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RESEARCH ARTICLE

FORMULATION, DEVELOPMENT AND EVALUATION OF OSMOTIC DRUG DELIVERY SYSTEM OF GLIBENCLAMIDE

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Abstract:

The purpose of present research work is to develop osmotic drug delivery of Glibenclamide. Glibenclamide belongs to a class of anti-diabetic (sulfonylurea), It works by Inhibition of ATP-dependent potassium channels. Glibenclamide is selected as model drug to study the effect of *in-situ* pore former osmotic capsule because it is an effective anti-diabetic drug. The proposed work is envisaged to carry out the preformulation, optimization, development of *in-situ* orifice forming osmotic capsule and evaluation of osmotic capsule. *In-situ* pore forming osmotic capsule of glibenclamide is the one which suit the concept of better patient compliance, delayed release, more efficacies and enough bioavailability to show required pharmacological action and less gastrointestinal side effects. The Glibenclamide osmotic drug delivery system was successfully developed and evaluated.

Key Words: Osmotic capsule, Glibenclamide, Osmotic pump, Anti-diabetic.

INTRODUCTION:

Dosage forms are a mixture of active drug components and nondrug components. Depending on the method of administration they come in several types. These are liquid dosage form, solid dosage form and semisolid dosage forms.[1]Osmotically controlled oral drug delivery systems (OCODDS) utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system.[2-4]

Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agents. Among the controlled release devices, osmotically controlled hold a stable place because of its reliability to deliver the API at predetermined zero order rate for prolonged period of time so these are used as the standard dosage forms for the constant delivery of contents.[5]

Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure.[6]

Mechanism of osmotic drug delivery

Core contain water soluble osmotically active agent and blended with water soluble or insoluble drug, additives and coating has been carried out which functions as semi permeable membrane.Since barrier is only permeable to water, initial penetration of water dissolves the critical part of the core, resulting in development of an osmotic pressure difference across the membrane. The device delivers a saturated volume equal to the volume of water uptake through the membrane. Initial lag time (per hour) during which delivery rate increases to its maximum value, drug release is zero order, until all solid material is dissolved.[7]

The relation between Osmotic pressure (Π) and the concentration of non-electrolyte is given for dilute solution which may be assumed to exhibit ideal behavior by the Van't Hoff equation,

$$\Pi V = n\,2\,RT$$

Where V = is the volume of solution.

n 2 = is number of moles of solute.

T = thermodynamic temperature and

R = is the gas constant. [7]

The purpose of present research work is to develop osmotic drug delivery system of glibenclamide. The oral route of administration is considered as the most widely accepted route but the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of paediatric, geriatric patients, dysphasic, bed ridden, and psychic patients. Also, solid oral delivery systems do not require sterile conditions and are, therefore less expensive to manufacture. The aim of this study was to develop a new delivery system as in situ pore former osmotic drug delivery system.

EXPERIMENTAL WORK

Materials: Glibenclamide (drug) was provided by Aristo Pharmaceutical Pvt Ltd. Sodium chloride, lactose, sodium lauryl sulphate, magnesium sterate, ethyl cellulose, ethyl alcohol and other chemicals were provided by Sagar Institute of Research Technology & Science-Pharmacy Bhopal. Hard gelatin capsule were purchased.

Method of preparation:

Filling of capsule body:

For the preparation of osmotic capsule first of all a hard gelatin capsule was taken ,then the mixture of Glibenclamide, Lactose, Nacl, Magnesium sterate and Sodium loarylsulphate was prepared. The prepared mixture was filled into the body part of capsule by the hand filling method, than the body cap of capsule is placed.

Optimization

To optimize the formulation we took Six formulations F-1,F-2, F-3, F-4, F-5 and F-6. In each formulation we changed concentration of the ingredients.The concentration of osmogen, sodium chloride and solubilizing agent, sodium lauryl sulphate were changed. Different concentration of osmogen gave the different release of the drug. When the concentration of the solubilizing agent was increased the solubility of the formulation was increased. More concentration of the sodium lauryl sulphate and Nacl gave the release rate of drug was increased. The all formulation F-1, F-2, F-3, F-4, F-5 and F-6 release rate were studied at dissolution apparatus and the F-2 formulation was the perfect for the preparation. 2 mg of Nacl gave the good osmotic pressure for the release of the drug and 1% of sodium lauryl sulphate gave the good solubility for the release of the drug hence we used the F-2

formula for the preparation. Thus, the formula is optimized for concentration of sodium chloride and Mg stearate, sodium lauryl sulphate.

