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# Formulation and Evaluation of Asymmetric Membrane Mediated Osmotic Drug Delivery System of Gliclazide by Applying Taguchi's L-8 Design

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## ABSTRACT

The purpose of the present study was to develop an osmotic drug delivery system for a Gliclazide by using asymmetric membrane technology (AMT). In the study, the tablets were formulated by using ethyl cellulose and chitosan as asymmetric membrane forming polymers. The asymmetric nature of the membrane coat was confirmed by scanning electron microscopy. The tablets were evaluated for various parameters like average weight, hardness, friability, assay and drug release. A zero order release was achieved in dissolution study and it was established that the release rates were unaffected by the pH of the medium and the speed of agitation. The ethyl cellulose coated AMT delivered the drug in an efficient zero order for about 20 hrs without any pharmacopoeial non-compliance. It was also observed that the level of osmogen, level of coating polymer and the level of pore former in the AM formulation emerged as the significant factors in the designing of an osmotic AMT. The level of plasticizer and the quenching time however did not have any effect on the formulation outcomes. The chitosan AMT delivered the drug gliclazide in a sustained manner for about eight hours. The results showed that the actual and predicted values of the optimized formulation, according to the desired response, are near and the Taguchi design can successfully predict the best conditions for fabricating the Gliclazide AMT for modified drug delivery.

**Keywords**: asymmetric membrane technology, gliclazide, osmotic cores, Taguchi's L-8 design.

## INTRODUCTION

Asymmetric membranes used for osmotic drug delivery systems are unique, as the water permeability through these membranes is dependent on the structure of the membrane. Asymmetric membranes are made up of porous regions that comprise the bulk of the membrane and relatively thin dense regions. Thus significant factors in determining the permeability of a given membrane is the porous nature of the membrane, and the thickness and extent of the dense regions, in addition to the composition of the membrane.[1, 2]

Asymmetric membrane (AM) film coated delivery systems are a unique embodiment of osmotic devices in the use of phase inversion technology to create the semipermeable asymmetric membrane. As with other osmotic pumps, the AM drug delivery system releases the active ingredient by an osomotically controlled mechanism which, when properly constructed, delivers the active agent independently of pH or external agitation. The critical differentiating features that distinguish AM dosage forms from other osmotic devices

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are the high water permeability and controlled porosity resulting from the specialized coating process. An elegantly simple appearing osmotic drug delivery technology was developed jointly by *Pfizer* and *Bend Research* and features an asymmetric membrane to control release.[3]

Gliclazide[4] is a second generation sulphonylurea drug. It is used for treatment of non-insulin dependent diabetes mellitus. Gliclazide works in several different ways, but its primary functions are to increase insulin sensitivity, improve glucose clearance and reduce the amount of hepatic glucose produced.

The ideal drug for diabetes treatment would be one that not only controls the glucose levels, but also deals with some of the complications and secondary effects of diabetes; for example, cardiovascular problems and the generation of free radicals.[5,6] Gliclazide fulfills all the above requirements and thus is an ideal drug for the treatment of Type 2 NIDDM related with above mentioned secondary effects.

The objective of the work was to formulate an optimized asymmetric membrane osmotic tablet of Gliclazide by using ethyl cellulose and chitosan as an asymmetric membrane forming polymer.

## MATERIAL AND METHODS

### *Material*

The active ingredient used in the study was Gliclazide B.P, gifted from Wockhardt Research Centre, Aurangabad (India). Chitosan (membrane forming polymer) was gifted from Qualigens Ltd, Mumbai. Sodium chloride (Osmogen), microcrystalline cellulose, polyethylene glycol-400 (plasticizer), glycerine (pore former), and ethyl cellulose (membrane forming polymer) were purchased from S.D Fine Ltd, Mumbai. All other chemicals used in the study were analytical grade.

### *Method*

*Drug-excipient compatibility study*

The drug-excipient compatibility study was carried out by using the differential scanning calorimetric (DSC) model DSC 823e made by Mettler Toledo.

*Formulation design of Gliclazide asymmetric membrane osmotic tablet*

The asymmetric membrane osmotic tablets were formulated as per Taguchi's L-8 orthogonal design using the software Qualitek 4.[7] In total there were five independent variables, which were used at their high and low levels respectively. The cumulative percent drug release was taken as the dependent variable.

**Table 1. Definition and Trial Levels of Factors in Taguchi's L-8 Experiment**

| Studied Variables | Levels | |
|---|---|---|
| | Low Level (-1) | High Level (+1) |
| Sodium Chloride (%w/w) | 06 | 12 |
| Ethylcellulose (%w/v) | 03 | 05 |
| PEG-400 (%v/w of EC) | 40 | 50 |
| Glycerine (% v/v of CS) | 01 | 02 |
| Quenching Time (min) | 03 | 06 |

**Table 2. Combinations of Independent Variables in the Orthogonal Array**

| Formulation Code | Sodium chloride | Ethylcellulose | PEG-400 | Glycerine | Quenching time |
|---|---|---|---|---|---|
| F-1 | -1 | -1 | -1 | -1 | -1 |
| F-2 | -1 | -1 | -1 | +1 | +1 |
| F-3 | -1 | +1 | +1 | -1 | -1 |
| F-4 | -1 | +1 | +1 | +1 | +1 |

| Formulation Code | Sodium chloride | Ethylcellulose | PEG-400 | Glycerine | Quenching time |
|---|---|---|---|---|---|
| F-5 | +1 | -1 | +1 | -1 | +1 |
| F-6 | +1 | -1 | +1 | +1 | -1 |
| F-7 | +1 | +1 | -1 | -1 | +1 |
| F-8 | +1 | +1 | -1 | +1 | -1 |

*Formulation of Gliclazide osmotic core tablet*

Osmotic tablet cores of Gliclazide were prepared by direct compression method using microcrystalline cellulose and mannitol as directly compressible excipients. All the ingredients (Table 3) were accurately weighed and passed through sieve No. 22. In order to mix the ingredients thoroughly, drug and excipient were blended geometrically in a mortar and pestle for 15 minutes; talc and magnesium stearate were added one by one. After thoroughly mixing these ingredients, the powder blend was again passed through sieve No. 22 .The formed blend was further evaluated for the flow properties and then the tablet blends were compressed using 10mm biconcave round punches (B tooling) of a 12 station single rotatory compression machine (Karnavati, Minipress – II). The tablet cores so formed were evaluated for weight variation, hardness, friability, assay, and dimensions respectively.

**Table 3. Formulation Batches of Ethylcellulose AMT as per Taguchi's L-8 Design**

| Batches / Variables | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 | F-8 |
|---|---|---|---|---|---|---|---|---|
| **A) Osmotic Core** | | | | | | | | |
| Gliclazide (mg) | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| NaCl (mg) | 15 | 15 | 15 | 15 | 30 | 30 | 30 | 30 |
| Mannitol (mg) | 47 | 47 | 47 | 47 | 47 | 47 | 47 | 47 |
| MCC(mg) | 155 | 155 | 155 | 155 | 140 | 140 | 140 | 140 |
| Magnesium stearate (mg) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Talc (mg) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total Wt.(mg) | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| **B) AM Coat** | | | | | | | | |
| Ethylcellulose (gm) | 3.0 | 3.0 | 5.0 | 5.0 | 3.0 | 3.0 | 5.0 | 5.0 |
| Ethanol:acetone:water(70:20:10) ( ml) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Glycerine (ml) | 1.0 | 2.0 | 1.0 | 2.0 | 1.0 | 2.0 | 1.0 | 2.0 |
| PEG-400 (ml) | 1.2 | 1.2 | 1.5 | 1.5 | 1.5 | 1.5 | 1.2 | 1.2 |
| Water quench (ml) | qs | qs | qs | qs | qs | qs | qs | qs |
| Quenching time (min) | 3 | 6 | 3 | 6 | 6 | 3 | 6 | 3 |

*Evaluation of Gliclazide osmotic blend* [8]

Blend was evaluated for bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio.

*Evaluation of Gliclazide osmotic core tablets* [9]

*A) Weight variation*

Weight variation was calculated as per method described in Indian Pharmacopoeia.

*B) Hardness test*

Five tablets from each batch were selected and hardness was measured using Pfizer hardness tester to find the average tablet hardness.

*C) Friability (%F)*

Twenty tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions (made by Veego).

*E) Thickness*

Ten tablets from each batch were selected randomly and evaluated for tablet thickness using vernier calipers (made by Equip Tronics).

