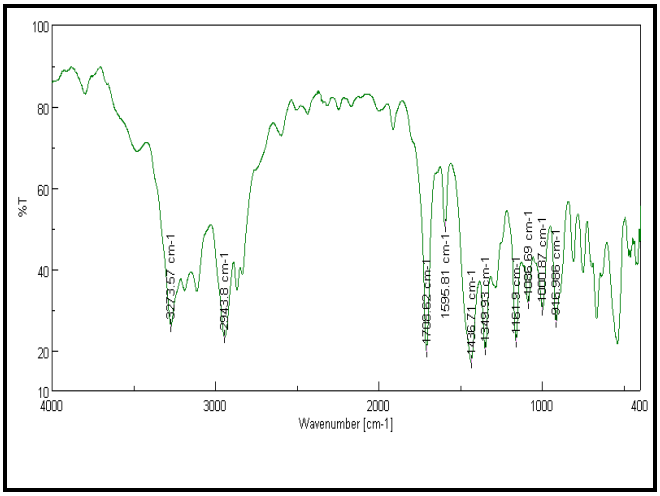


Figure: 5 FTIR Spectrum of Gliclazide and HPMC 15cp

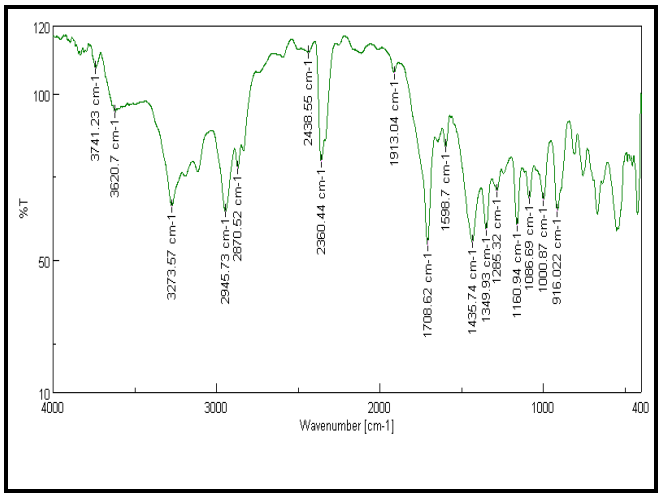


Figure: 6 FTIR Spectrum of Gliclazide and Sodium Bicarbonate

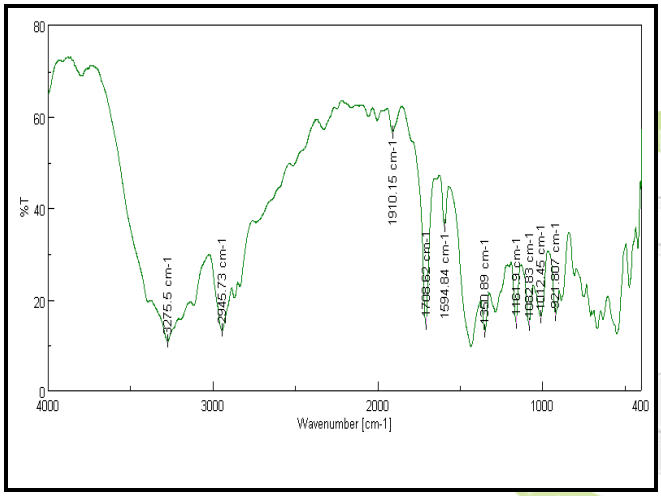


Figure: 7 FTIR Spectrum of Physical Mixture

Drug-Excipients Compatibility Study by DSC

The thermal behavior of GLZ and Excipients mixture was investigated by heating the respective samples at 20°C/min. For this sample an endothermic peak was observed at 168.01°C. The pure GLZ had endothermic peaks at 174.2°C. This clearly showed that there was no interaction between the drug and other excipients used in the study.