Table no. 1 optimization of Glibenclamide osmotic capsule

S No.	Ingredients	F-1	F-2	F-3	F-4	F-5	F-6
1	Glibenclamide	15mg	15mg	15mg	15mg	15mg	15mg
2	NaCl	1mg	2mg	3mg	1mg	2mg	3mg
3	Lactose	40mg	40mg	40mg	40mg	40mg	40mg
4	Sodium lauryl sulphate	1%w/w	1%w/w	1.5%w/w	1.5%w/w	2%w/w	2%w/w
5	Mg stearate	3mg	3mg	3mg	3mg	3mg	3mg

Coating of capsule body:

To make insoluble in water, hard gelatin capsule was treated with 1% ethyl cellulose in ethyl alcohol. Hard gelatin capsules were coated by dip coating method at the room temperature. The coated capsules were then dried at different temperatures ranging from approximately 25 to 50 ℃ for 15 min. In order to find an optimum temperature for obtaining smooth coat without any shrinkage. Smooth coating was formed when the temperature was 25 ℃. Thickness of the semi-permeable film applied to the capsule could be varied by altering the number of coats applied. Number of coats was between 2-5 times and each coating process was carried out after drying the previous coat.

Table no. 2 Formula for osmotic capsule

S.No.	Ingredients	Quantity (mg)
1.	Glibenclamide	15
2.	Nacl	2
3.	Lactose	40
4.	Sodium lauryl sulphate	1%w/w
5.	Magnesium stearate	3

CHARACTERIZATION

PREFORMULATION STUDIES

Preformulation testing is the first step in the rational development of dosage forms of a drug substance.

Organoleptic property: The physical characteristic like organoleptic properties of drug sample was performed and it was found to be bitter in taste, color was white crystalline powder and was odourless. And hence the drug sample was found to be as per specifications.

Solubility of Glibenclamide: The quantitative solubility of drug was determined and it was found that drug freely soluble in methanol and ethanol, sparingly soluble in chloroform and slightly soluble in water.

Table no. 3 Solubility of Glibenclamide

Solvent	Solubility	Observation
Water	Insoluble	Not soluble
Hexane	Insoluble	Not soluble
Methanol	Soluble	Freely soluble
Ethanaol	Sparingly soluble	Soluble
Ethyle acetate	Slightly soluble	Soluble with opaque color
Ether	Very slightly soluble	Very slightly soluble
Dimethyleformamide	Freely soluble	Freely soluble

IR Test sample: Glibenclamide sample was confirmed by IR spectroscopy using Bruker Alpha FT-IR Spectroscopy. The characteristic peaks were compared with IR spectrum as given in pharmacopoeia.

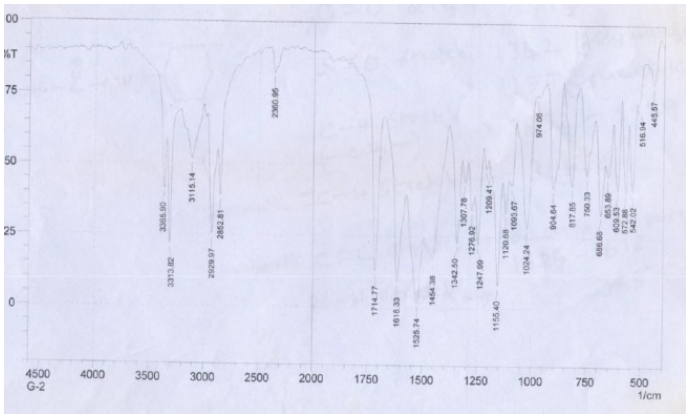


Fig 1. IR identification test of Glibenclamide

UV Spectroscopy: Identification and authentication of drug sample was done by ultraviolet spectroscopy and it was scanned in the range of 200-400 nm. Drug absorption maximum λ_{max} was found to be at 300 nm. Absorption maximum showed that drug sample was authenticated.

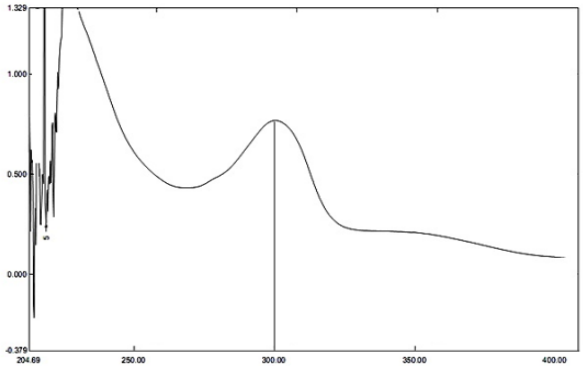


Fig 2. UV identification test of Glibenclamide

Standard calibration curve for Glibenclamide: Quantitative estimation of drug sample was done by different calibration curves which were prepared in phosphate buffer solution pH 6.8 in concentration range of 0-20µg/ml and the R^2 value was found to be 0.9979 and 0.9991 respectively which indicated the linearity of the graph.