*F) Uniformity of drug content*[10]

Uniformity of drug content was determined by using UV spectrophotometer (UV-1800, Shimadzu) at 228 nm.

*Preparation of the AM coating solution*

The coating solution for the asymmetric membrane tablet coating was prepared by dissolving the required quantity of ethylcellulose (10 CPS) in 100 ml of solvent mixture, which was composed of ethanol, acetone, and water in the ratio of 70:20:10. Next, the required quantity of plasticizer (PEG-400) and pore former (glycerine) were added to the polymer solution. The resulting solution was finally sonicated.

*Dip coating of the osmotic cores* [3,11,12]

The asymmetric membrane was formed on the gliclazide tablets by dip coating and wet precipitation technique. The tablet was dipped in the coating solution using a forceps. It was then withdrawn and air dried at room temperature for 10 seconds, and was finally precipitated in the precipitating bath (water) for the specified period of time. The tablets were dip coated in such a manner that the total time involved for dipping in polymer solution and withdrawal of tablet was approximately three seconds. The tablets were then allowed to completely air-dry for at least 12 hours at room temperature.

*Evaluation of ethylcellulose AM Gliclazide tablet*

Ethyl cellulose AM gliclazide tablets were evaluated for weight variation, thickness, drug content and dissolution.

*A) Dissolution studies*[13]

The dissolution test was carried out using a USP Type II dissolution test apparatus at 37±2°C and 100 rpm speed. 900ml of phosphate buffer of pH 7.4 was used as the dissolution medium. The drug released from the tablet was analyzed spectrophotometrically (Shimadzu 1800) at 228 nm.

*B) Scanning electron microscopy of the optimized batch of AMT*

Scanning electron microscopy of the optimized coated formulation was done using a JSM-6380 LV JEOL scanning electron microscope (VNIT, Nagpur). The optimized AMT were studied for their surface properties and membrane morphology.

*C) Study on the effect of pH on the release profile of Gliclazide AMT*[14]

To study the effect of pH and to ensure a reliable performance of the optimized formulation independent of pH, in vitro release studies were conducted in media of different pH. The release media was SGF (pH 1.2), buffer (pH 4.6), and simulated intestinal fluid (pH 7.4). Tween 80 (0.5%V/V of dissolution fluid) was added to the SGF and acetate buffers in order to enhance the solubility of gliclazide.[16]

*D) Study on the effect of agitational intensity on the release profile of Gliclazide AMT* [12]

In order to study the effect of agitational intensity of the release media, release studies were performed in a dissolution apparatus at various rotational speeds. A USP-2 paddle type dissolution apparatus with rotational speeds of 50, 100, and 150 rpm was used. Phosphate buffer pH 7.4 was used as the dissolution medium.

*Formulation of check point batches*

Three checkpoint batches were also formulated to

cross check the release profile of the optimized formulation of Gliclazide AM osmotic tablet. These batches were formulated by altering the formulation variables in the optimized batch and furthermore, the comparative study of these batches was done with the optimized batch from the L-8 orthogonal design.

The alterations were made in the following manner:

1. Optimized tablet batch without AM coating.
2. Optimized AM tablet without osmogen in the tablet core.
3. Optimized coated tablet without phase inversion (i.e. quenching)

Check point batches were formulated in the manner similar to the batches in L-8 orthogonal design but with alterations in the formulation variables. Furthermore, these batches were evaluated for their dissolution profiles using a USP Type II dissolution test apparatus.

*Formulation of extra design batches*

Extra design batches using chitosan as an AM forming polymer were made to apply the asymmetric membrane forming ability of chitosan in osmotic drug delivery. Previously, chitosan had been used as an AM polymer in the fabrication of drug carrying membranes in which the chitosan was linked with sodium tripolyphosphate through ionotropic gelation. [14,15,16,17]

Extra design batches were fabricated using the optimized osmotic core tablets from the L-8 orthogonal design. The chitosan was used as an AM forming polymer at two levels, 3% and 6% wt/vol in coating solution. The required quantity of chitosan was dissolved in 100 ml 2% v/v of dilute acetic acid. Furthermore, 2.4% v/v of PEG-400 was added to the polymer solution. The resulting solution was sonicated for five minutes to remove any soluble gases from the coating solution.

**Table 4. Formulation Design for Checkpoint and Extra Design Batches for AMT.**

| **Batches** / **Variables** | **CB1*** | **CB2** | **CB3** | **ED1#** | **ED2** |
|---|---|---|---|---|---|
| **Osmotic Core** | | | | | |
| Gliclazide (mg) | 30 | 30 | 30 | 30 | 30 |
| NaCl (mg) | 30 | - | 30 | 30 | 30 |
| Mannitol (mg) | 47 | 47 | 47 | 47 | 47 |
| MCC(mg) | 140 | 140 | 140 | 140 | 140 |
| Mag. stearate(mg) | 2 | 2 | 2 | 2 | 2 |
| Talc (mg) | 1 | 1 | 1 | 1 | 1 |
| Total wt.(mg) | 250 | 250 | 250 | 250 | 250 |
| **AM Coat** | | | | | |
| Chitosan (gm) | - | - | - | 6 | 3 |
| Ethyl cellulose (gm) | - | 3.0 | 3.0 | - | - |
| Ethanol:acetone:water(35:10:05) (ml) | - | 100 | 100 | - | - |
| Dil. acetic acid (02%v/v) (ml) | - | - | - | 100 | 100 |
| Glycerine (ml) | - | 2.0 | 2.0 | - | - |
| PEG-400 (ml) | - | 1.5 | 1.5 | 2.4 | 2.4 |
| Water quench (ml) | - | qs | - | - | - |
| Quenching sol (0.5% TPP w/w in 0.05 N NaOH+1% w/w glycerine) | - | - | - | qs | qs |
| Quenching time (min) | - | 3 | - | 6 | 6 |

* Check point batch # Extra design batch

*Comparative study of optimized formulation with marketed formulations of Gliclazide*

The release profile of the optimized formulation was compared with the marketed conventional and modified release tablets of gliclazide, i.e. GLIX-40 and GLIX-MR.

**RESULT AND DISCUSSION**

*Differential scanning calorimetric analysis*

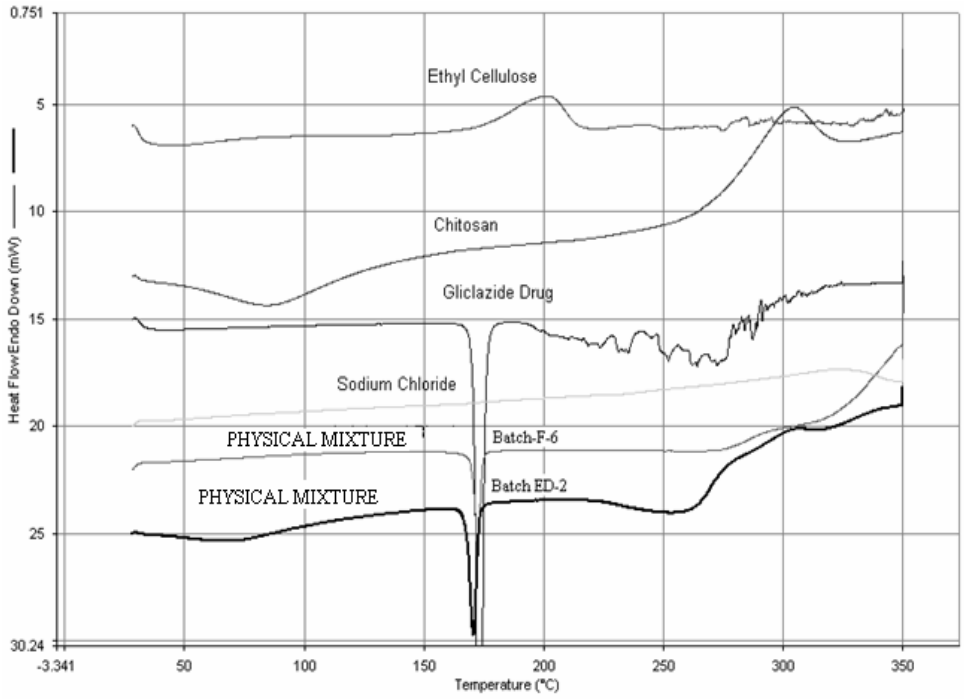



**Figure 1. DSC Thermographs of Drug and Excipients Used in the AMT.**

The DSC curve (Figure 1) of pure gliclazide exhibits a single endotherm corresponding to the melting point of the drug. The onset of melting was observed at 170.8 °C and the corresponding heat of fusion (Δ*H*F) was 0.312 KJ/mol. Furthermore, in case of ethyl cellulose, chitosan and sodium chloride, there were no sharp endothermic or exothermic peaks near to the exothermic peak of gliclazide. Thus it can be concluded that there were no signs of incompatibility seen between the key excipients and the drug.