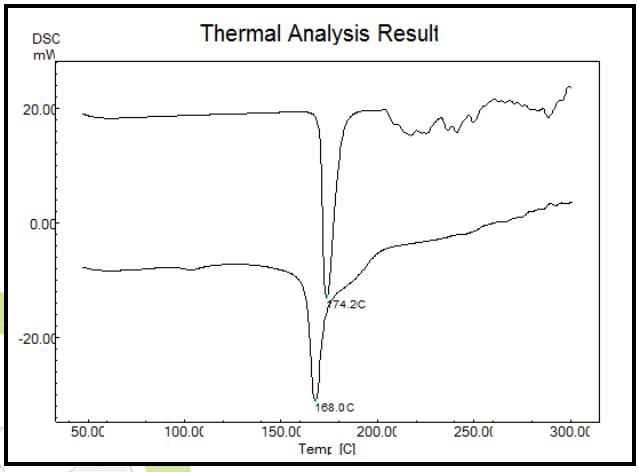


Figure: 8 Overlay DSC Thermogram of Pure Gliclazide and Physical Mixture.

Physical Characterization of Prepared AMCs

All the observed physical characterization parameters of asymmetric membrane capsules are reported in table 3.

Table: 3 Physical Characterizations of Prepared AMCs

Type of Capsules	Appearance	Dimensions, mm*					Thickness (µm)
		Body		Cap		Sealed	
		Length	Diameter	Length	Diameter	Length	
AMC1	Opaque	19.6 ±0.41	4.67 ±0.11	13.4± 0.32	6.05 ±0.26	22.83 ±0.32	764 ±13.3
AMC2	Opaque	19.4 ±0.25	4.73 ±0.28	13.2 ±0.17	6.10 ±0.36	22.35 ±0.48	837 ±8.6

*Values are expressed as mean ± SD of 3 readings (n=3).

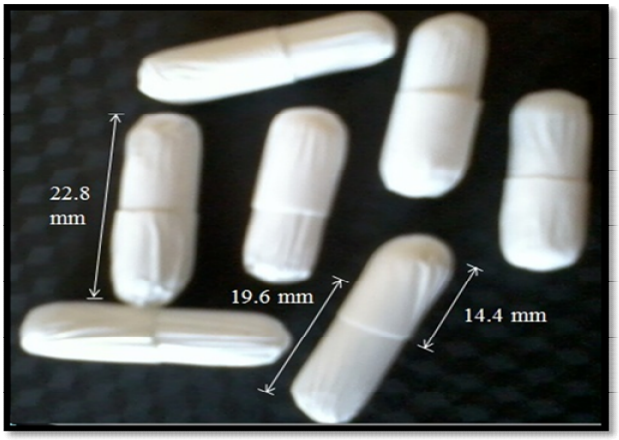
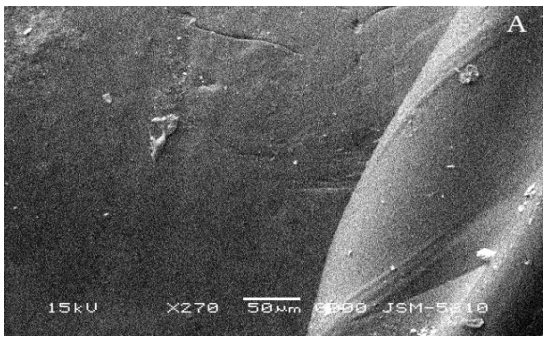


Figure: 9 Digital Photograph of Prepared Asymmetric Membrane Capsules

Scanning Electron Microscopy

Various asymmetric membrane capsules of EC and CA membranes with 20% of pore forming agent were subjected to study by SEM before and after complete dissolution. Membrane (AMC1) obtained before dissolution showed outer, dense, nonporous region (Figure 10A). After complete dissolution, the exhausted membrane showed a large number of pores similar to a net-like structure (Figure 10B), and the formulation prepared with this membrane did not show swelling or rupturing. Membrane of AMC2 showed similar nonporous and porous regions (Figure 10C) and larger pore formation after dissolution (Figure 10D). The formulation with this membrane showed slight swelling or elongation but no rupture. Membrane of AMC2 shows relatively larger pore than AMC1. The SEM study suggested that AMC2 can be used as an optimized membrane to obtain maximum release rate of drugs without rupturing of coating membrane for the core composition presented in this study.