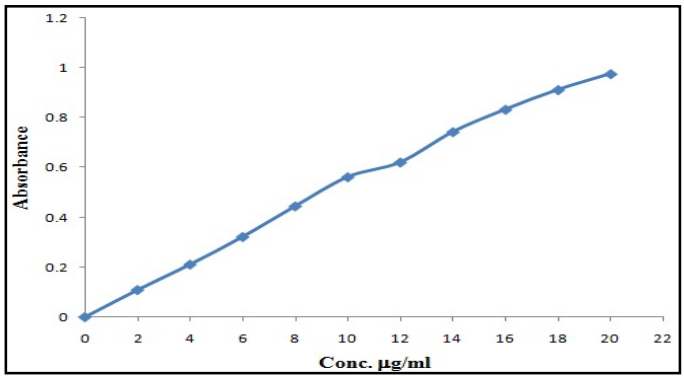


Fig 3. Calibration Curve of Glibenclamide

Compatibility study: DSC thermogram showed endothermic and exothermic peaks. Drug and polymer displayed their characteristic individual melting trends without any appreciable deviation. From this it is observed that there is no interaction between drug and polymer.

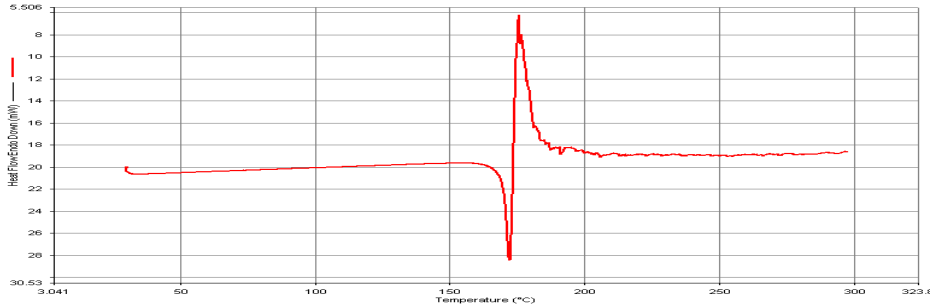


Fig 4. DSC characterization of glibenclamide

On the basis of preformulation study the drug sample of Glibenclamide was found pure and authenticated and the sample was used for the further preparation.

CHARACTERIZATION OF DOSAGE FORM

Morphological study and organoleptic properties:

Shape, surface and color of capsule is examined by naked eye. Surface study is performed to find out color change and smoothness of osmotic pump after formulation.

Table 4. Orgenoleptic Properties of Glibenclamide

S.no.	Description	Glibenclamide drug
1.	State	Solid
2.	Colour	White
3.	Odour	Odourless
4.	Texture	Crystalline powder

Osmotic release study

The capsule shell of asymmetric membrane containing different types of pore forming agent were filled with a highly water soluble amaranth dye. The dye was filled in each of the capsule body manually and the cap was singly fitted to the body of capsule and finally sealed with a sealing solution of ethyl cellulose to ensure that the no release takes place from the seal. The capsule containing the dye were placed in the distilled water and the solution of sodium chloride(10%w/v) respectively. The capsule were than observed for release of the

coloured dye in each of the media.

Drug content

From accurately weighted samples of prepared osmotic capsules was extracted into buffer pH 7.4. Then extracts diluted using buffer solution (pH–7.4). Resultant extract analyzed for Glibenclamide spectrophotometricaly at 300 nm.[5]

The drug content was calculated from standard curve.

$$\% \text{ Drug content} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Table 5. % drug content in prepared osmotic capsule batches

F-1	F-2	F-3	F-4	F-5	F-6
99.7 ± 1.03%	101.19 ± 1.03%	100.02 ± 2.28%	99.65 ± 0.55%	99.07 ± 1.41%	98.58± 1.11%

***In-vitro* release**

For the release study during dissolution apparatus USP apparatus type II was used. In this apparatus 900 ml of solution of phosphate buffer 6.8 pH at 75 rpm and 37±1°C used. The capsules are placed inside the apparatus and release of drug is evaluated. The samples were filtered and suitably diluted to determine the absorbance at 300 nm in UV spectrophotometer.