Further sharp peaks in the region of 168°C to 170°C were obtained in the case of physical mixtures of the formulations *viz* Batch F-6 and Batch ED-2 which was due to the melting of the drug gliclazide at its melting point. Thus it can be concluded that there was no incompatibility between the drug gliclazide and the tablet excipients used for the fabrication of the gliclazide asymmetric membrane osmotic tablet.

***Evaluation of Gliclazide osmotic blend***

Two tablet blends based on high and low levels of osmogen were prepared and analyzed for various micromeritic and flow properties which is given in Table 5. Values of the compressibility index were less than 15. Hausner's ratio were 1.083 and 1.098 respectively. The angle of repose was less than 30°.

The outcomes of these parameters indicated good flow properties and the blends were suitable for direct compression.

**Table 5. Evaluation of Physical Properties of Tablet Blends**

| Formulation Code | Bulk density (gm/ml)±SD | Tapped density (gm/ml)±SD | Hausner's ratio | Compressibility index | Angle of repose |
|---|---|---|---|---|---|
| C-1 | 0.585±0.02 | 0.634±0.03 | 1.083 | 7.72 | 29.14$^o$ |
| C-2 | 0.591±0.05 | 0.649±0.04 | 1.098 | 8.93 | 28.52$^o$ |

*Average values from N=3

***Evaluation of Gliclazide osmotic core tablets***

**Table 6. Evaluation Parameters for Gliclazide Osmotic Core Tablets**

| Formulation Code | Average Wt. (mg) ±SD | Hardness±SD (kg/cm$^2$) | Friability (%)±SD | Thickness (mm) ±SD | Assay (mg) ±SD |
|---|---|---|---|---|---|
| C-1 | 249.89±1.2 | 6.8±1.4 | 0.46±0.06 | 3.23±0.06 | 29.98±0.87 |
| C-2 | 250.34 ±0.92 | 7.3±1.0 | 0.88±0.04 | 3.46±0.05 | 30.22±0.45 |

* Average values from N=3

The tablets were within limits of weight variation allowed by I.P. Hardness of the tablets was within 6.8-7.3 kg/cm$^2$ which indicated adequate mechanical strength. Thickness varied from 3.2 to 3.46 mm. Also the assay procedure complied for almost 30 mg of drug in a single tablet which was the required dose. The friability of the formulations was found to be less than 1.0 %.

***Evaluation of Ethylcellulose AM gliclazide tablet***

From Table 7 it was concluded that the coated AM tablets were within the limits of weight variation according to I.P. 1996. Average weight of the coated tablet was found to be between 276.12 and 278.33 mg. Thickness varied from 3.78 to 4.57 mm. Also, the diameter of the coated AM tablet was found between 10.34 and 10.57 mm. The average drug content per tablet varied from 29.7 to 31.3 mg.

**Table 7. Evaluation Parameters for Gliclazide AMTs**

| Formulation code | Average wt. ±SD (mg) | Thickness ±SD (mm) | Diameter±SD (mm) | Drug content±SD (mg) |
|---|---|---|---|---|
| F-1 | 278.33±1.02 | 4.23±0.04 | 10.54±0.03 | 30.12±0.01 |
| F-2 | 276.56 ±1.1 | 3.98±0.03 | 10.43±0.02 | 30.06±0.02 |
| F-3 | 275.33 ±0.98 | 3.78±0.02 | 10.57±0.05 | 31.34±0.02 |
| F-4 | 278.44 ±0.86 | 4.22±0.05 | 10.34±0.06 | 29.98±0.12 |
| F-5 | 275.34 ±0.99 | 4.56±0.04 | 10.42±0.04 | 30.14±0.04 |
| F-6 | 274.55 ±1.1 | 4.34±0.02 | 10.39±0.03 | 30.01±0.03 |
| F-7 | 276.12±0.89 | 4.57±0.03 | 10.52±0.02 | 30.45±0.04 |
| F-8 | 276.90 ±1.0 | 4.04±0.02 | 10.38±0.03 | 29.78±0.06 |

*Average values from N=3

***Release profiles of AM Gliclazide osmotic tablet***

All the batches of the L-8 orthogonal design fulfilled the minimum 80% release criteria as per British Pharmacopoeia. The average cumulative drug release

from L-8 design batches ranged from 83.29% cumulative drug release to 98.75% as shown in Table 8.The release order of all the formulations was found to be of "zero order" respectively. From the release data it was found that the batch F-6 released the maximum amount of drug, corresponding to 98.75%, in about 20 hrs. Thus the Batch F-6 was selected as the optimized batch of L-8 design.

An important feature of any osmotic drug delivery system is that it maintains its mechanical stability and resistance of the film coating to rupture during passage through the gastrointestinal tract. None of the tablets ruptured during the dissolution studies. Empty polymeric shells retained their original shape and floated on the dissolution medium after the completion of drug release.

**Table 8. Cumulative Drug Release Profiles from L-8 Design Gliclazide AMTs**

| Time (hrs) | Percent cumulative drug released (average value from N=3) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Formulations code | | | | | | | |
| | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 | F-8 |
| 2 | 18.67 | 11.75 | 11.90 | 11.90 | 13.25 | 15.06 | 8.58 | 13.55 |
| 4 | 40.92 | 21.15 | 25.37 | 25.68 | 22.36 | 25.08 | 20.23 | 22.52 |
| 6 | 52.44 | 34.07 | 38.91 | 38.42 | 35.29 | 38.93 | 37.21 | 34.99 |
| 8 | 66.29 | 45.70 | 46.06 | 49.37 | 46.33 | 53.00 | 49.31 | 47.53 |
| 10 | 77.95 | 56.35 | 60.32 | 62.59 | 57.58 | 62.93 | 60.88 | 58.19 |
| 12 | 86.96 | 66.15 | 71.19 | 74.99 | 67.08 | 73.22 | 68.60 | 68.60 |
| 14 | 90.45 | 73.44 | 76.70 | 84.43 | 74.38 | 85.97 | 81.92 | 74.70 |
| 16 | 93.20 | 81.22 | 83.29 | 89.11 | 81.71 | 90.96 | 88.10 | 82.64 |
| 18 | _ | 85.88 | _ | _ | 90.89 | 95.97 | _ | 85.65 |
| 20 | _ | 92.06 | _ | _ | 95.153 | 98.75 | _ | 90.33 |

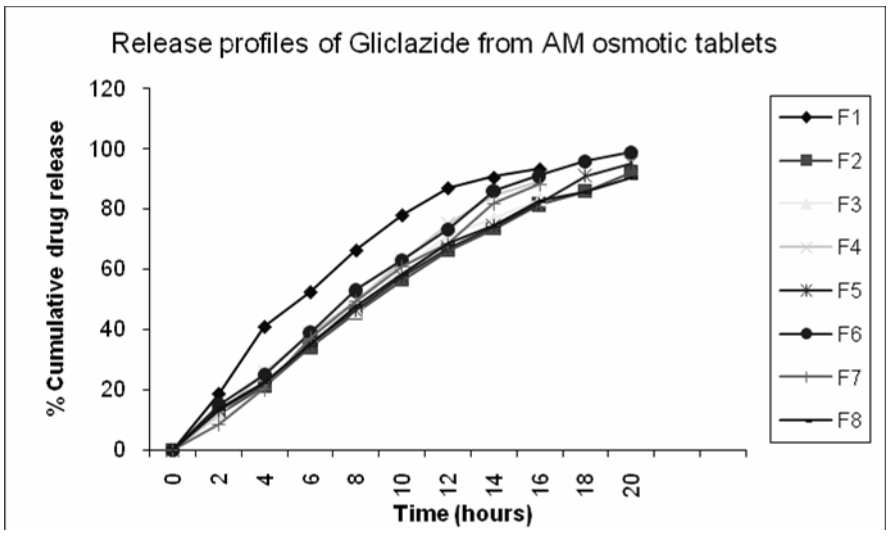



**Figure 2. Release Profiles of Gliclazide AM Tablets**

**Table 9. Responses w.r.t. Different Combination of Factors in L-8 Orthogonal Design**

| Formulation code | Sodium chloride | Ethyl cellulose | PEG-400 | Glycerine | Quenching time | Response* (% cumulative drug release) |
|---|---|---|---|---|---|---|
| F-1 | -1 | -1 | -1 | -1 | -1 | 93.20 |
| F-2 | -1 | -1 | -1 | +1 | +1 | 92.06 |
| F-3 | -1 | +1 | +1 | -1 | -1 | 83.29 |
| F-4 | -1 | +1 | +1 | +1 | +1 | 89.11 |
| F-5 | +1 | -1 | +1 | -1 | +1 | 95.15 |
| F-6 | +1 | -1 | +1 | +1 | -1 | 98.75 |
| F-7 | +1 | +1 | -1 | -1 | +1 | 88.10 |
| F-8 | +1 | +1 | -1 | +1 | -1 | 90.33 |