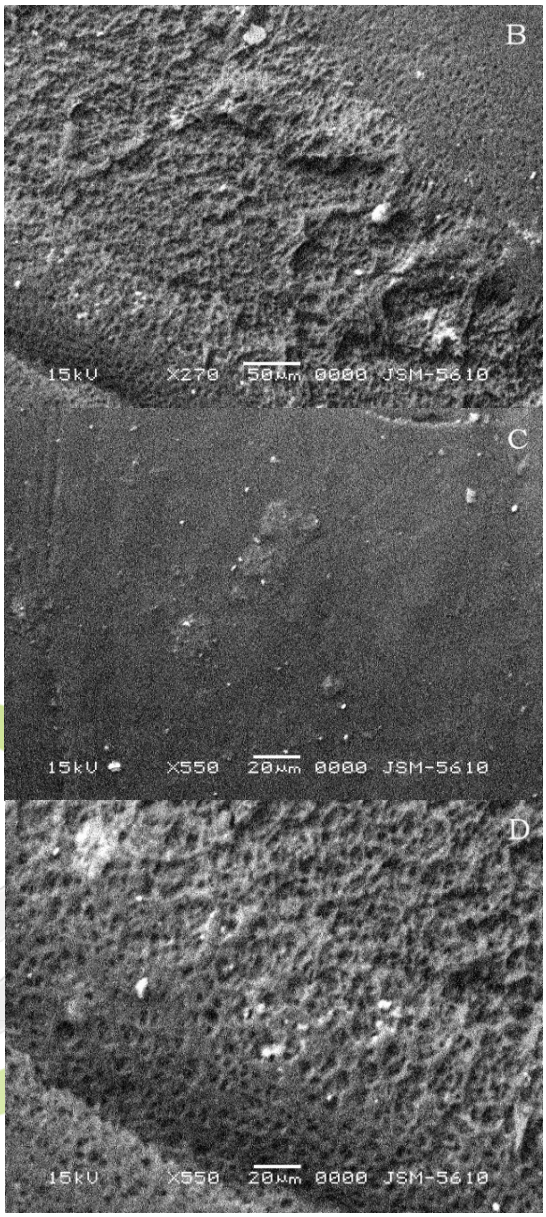


Figure: 10 Scanning Electron Micrographs of Asymmetric Membranes Porous Region of (A) AMC1 Membrane, (B) AMC1 Membrane After Dissolution, (C) AMC2 Membrane, (D) AMC2 Membrane After Dissolution

Content Uniformity (%)

The content uniformity of all (F1-F8) formulations is given in table 4. It ranges in between 97.68% - 98.94%. The values are acceptable as per British pharmacopeia standards.

In Vitro Drug Release

The *in-vitro* drug release of the asymmetric membrane capsules were carried in 0.1N HCl and Phosphate buffer pH 7.4 from 0 to 24 hrs by USP type-II apparatus. The plot of % Cumulative drug release v/s time (hrs) was plotted and depicted as shown in figure 11.

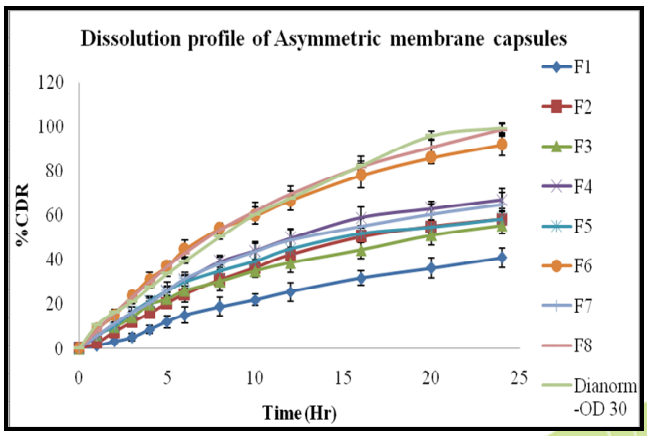


Figure: 11 Dissolution Profile of Asymmetric Membrane Capsules Formulations

In vitro studies were performed in 2 groups for the design batches. The first group (group 1) consisted of AMC1 and denoted as F1, F3, F5 and F7 formulation batches with other two variables at lower level and higher level. The second group (group 2) consisted of AMC2 and denoted as F2, F4, F6, and F8 with other two variables at lower level and higher level.