Table 6. *In-vitro* dug release from osmotic capsule

S. no	Time (hr)	% Drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	8.45	9.45	7.594	6.453	6.472	5.625
3	2	13.748	15.408	13.16	16.42	13.532	16.235
4	3	25.759	29.759	25.654	27.563	25.593	27.895
4	4	37.62	42.62	38.147	37.698	38.398	34.251
5	6	65.65	68.65	62.157	64.235	63.564	65.894
6	8	83.746	87.746	85.245	88.662	84.65	83.563
7	10	97.54	95.24	97.59	96.536	98.38	94.758

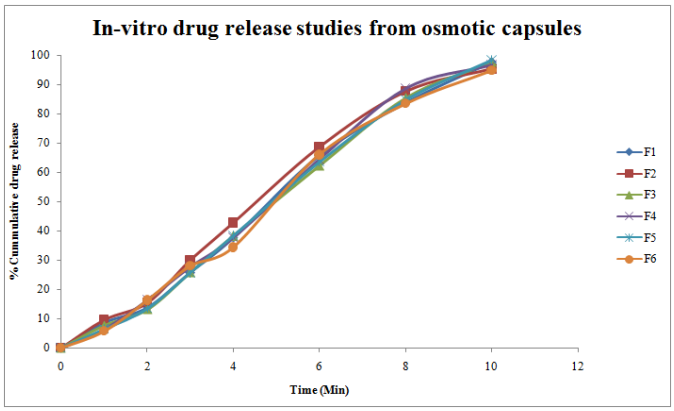
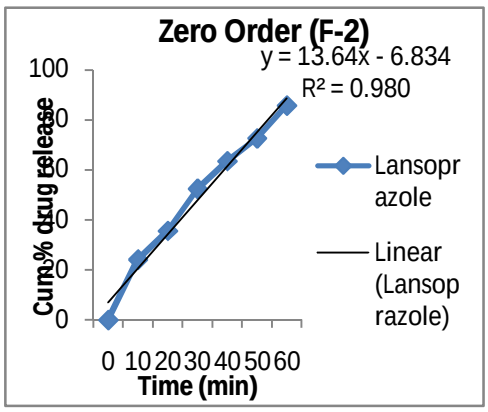


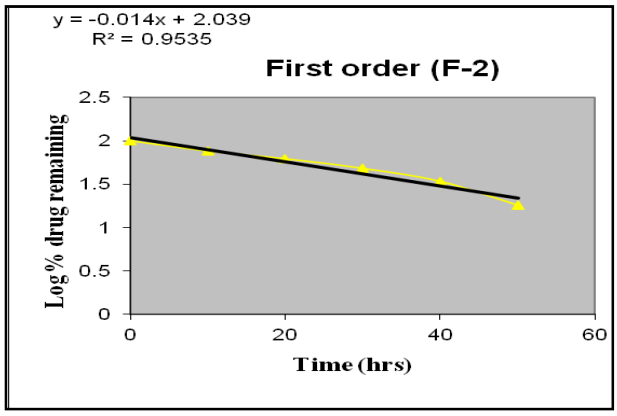
Figure 5. *1n-vitro* drug release from osmotic capsule

On the basis of characterization parameters formulation F2 is considered optimized and studied for release kinetics.

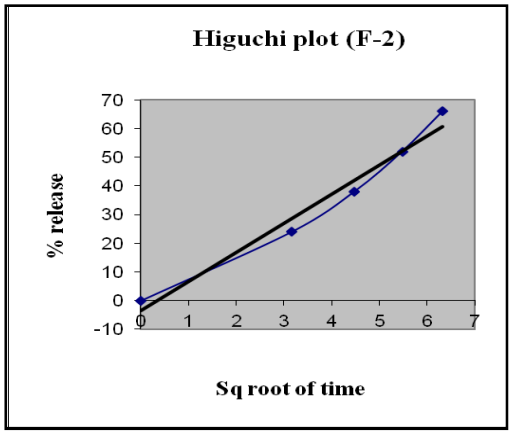
Drug release kinetics



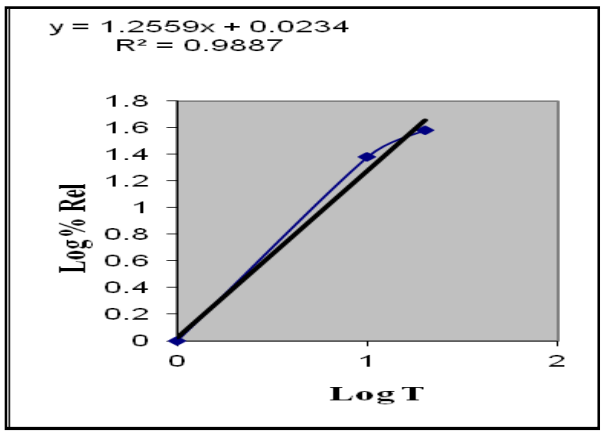
(A)