*Average of N=3

***Effect of pH on the release profile of Gliclazide AMT***

To verify that the drug delivery profile from the Gliclazide AMT is independent of the pH of dissolution medium, the dissolution test was carried out in dissolution mediums with pH 1.2, pH 4.6 and pH 7.4. This is an important test to mark the distinguishing characteristic of the osmotic drug delivery system and its advantage over other delivery systems. The release profiles were plotted as in Figure 3. The average release rate in different pH media was tested for any statistically significant difference and has resulted in no significant difference.

**Table 10. Cumulative Drug Release from the Gliclazide AMTs at Different pH Conditions**

| Percent cumulative drug released (average value from N=3) | | | |
|---|---|---|---|
| | pH of the dissolution media | | |
| **Time (Hrs)** | **pH 1.2** | **pH 4.6** | **pH 7.4** |
| 2 | 13.17 | 13.83 | 15.06 |
| 4 | 22.29 | 19.94 | 25.08 |
| 6 | 38.64 | 28.39 | 38.93 |
| 8 | 47.77 | 45.86 | 53.00 |
| 10 | 58.41 | 52.92 | 62.93 |
| 12 | 67.24 | 60.65 | 73.22 |
| 14 | 73.86 | 71.11 | 85.97 |
| 16 | 81.31 | 77.53 | 90.96 |

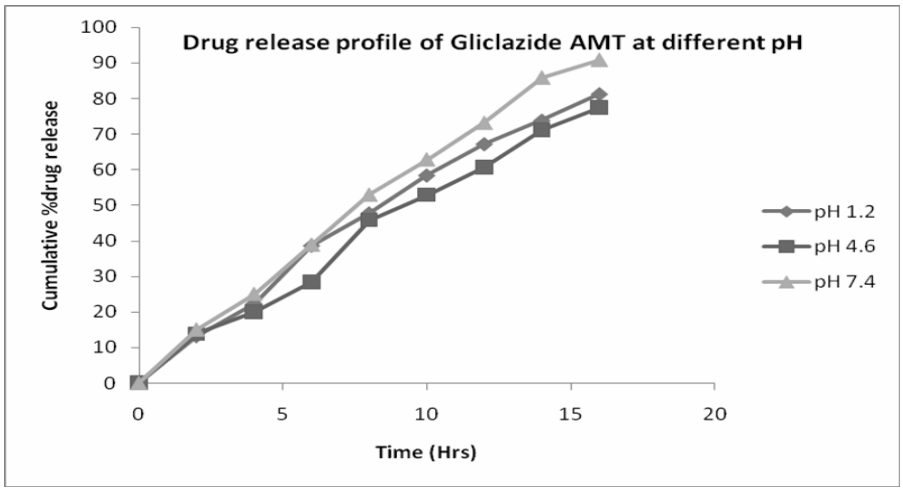



**Figure 3. Release Profile of Gliclazide AMT at Different pH Conditions**

***Effect of agitational intensity on the release profile of Gliclazide AMT***

The asymmetric membrane mediated osmotic drug delivery system is unaffected by the environmental condition of agitation intensity. To characterize this feature of AMT, the optimized batch F-6 of the L-8 design batches was evaluated for dissolution studies at 50, 100 and 150 rpm respectively. The release profile did not show any significant changes, even on the increase of stirring rate. This can be observed from the graph (Figure 4).

**Table 11. Cumulative Drug Release from the Gliclazide AMTs at Different Agitation Intensities**

| **Percent cumulative drug released (average value from N=3)** | | | |
|---|---|---|---|
| **Agitational intensity in the dissolution media** | | | |
| **Time (Hrs)** | **50 RPM** | **100 RPM** | **150 RPM** |
| 2 | 13.55 | 15.06 | 11.90 |
| 4 | 22.06 | 25.08 | 18.74 |
| 6 | 38.90 | 38.93 | 35.56 |
| 8 | 52.52 | 53.00 | 45.40 |
| 10 | 59.44 | 62.93 | 56.34 |
| 12 | 66.84 | 73.22 | 69.75 |
| 14 | 76.25 | 85.97 | 80.38 |
| 16 | 85.70 | 90.96 | 83.83 |

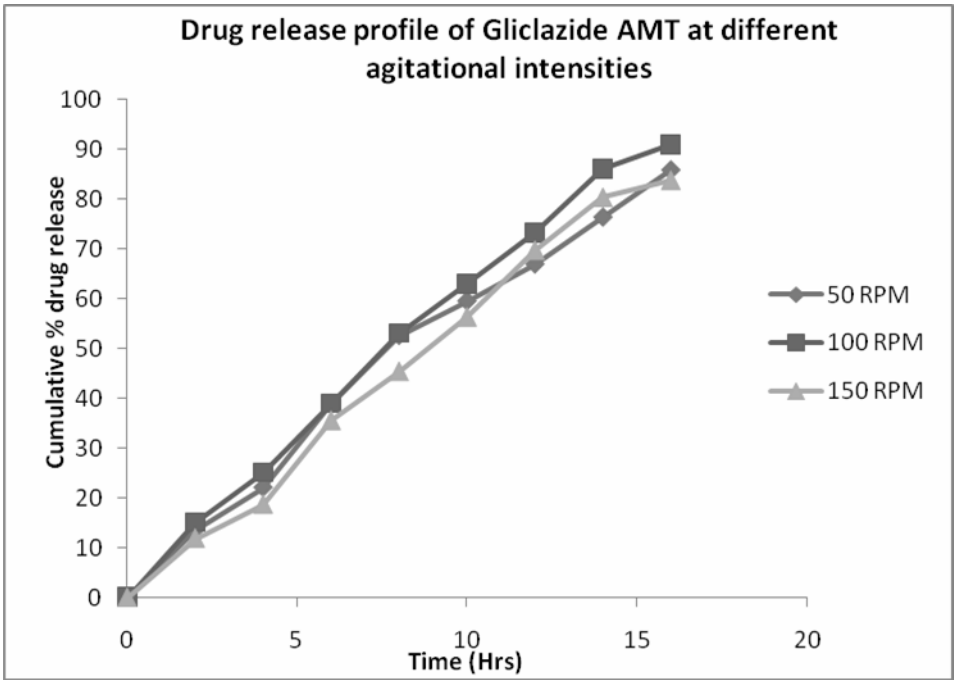



**Figure 4. Release Profile of Gliclazide AMT at Different Agitational Intensities**

***Dissolution profile of extra check point batches***

The release profile of the check point batches revealed that the asymmetric polymer membrane on the osmotic core is the prerequisite for the oral control delivery of Gliclazide by asymmetric membrane technology. The batch CP-1, which was an uncoated osmotic core, released about 98.8% of the gliclazide in about 2 hrs, which shows that an uncoated osmotic core tablet behaved like a conventional tablet without the AM coat (Figure 5). Also, the AMT without the osmogen, batch CP-2, released about 49.3% gliclazide in 16 hours, showing that the drug release profile from an osmotic drug delivery system depends on the osmogen content of the dosage form. It may be possible that the 49.3% drug release from the batch CP-2 was due to the combined action of mannitol (which may possess some osmotic pressure) and diffusion gradients across the ethyl cellulose asymmetric membrane.

The batch CP-3 (without phase inversion) released only 73.31 % of the drug in 16 hours. The decreased cumulative drug release profile of batch CP-3, as compared to the optimized batch of L-8 design, revealed that the asymmetricity due to the phase inversion process "quenching" is responsible for higher water gradients in the AMT and thus higher drug release successively (Figure 5).