From the *in-vitro* dissolution data, it was found that the drug release from marketed sample Dianorm-OD-30 containing Gliclazide is 99.29% in 24 hrs. The *in-vitro* drug release from AMC1 group capsules was found to be 40.93%, 55.59%, 58.59% and 64.94% in 24 hrs. for F1, F3, F5, F7 batches, respectively and 58.59%, 67.05%, 91.05% and 98.56% in 24 hrs for F2, F4, F6, F8 batches (AMC2 group capsules), respectively.

From this drug release data it was observed that F8 batch shown maximum drug release in controlled manner.

The results showed that incorporation of higher amount of D-mannitol resulted in development of significant osmotic pressure inside the capsular system, which increased the release rate of GLZ. And increased amount of Sodium bicarbonate resulted in increased pH in capsular system which enhanced the solubility of GLZ which resulted in increased release rate of GLZ. The *in vitro* drug release was found to be higher for cellulose acetate than ethyl cellulose which indicates less permeability of ethyl cellulose than cellulose acetate. So it was better to use cellulose acetate than ethyl cellulose to obtain maximum release of drug from AMCs.

Kinetic of Drug Release

The dissolution data obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, Korsmeyer-Peppas models, Hixson-Crowell model. While considering the higher correlation coefficient value (R^2) and lower SSQ value, the release data seem to fit the first order better. The value of the release exponent in Gliclazide AMCs (F8) obtained as 0.739 which indicates the anomalous type of release. Except F1 batch, other all batches show the range of release exponent in between 0.45-0.89, indicates anomalous type of release. Results were shown in table 5.

Table: 4 Results of Content Uniformity of All Formulation of Gliclazide

Batches	F1	F2	F3	F4	F5	F6	F7	F8
Content Uniformity (%)*	98.94 ±0.40	98.94 ±0.40	99.75 ±0.33	99.75 ±0.33	97.68 ±0.27	97.68 ±0.27	98.75 ±0.42	98.75 ±0.42

*Values are expressed as mean ± SD of 3 readings (n=3).

Table: 5 Different Kinetic Models Applied on AMCs and Marketed Preparation

Batch Code	Zero Order Model			First Order Model			Higuchi Square Root Model			Korsmeyer-Peppas Model				Hixson-Crowell Model			Best Fit Model
	K_0	SSQ	R^2	K_1	SSQ	R^2	K_H	SSQ	R^2	n	K_{KP}	SSQ	R^2	K_{HC}	SSQ	R^2	
F1	1.900	77.35	0.9653	0.023	21.73	0.9903	7.173	257.03	0.8848	0.923	2.554	16.42	0.9852	0.007	33.43	0.9850	First
F2	2.937	437.75	0.9081	0.041	59.83	0.9874	11.293	355.52	0.9254	0.838	5.141	23.02	0.9916	0.013	130.80	0.9725	First
F3	2.784	590.43	0.8367	0.037	158.46	0.9562	10.879	97.81	0.9729	0.651	7.611	18.92	0.9905	0.012	262.54	0.9274	First
F4	3.460	882.44	0.8530	0.052	85.13	0.9858	13.465	286.66	0.9523	0.751	7.643	27.56	0.9924	0.016	226.19	0.9623	First
F5	3.072	937.22	0.7865	0.043	229.46	0.9477	12.075	144.12	0.9672	0.682	8.146	30.21	0.9890	0.014	394.09	0.9102	First
F6	4.717	1800.86	0.8315	0.099	18.99	0.9982	18.430	383.86	0.9641	0.695	11.851	71.51	0.9886	0.027	77.86	0.9927	First
F7	3.349	932.21	0.8290	0.049	134.31	0.9754	13.085	221.31	0.9594	0.709	8.191	45.14	0.9862	0.015	293.95	0.9461	First
F8	4.935	1483.81	0.8790	0.132	119.38	0.9903	19.134	563.40	0.9541	0.739	10.959	44.45	0.9936	0.028	8.99	0.9993	First
Dianorm OD-30	4.945	1055.75	0.9174	0.151	301.64	0.9764	19.022	775.25	0.9393	0.777	9.749	14.68	0.9978	0.027	67.01	0.9948	First

*R^2-Correlation coefficients, SSQ-Sum of Square, K_0, K_1, K_H, K_{HC}, K_{KP} Release rate constant for zero order, First order, Higuchi, and Hixson Crowell, Korsmeyer- Peppas release equation, respectively, n, diffusional exponent, indicative of release mechanism in Korsmeyer equation. All formulations F1 to F8, followed Non-Fickian (Anomalous) release.