(B)



(C)



(D)

Figure 6. Release Kinetics of formulation F-2 ; (A) Zero Order Release, (B) First Order Release, (C) Higuchi Kinetic Study, (D) Pappas Equation for Kinetic Study

Result and Discussion:

The present study an attempt has been made to formulate osmotic pump using lactose, sodium lauryl sulphate, NaCl, magnesium stearate and Glibenclamide as a model drug. Total six formulations are prepared depending on various formulation variables. For the preparation of osmotic pump gelatin capsule was used. These capsules are coated with 1% solution of ethyl cellulose. There was a negligible weight variation of the formulated capsule, which was due to variation in weight of coating material and solubilizing agents.

The *in-vitro* drug release rate studies showed that the concentration of sodium lauryl sulphate is increased the rate of release of Glibenclamide. On increasing sodium lauryl sulphate content in the solid dispersion from 1 to 1.5 % w/v leads to an increased degree of solubility and therefore higher rate and extent of drug release. The concentration of solubilizing agent plays a major role in improving drug release of formulations.

The entire range optimized capsules exhibited a constant and controlled drug release profile from one hour onwards, though showing slow drug release till first one hour that must have elapsed in imbibition's of the core with the release medium and coating of ethyl cellulose which retarded the flow of fluid from outer compartment to inner compartment. Capsule did not show any significant effect on rate and extent of drug release; since no burst effect was observe during drug release study.

It can be inferred these orifice size has successfully prevented the membranes from rupturing effectively releasing the hydrostatic pressure developed inside the system and at the drug and constant rate over a significantly long period of time. The coating thickness of the osmotic pressure varied with increase in concentration of coating material it also has an effect on the release pattern, which can confirmed from *in vitro* release.

The asymmetric membrane capsule prepared with various types of pore forming agent appeared to be opaque with no visible physical defects. *In-situ* pore formation for delivery was demonstrated by dye test. The dye release is depend upon the concentration and type of pore forming agent used. It was observed that the dye release decreased as the concentration of pore forming was increase. The observation suggests that when ethyl cellulose is used as a pore forming agent the lag time for release can be reduced.

Dye test also revealed that all the prepared systems followed osmotic release. All the asymmetric membrane capsule released dye after a lag time when suspended in distilled water, but none of the system showed the release of the dye when suspended in sodium chloride (10%w/v). This may be attributed to the fact that the osmotic release from the system was inactivated by the higher osmotic pressure of the surrounding medium i.e.10%

w/v sodium cholride solution, which did not allowed the system to osmotically release the dye. Thus the system was shown the osmotic release.

CONCLUSION

A porous osmotic pump based drug delivery system can be designed for controlled release of poorly water soluble drug Glibenclamide. It was evident from the result that the rate of drug release can be controlled through osmotic pressure of osmogens, level of pore former and solubilizing agent with release to be fairly independent of pH and hydrodynamic condition of the body.

Glibenclamide release from the developed formulation was directly proportional to the osmogens, pore former and solubilizing agent. Based on the finding of the present investigation, it was concluded that desired environmentally independent and controlled drug delivery of like Glibenclamide from oral osmotic pump can be achieved by approximately selecting dispersion, type of membrane and optimizing its thickness, by adjusting the concentration of solubilizing agent (Sodium lauryl sulphate) and incorporating optimized amount of osmogens (NaCl).

All formulations were found to be smooth and capsular. There thicknesses of all the osmotic pumps are similar. Glibenclamide was used as a marker or model agent. On basis of *in vitro* release profile of Glibenclamide, it was concluded that the osmotic pump containing sodium lauryl sulphate provided sustained release for 7 hour and remain stable and intact.

Acknowledgement

First of all, I sincerely acknowledge my gratitude to almighty for compassion and bountiful blessings that directed me in the right angle, sculptured me appropriately, and made me see this wonderful moment. I consider myself fortunate enough to be in right place with person I take this opportunity to express my deep sense of gratitude and hearty thanks to my guide Dr. Jitendra Banweer (Director, S.I.R.T.S.- Pharmacy) and co-guide Mr. Praveen Tahilani for their valuable guidance and support for the project. I am hearty thankful to them for providing me valuable suggestion and remarks to complete this work. Last but not the least and most essential my beloved Parents and family for whom even word used to express thanks will be miserable to acknowledge them. Their care, wishes and belief in me has played a major contribution in prolifically completion of this project.

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