**Table 12. Cumulative Drug Release Profile from Extra Check Point Batches**

| **Percent cumulative drug released (average value from N=3)** | | | |
|---|---|---|---|
| **Formulation code for extra check point batches** | | | |
| **Time (Hrs)** | **CP-1** | **CP-2** | **CP-3** |
| 2 | 99.85 | 3.6 | 7.23 |
| 4 | - | 14.93 | 20.52 |
| 6 | - | 23.75 | 30.12 |
| 8 | - | 27.19 | 37.52 |

| Percent cumulative drug released (average value from N=3) | | | |
|---|---|---|---|
| **Formulation code for extra check point batches** | | | |
| **Time (Hrs)** | **CP-1** | **CP-2** | **CP-3** |
| 10 | - | 32.16 | 48.87 |
| 12 | - | 39.27 | 58.03 |
| 14 | - | 45.81 | 64.97 |
| 16 | - | 49.37 | 73.31 |

***Evaluation of chitosan AM gliclazide tablet (extra design batches)***

**Table 13. Evaluation Parameters of Chitosan AM Gliclazide Tablet for Extra Design Batches**

| Formulation code | Weight (mg) | Thickness (mm) | Drug content (mg) |
|---|---|---|---|
| ED-1 | 279.33 | 4.23 | 30.02 |
| ED-2 | 276.56 | 3.93 | 30.0 |

**Table 14. Cumulative Drug Release Profiles of Extra Design Batches**

| Percent cumulative drug released (average value from N=3) | | |
|---|---|---|
| **Formulation code for extra design batches** | | |
| **Time (Hrs)** | **ED-1** | **ED-2** |
| 2 | 18.67 | 19.28 |
| 4 | 52.19 | 43.01 |
| 6 | 79.23 | 53.74 |
| 8 | - | 80.49 |

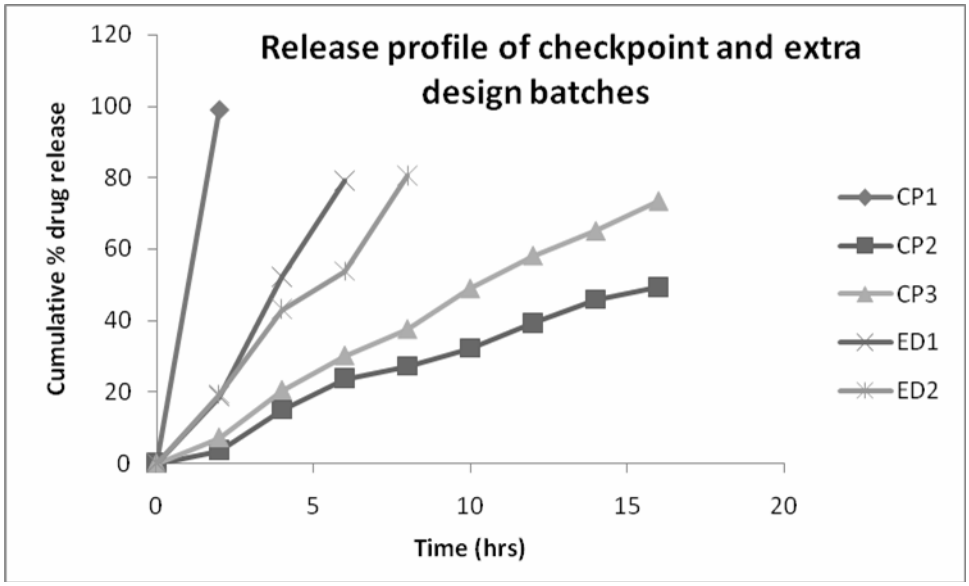



**Figure 5. Release Profile of Check Point and Extra Design Gliclazide Tablets**

The extra design batches were fabricated using chitosan as an asymmetric membrane forming polymer. The chitosan with a degree of deacetylation, 90.0% was used. The optimized core from the L-8 design batches was used as the tablet core in extra design batches.

The fabricated batches ranged from 276.5 to 279.3 mg in their average weights, complying with the B.P. standards. The average thickness of the coated tablets was found to be 4.23 and 4.93 mm respectively. The average drug content of the AMTs was found to be close to 30 mg, depicting the dose of the single dosage form.

The dissolution profiles of the chitosan coated AMTs of Gliclazide resembled a non-zero order drug release. Batch ED-1 released about 79.2 % of the drug in 6 hrs and the batch ED-2 released about 80.4% of the drug in 8 hrs. The release profiles of the ED batches suggests that the chitosan concentration used for the phase inversion dip coating of the Gliclazide osmotic tablet cores is responsible for the modified release profile of the Gliclazide. In both cases, a cumulative total of about 80% of the drug is released, but the release duration was greater in the batch with the higher concentration of chitosan in the coating solution.

A high degree of ionotropic gelation between the chitosan and sodium tripolyphosphate is responsible for the higher release duration of batch ED-2 (eight hours). A higher amount of chitosan is used in this case and provides more free $NH_2$ to crosslink with the polyphosphate. Thus we can say that the strong and high degree of ionotropic crosslinking between the chitosan and TPP is responsible for the release of the drug in a sustained manner.

***Evaluation of marketed preparations of Gliclazide***

**Table 15. Cumulative Drug Release Profiles of Marketed Gliclazide Formulations**

| **Percent cumulative drug released (average value from N=3)** | | |
|---|---|---|
| **Marketed Gliclazide formulations** | | |
| **Time (Hrs)** | **GLIX-40** | **GLIX-MR** |
| 2 | 99.70 | 5.87 |
| 4 | - | 19.16 |
| 6 | - | 28.75 |
| 8 | - | 37.35 |
| 10 | - | 49.45 |
| 12 | - | 59.51 |
| 14 | - | 66.77 |
| 16 | - | 76.62 |
| 18 | - | 84.27 |
| 20 | - | 92.56 |

The release profile of the marketed preparations, the GLIX-40 conventional tablet and the GLIX-MR, was observed as expected. The conventional GLIX-40 released about 99.7% of the drug in 2 hrs. The GLIX-MR released 92.56 % of the drug in 20 hrs. A Zero order drug release was seen in the case of GLIX-MR.

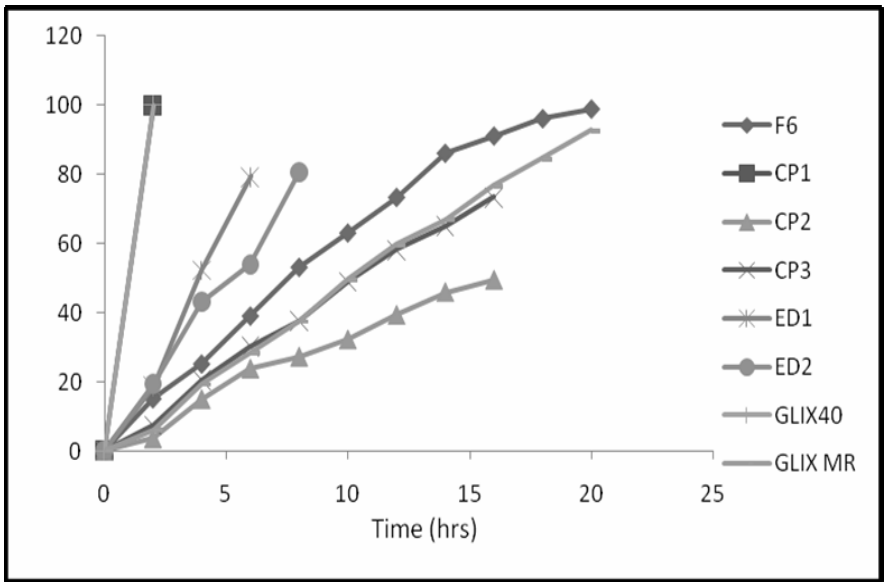



**Figure 6. Release Profiles of the Optimized Batch, Check Point Batches, Extra Design Batches and Marketed Formulations for Comparative Study**