Similarity factor (f_2) and Difference factor (f_1)

In-vitro drug release profile of formulated AMCs was compared with commercially available product (Dianorm-OD-30 MR Tab.) containing 30 mg of Gliclazide. Drug release from reference marketed tablets, after 24 hrs. was found to be 99.29%. About 40.93%, 58.31%, 55.60%, 67.06%, 58.52%, 91.88%, 64.95% and 98.56% drug released from the AMCs F1, F2, F3, F4, F5, F6, F7 and F8, respectively, after the same interval of time.

Batch F6 and F8 had similar release profile with reference. The similarity factor (f_2-value) and Difference factor (f_1-value) were applied to reveal the similarity between the release profile of reference and the formulated AMCs. f_2-values in between 50-100 and f_1-value in between 0-15 indicates similarity of drug release profile. F8 shows maximum similarity with reference as shown in table 6.

Table: 6 f_2-values and f_1-values Determined From Drug Release Data of Test AMCs of Different Formulations vs. Reference.

Sr. No.	Comparison	f_2-value	f_1-value	Similarity of Ref. & Test
1	Reference vs. F1	22.91	63.57	Reject
2	Reference vs. F2	32.08	41.17	Reject
3	Reference vs. F3	30.62	41.55	Reject
4	Reference vs. F4	38.79	28.47	Reject
5	Reference vs. F5	33.77	34.89	Reject
6	Reference vs. F6	67.28	7.43	Accept
7	Reference vs. F7	37.23	30.06	Reject
8	Reference vs. F8	78.36	4.49	Accept

Statistical Analysis

F6 and F8 were relatively better systems obtained from initial studies. Release rates of F6 and F8 were statistically compared to those obtained from marketed product. With reference to marketed product release rates, F6 and F8 showed insignificant difference (P>0.05), suggested that systems provided comparable GLZ release rate with marketed product. In case of F6 and F8 provided significant results while others yielded non-significant values (P>0.05), indicating that F8 systems (P=0.2809) provided comparable GLZ release rate with marketed product. In conclusion, statistical analysis revealed that F8 provided approximately similar GLZ release to marketed product and better controlled release.

Stability Testing

The selected Formulation F8 were evaluated for stability studies which were stored at 25ºC±2ºC/60%RH±5%RH and 40ºC±2ºC/ 75%RH±5%RH tested at 1 month, and were analyzed for their drug content and drug release. The residual drug contents of formulations were found to be within the permissible limits. The results of 1 month duration stability study are shown in the table 7.

CONCLUSION

A porous osmotic pump based drug delivery system successfully designed for controlled release of drug gliclazide. It is evident from the results that showed, the rate of drug release can be controlled through osmotic pressure of the core, level of pore forming agent and weight of membrane with release to be fairly independent of pH and hydrodynamic conditions of the body. From that *in vitro* drug release data was found to be affected by membrane polymer, amount of D-mannitol and Sodium bicarbonate. Gliclazide released was increased proportional to the amount of D-mannitol and sodium bicarbonate. Drug release from developed formulations was independent of pH change in GIT. Polymer used in capsule preparation had shown the effect on drug release of gliclazide from capsules. It was observed that ethyl cellulose have less permeability than cellulose acetate. Drug release kinetic models were applied to all batches which shown that optimized batch and other batches release gliclazide in first order manner with anomalous mechanism. Results of SEM studies inveterate the formation of pores in the asymmetric membranes after coming into contact with the aqueous environment.