**Table 16. Fitting of the Kinetic Models for Gliclazide Osmotic AMT**

| Formulation system | Formulation code | Zero-order ($R^2$) | Higuchi-matrix ($R^2$) | Hixon-Crowell ($R^2$) | Korsmeyer-Peppas | |
|---|---|---|---|---|---|---|
| | | | | | N | ($R^2$) |
| L-8 design | F1 | **0.9948** | 0.9502 | -0.8399 | 1.08 | 0.9859 |
| | F2 | **0.9949** | 0.9496 | -0.840 | 1.0898 | 0.9871 |
| | F3 | **0.9957** | 0.9491 | -0.9580 | 1.0917 | 0.9872 |
| | F4 | **0.9957** | 0.9494 | -0.9755 | 1.1067 | 0.9876 |
| | F5 | **0.9959** | 0.9471 | -0.9762 | 1.206 | 0.9873 |
| | F6 | **0.9958** | 0.9456 | -0.9762 | 1.132 | 0.9862 |
| | F7 | **0.9961** | 0.9451 | -0.9824 | 1.140 | 0.9857 |
| | F8 | **0.9961** | 0.9450 | -0.9855 | 1.439 | 0.9846 |
| | GLIX-MR | **0.9962** | 0.9421 | -0.9826 | 1.1424 | 0.9826 |
| Extra design batches | ED-1 | 0.6066 | **0.9290** | 0.9127 | 0.2421 | 0.9032 |
| | ED-2 | 0.5755 | **0.9171** | 0.9161 | 0.2402 | 0.9106 |

The result for the fitting of the kinetic models for drug release from the L-8 design Gliclazide AMT and the extra design AMT batches are shown in Table 16. The correlation coefficient ($R^2$) was used as an indication of the best fit for each of the models considered. In the case of L-8 design batches which were composed of ethylcellulose coated AMT, the best fit model was obtained when the zero order model was applied ($R^2$ = 0.9961). In case of chitosan coated AMT, the best fit model was obtained when the matrix Higuchi model was applied ($R^2$ = 0.9290). Thus it can be concluded that the fabricated ethyl cellulose coated AMT of Gliclazide delivered the drug at a zero order, which is the characteristic property of the osmotic drug delivery systems. Also the zero order release of the marketed preparation was confirmed.

***SEM micrographs of optimised Gliclazide AMTs***

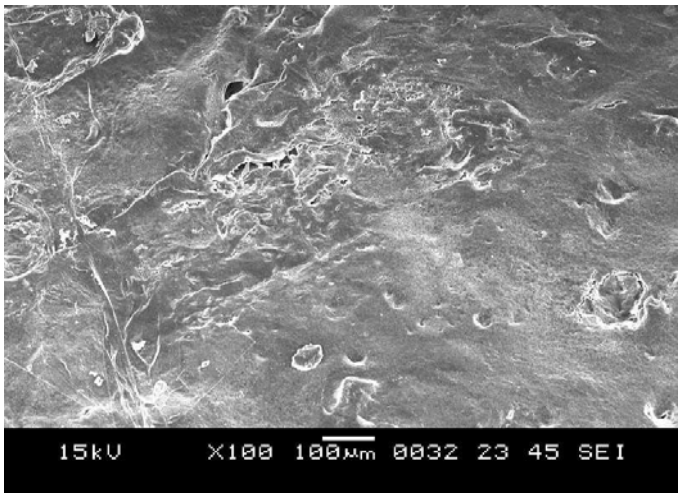



**Figure 7. SEM of EC Coated Gliclazide AMT Surface Before the Dissolution Studies**

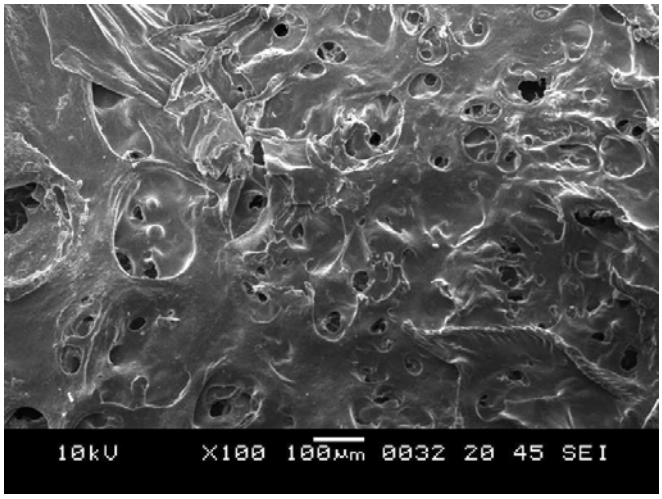



**Figure 8. SEM of EC Coated Gliclazide AMT Surface After the Dissolution Studies**

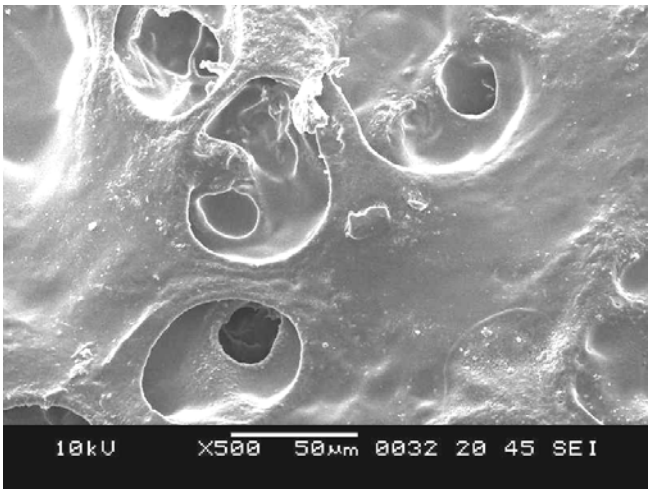



**Figure 9. SEM Showing the Generated Pores After the Dissolution of Gliclazide AMT**

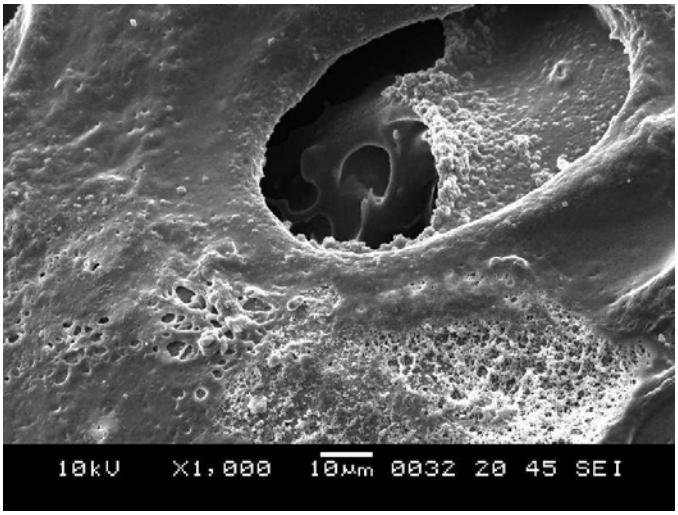



**Figure 10. SEM Showing the Developed Asymmetry Through the Membrane Pores**

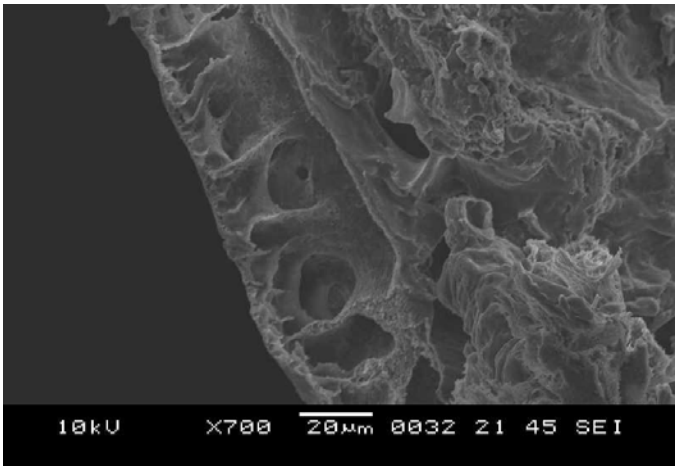



**Figure 11. SEM Showing the Cross Section of Gliclazide AMT Batch-F6 (Optimized Batch)**

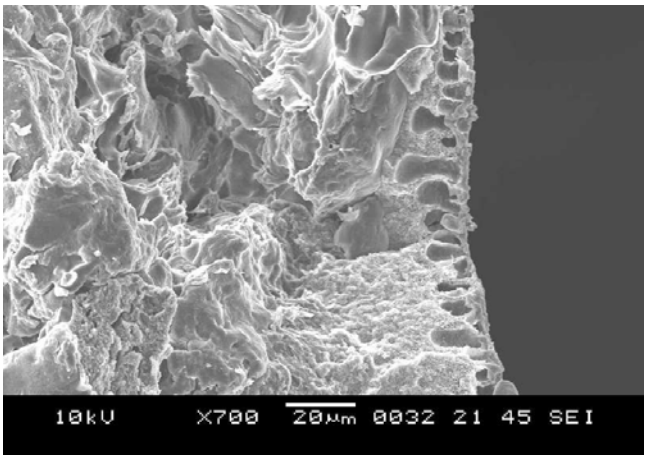



**Figure 12. SEM Showing the Cross Section of Chitosan Coated Gliclazide AMT Batch- ED2**

The scanning electron micrographs of the AM Gliclazide tablet coated with ethylcellulose and chitosan revealed the following information:

a) Figure 7 depicted the nearly smooth surface of the AMT. This shows efficient and proper dip coating of the core tablets. Also the elegant and uniform coat membrane on the core tablet was seen, which shows that the concentration of the polymer (ethylcellulose) and plasticizer (PEG-400) was sufficiently accurate to give a good film property.