Table: 7 Stability Testing Data of Optimized Batch(F8)

Results of stability testing			
Condition (1)		25ºC±2ºC/60%RH±5%RH	
Condition (2)		40ºC±2ºC/75%RH±5%RH	
Batch No.		F8	
% Drug release at 24 Hr			
Time (Hrs)	**Initial**	**After 1 month at 25ºC±2ºC/60%RH±5%RH**	**After 1 month at 40ºC±2ºC/75%RH±5%RH**
24	98.56±2.82	96.73±2.83	94.38±3.28
Similarity factor(f_2)			
Value	78.36	67.59	66.12
Difference factor (f_1)			
Value	4.49	7.35	8.16
Drug Content			
% Potency	98.75	98.57	98.48
Physical appearance*			
Morphology	+++	+++	++

*+++ = Same as on zero day, ++ = Slight change

The *in vitro* drug release was fitted into different kinetic models. The line of equation and regression value shown that the system formulated followed first order release kinetic because the regression values in first-order graph were closer to one.

REFERENCES

1. Theeuwes F, "Elementary Osmotic Pump", Journal of Pharmaceutical Sciences, 1975, 64, 1987–1991.
2. Zentner GM, Rork GS, Himmelstein KJ, "The Controlled Porosity Osmotic Pump", Journal of Cont. Release, 1985, 1, 269-282.
3. Baker RW, Brooke JW, "Pharmaceutical drug delivery", US Patent 4,687,660 1987, www.google.com/patents/US4687660, Accessed date: 25/12/2011.
4. Lindstedt B, Sjorberg M, Hjarstam J, "Osmotic Pumping Release of KCl Tablets With Porous and Non-Porous Ethyl Cellulose", International Journal of Pharmaceutics, 1991, 67, 21–27.
5. Herbig SM, Cardinal JR, Korsmeyer RW, Smith KL, "Asymmetric-Membrane Tablet Coatings for Osmotic Drug Delivery", Journal of Controlled Release, 1995, 35, 127–136.
6. Theeuwes F, "Osmotic System for Delivering Selected Beneficial Agents Having Varying Degrees of Solubility", US Patent 4,111,201, 1978, www.google.com/patents/US5340376.pdf.
7. Kuczynski AL, Ayer AD, Wong PS, "Dosage Form for Administering Oral Hypoglycemic Glipizide", US Patent 5,545,413, http://www.wikipatents.com/US-Patent-5545413/dosage-form-for-administering-oral-hypoglycemic-glipizide, Accessed date: 25/12/2011
8. Thombre AG, Cardinal JR, DeNoto AR, Herbig SM and Smith KL, "Asymmetric Membrane Capsule for Osmotic Drug Delivery I. Development of Manufacturing Process", Journal of Controlled Release, 1999, 57, 55-64.
9. Liu H, Yang XG, Nie SF, Wei LL, Zhoub LL, Tang R, Pan WS, "Chitosan- Based Controlled Porosity Osmotic Pump for Colon-Specific Delivery System, Screening of Formulation Variables and *In Vitro* Investigation", International Journal of Pharmaceutics, 2007, 332, 115–124.
10. Verma RK, Krishna DM, Garg S, "Formulation Aspects in the Development of Osmotically Controlled Oral Drug Delivery Systems", Journal of Controlled Release, 2002, 79, 7–27.
11. Gondaliya D, Pundarikakshudu K, "The Fabrication and Evaluation of the Formulation Variables of A Controlled-Porosity Osmotic Drug Delivery System with Diltiazem Hydrochloride", Pharma. Technology, 2003, 38, 58-68.
12. Jian-Hwa G, "Effect of Plasticizers on Water Permeation and Mechanical Properties of Cellulose Acetate: Antiplasticization in Slightly Plasticized Polymer Film", Drug Dev. and Industrial Pharmacy, 1993, 19(13), 1541–1555.
13. Ende MT, Herbig SM, Krsmeyer RW, Childlaw MB, Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker Inc, New York, 751-85.
14. Lin Y, Ho H, "Investigation on the Drug Releasing Mechanism From an Asymmetric Membrane Coated Capsule with an *In Situ* Formed Delivery Orifice", Journal of Controlled Release, 2003, 89, 57-69.
15. Zentner GM, Rork GS, Himmelsteine KJ, "Osmotic Flow Through Controlled Porosity Films: An Approach to Deliver Water-Soluble Compounds" Journal of Controlled Release, 1985, 2, 217–229.
16. British Pharmacopoeia, British Pharmacopoeia Commission, volume I, 2007, 995.
17. Sweetman SC, Martindale: The Complete Drug Reference, 37th edn, The Pharmaceutical press, London, 2011, 589.