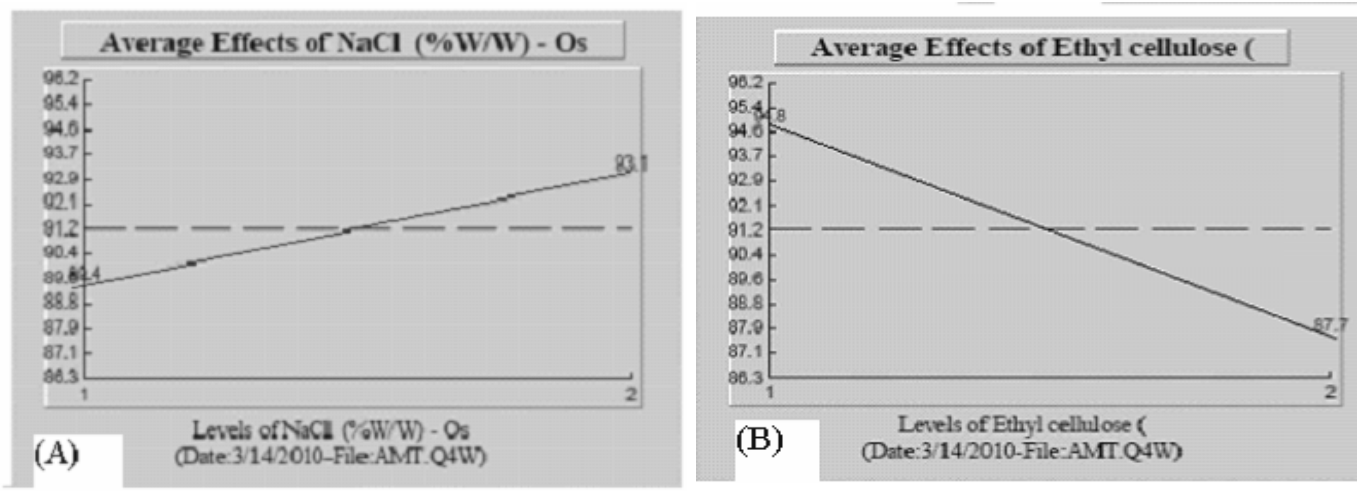
b) Figure 8 shows the generated pores on the AMT after dissolution. Nearly uniform pore formation was seen throughout the tablet surface, which shows the optimum level of pore former and plasticizer were incorporated into the coating solution. Pores of average pore sizes of 50µm were visible on the tablet surface (Figure 9).

c) The asymmetricity developed in the film coat was visible from the generated pores (Figure 10).

d) The SEM of the cross section of the optimized F-6 batch (Figure 11) showed the developed asymmetricity on the tablet core. The total tablet AM coat was found to be about 30-35µm thick. A thin dense layer of about 5µm, supported by a porous substructure, was seen. In all, this shows that an efficient asymmetric membrane tablet of Gliclazide was fabricated that delivered the required dose in around 20 hours in a controlled manner.

e) Figure 12 represented the cross section of the chitosan coated AMT of gliclazide. An asymmetric membrane with a thickness of about 15 to 20 µm was seen. A thin dense layer of about 5µm was supported by a porous substructure of about 10 to 15 µm. The asymmetricity developed in chitosan coated AMT was less than as compared to the ethylcellulose coated AMT. This suggests the need for more time for phase inversion (quenching), particularly in the case of chitosan AMT. Also, the less asymmetric nature of the chitosan AMT was responsible for less cumulative drug release as compared to ethyl cellulose AMT.

***Statistical analysis of the results by Qualitek-4 software***



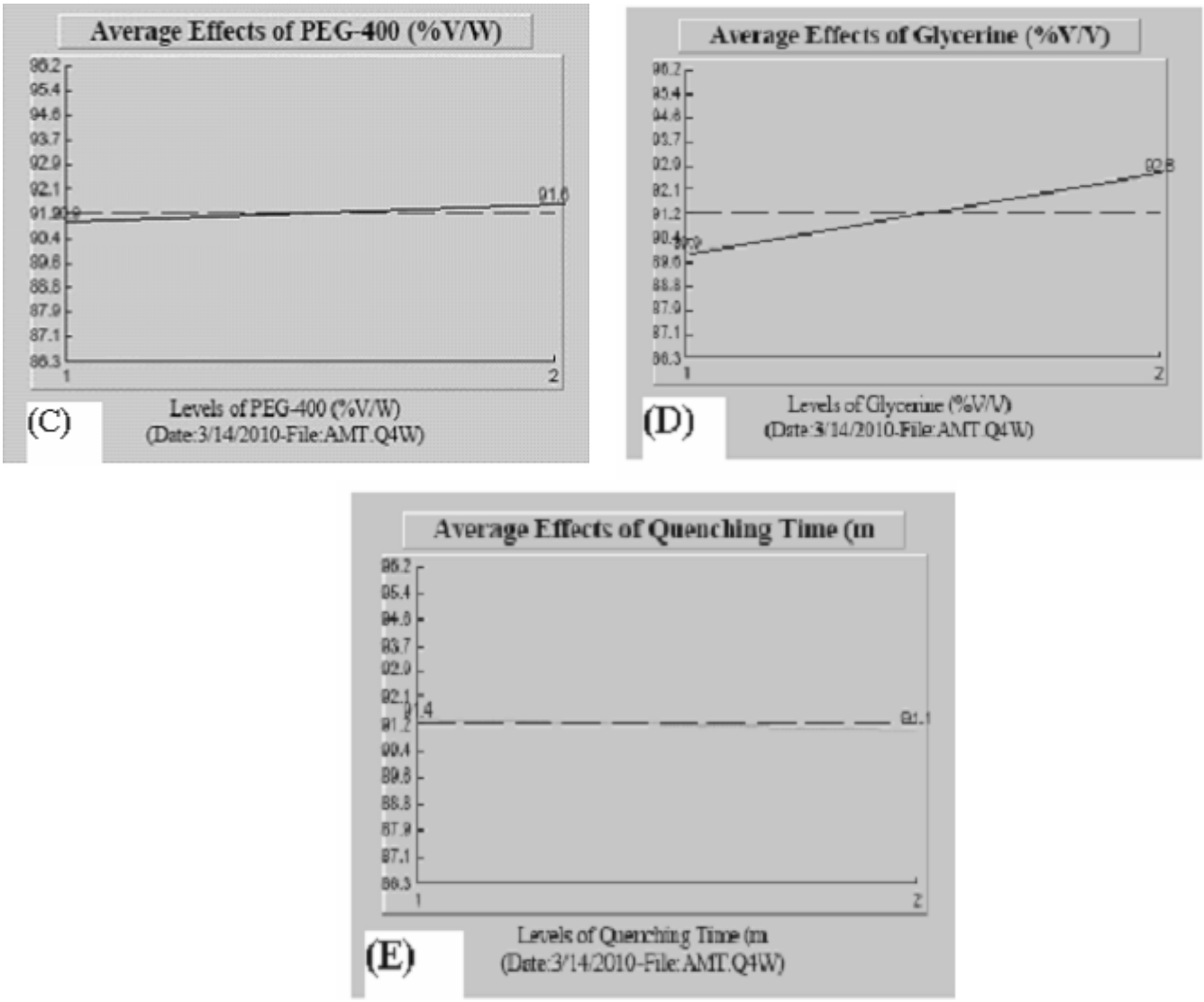



**Figure 13*. Effect of Different Levels of Studied Variables: (A) Level of Osmogen, (B) Level of AM Polymer, (C) Level of Plasticizer, (D) Level of Pore Former, (E) Quenching Time on Mean Cumulative Drug Release from AM Gliclazide Tablet**

*The vertical axis shows the mean cumulative drug release and the horizontal axis shows two levels of the studied variables.

**Table 17. ANOVA for Gliclazide AM Tablets Designed by Taguchi Design**

| S.No | Factors | DOF | Sum of squares | Variance | F-ratio | Pure sum | Percent |
|---|---|---|---|---|---|---|---|
| 1 | NaCl (%w/w) | 1 | 26.899 | 26.899 | 4.278 | 20.612 | 13.330 |
| 2 | Ethyl cellulose | 1 | 100.327 | 100.327 | 15.956 | 94.040 | 60.816 |
| 3 | PEG-400 | 1 | 0.850 | 0.850 | 0.135 | 0.000 | 0.000 |
| 4 | Glycerine | 1 | 13.806 | 13.806 | 2.195 | 7.518 | 4.862 |
| 5 | Quenching time | 1 | 0.169 | 0.169 | 0.026 | 0.000 | 0.000 |
| 6 | Other/error | 2 | 12.574 | 6.287 | | | 20.992 |
| 7 | Total | 7 | 154.628 | | | | 100.00% |

**Table 18. Expected Result at Optimum Conditions for AM Gliclazide Tablet**

| S.No | Factors | Level desc. | Level | Contribution |
|---|---|---|---|---|
| 1 | NaCl (%w/w) | 12 | 2 | 1.833 |
| 2 | Ethyl cellulose (%w/v) | 03 | 1 | 3.541 |
| 3 | PEG-400 (%v/w) | 50 | 2 | 0.326 |
| 4 | Glycerine (%v/v) | 02 | 2 | 1.313 |
| 5 | Quenching time (min) | 03 | 1 | 0.143 |
| Total contribution from all factors | | | | 7.155 |
| Current grand average of performance | | | | 91.248 |
| Expected conditions at optimum condition | | | | 98.404 |

**Table 19. Cumulative Drug Release Profile of the Predicted Batch**

| Percent cumulative drug released | |
|---|---|
| **Time** | **Predicted best batch** |
| 2 | 11.60 |
| 4 | 23.71 |
| 6 | 32.88 |
| 8 | 45.26 |
| 10 | 59.06 |
| 12 | 69.78 |
| 14 | 81.91 |
| 16 | 92.00 |
| 18 | 96.56 |

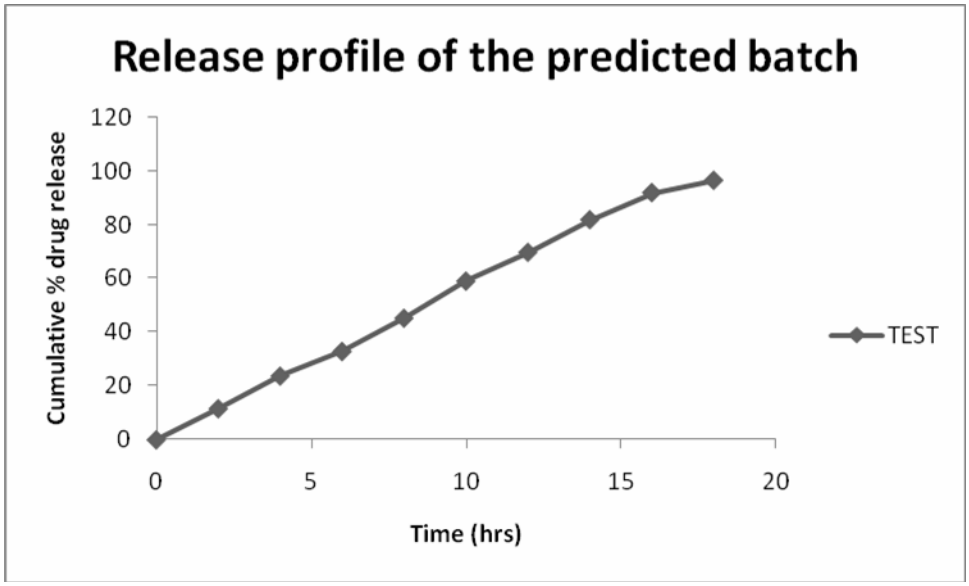



**Figure 14. Release Profile of the Predicted Batch for Best Response**
**Predicted response = 98.40 % cumulative release**
**Observed response = 96.56% cumulative release**

According to the statistical analysis, the result shows that the concentration of the AM polymer ethyl cellulose and sodium chloride are the most significant factors influencing the cumulative drug release from the Gliclazide AMT.

As per ANOVA, both factors shared 60.81% and 13.30% contribution for the cumulative drug release respectively (Table 17).The third factor that played an important role in the total percent of cumulative drug release was found to be the pore former (glycerine), with a 4.86% contribution. The plasticizer (PEG-400) and the quenching time, however, do not impart any effect on the desired response.

Per Figure 13 (A), changing the osmogen concentration from 6%w/w to 12%w/w increased the percent of cumulative drug release. The lower level contributed to an 82.4% cumulative release while the higher limit gave a 93.1% drug release.

Per Figure 13 (B), changing the EC level from 3% w/v to 5% w/v had the most significant decreasing effect on the cumulative drug release. The lower level contributed to a 94.8% drug release while the high level gave an 87.7% drug release. This decline in the drug release with a rise in the AM forming polymer concentration was due to the formation of a more complex and rigid AM coat on the tablet surface as compared to the coat formed with lower level of ethyl cellulose. Also the permeability developed on the membrane was less at higher AM polymer levels.

Per Figure 13 (C), no significant and noticeable effect was imparted by the plasticizer, PEG-400. And as per Figure 13 (D), changing the glycerine (pore former) concentration from 1% to 2% has an increasing effect on the cumulative drug release. The lower level contributed to a 89.9% drug release while the higher level aided in a 92.5% release. This enhancement in drug release due to a higher pore former level was due to an increment in the generated pores on the AMT which provided a comparatively higher flux of the dissolution fluids. Finally, it was also observed that the quenching time did not have a significant effect on cumulative drug release.

Accordingly, Taguchi's design predicted the optimized situation of the Gliclazide AMT formulation (Table 18). This predicted formulation was prepared and

the cumulative drug release was determined experimentally as done before with the L-8 batches. The results showed that the actual and predicted values of the optimized formulation, according to the desired response, are close and that Taguchi's design can successfully predict the best situation for fabricating the Gliclazide AMT for modified drug delivery.

**CONCLUSION**

Drug delivery using principles of osmotic pressure is a versatile technology and AMT further extends the scope. Asymmetrical membrane can be prepared by using either of the polymers, ethyl cellulose and chitosan. The asymmetricity developed in chitosan coated AMT was less as compared to the ethyl cellulose coated AMT. The less asymmetric nature of the chitosan AMT was responsible for lesser cumulative drug release as compared to ethyl cellulose AMT. By applying Taguchi's L-8 design, we can predict the best situation of fabricating the Gliclazide AMT for modified drug delivery. The optimized formulation F6, with a cumulative release of 98.75%, can be considered as a promising AM osmotic drug delivery system of Gliclazide providing a nearly zero order drug release over a period of 20 hours.

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# صياغة وتقييم الأغشية غير المتناظر التناضحية في نظام تسليم الأدوية Gliclazide من خلال تطبيق تصميم تاجوشى ل8-L

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## ملخـص

تهدف هذه الدراسة لوضع نظام لتقديم الأدوية التناضحي لGliclazide غير المتماثلة باستخدام تكنولوجيا الأغشية (AMT). ففي هذه الدراسة، تم وضع أقراص باستخدام إيثيل السليلوز والشيتوزان كغشاء غير متماثل لتشكيل البوليمرات. وتم التأكد من الطبيعة غير المتكافئة للغشاء بواسطة المجهر الإلكتروني. تم تقييم أقراص لمعلمات مختلفة مثل متوسط الوزن، والصلابة، و تفتيت. لوحظ أن مستوى osmogen، ومستوى طلاء البوليمر ومستوى المسام السابق في صياغة AM عوامل هامة في تصميم لAMT التناضحي. ولكن مستوى المادنات لم يكن له أي تأثير على نتائج الصياغة.

الكلمـات الدالـة: تكنولوجيا الأغشية غير المتماثلة ، gliclazide، ، تصميم تاجوشى L-8.

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