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DEVELOPMENT AND CHARACTERIZATION OF OSMOTIC PUMP TABLETS BEARING ANTIDIABETIC DRUG

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ABSTRACT

The present study was to develop Elementary osmotic pump tablets of Metformin HCl and Glipizide of which Metformin HCl and Glipizide as controlled release. Elementary osmotic pump tablets were prepared by wet granulation method using Mannitol, Lactose, and PVPK30. The tablets were evaluated for Bulk density, Tapped density, Carr's index, and angle of repose. All the values were found within limits of standard. In vitro release studies were carried out by USP type2 paddle apparatus. The Elementary osmotic pump tablets had a good controlled effect in comparison with the conventional products.

KEYWORDS: Elementary Osmotic Pump Tablets, Controlled Release, Metformin HCl, Glipizide.

• INTRODUCTION

Osmotic pumps are controlled drug delivery devices based on the principle of osmosis. A wide spectrum of osmotic devices are in existence, out of them osmotic pumps are unique, dynamic and widely employed in clinical practice.[9] Osmotic pumps offer many advantages like they are easy to formulate and simple in operation, improved patient compliance with reduced dosing frequency, more consistent and prolonged therapeutic effect is obtained with uniform blood concentration and moreover they are inexpensive and their industrial adaptability vis-à-vis production scale up is easy.[2,9] The osmotic pump tablet system for oral administration has advantages such as,

- Osmotic pump tablets has excellent zero-order release kinetics.
- Constant delivery rate and there by reduce risk of adverse reactions.

- Delivery of drugs takes place in solution from which is ready for absorption.
- In – vivo delivery rate can be accurately predicted on the basis of in-vitro data.

The delivery rate from osmotic devices is not influenced by gastric pH and hydrodynamic conditions.

Elementary osmotic pumps are systems for the delivery of a drug in the form of a solution that release the active material at controlled rates. These systems work with the principle of osmosis, osmotic pressure is produced by active material in itself and /or an accompanying osmotic agent. The preparation consists of the core that contains the active material and a semipermeable membrane that coats the core, having an orifice produced by a microdrill in order to release the active material. When the system is in the gastrointestinal tract, fluid enters into the preparation and dissolves the active material in the core. Thus, the pressure formed in the preparation induces a release of the solution at a slow but continuous rate.

Here the aim of study was to formulate a simple EOP prepared with Metformin HCl and Glipizide as a model drugs. Metformin HCl and Glipizide are hypoglycemic agents. Generally, they are individually used in the treatment of type II noninsulin dependent diabetes mellitus. Metformin HCl used as hypoglycemic and Glipizide lowers glucose concentrations by stimulating the release of insulin from pancreatic β-cells. Metformin HCl and Glipizide has a similarly biological half -life (2-4 h), depending upon the individual and the dose is 500 mg for Metformin HCl and 5 mg for Glipizide two to three times a day.[1]

Hence in this Metformin HCl and Glipizide were chosen as a model drugs. It was supposed that controlled release of Metformin HCl and Glipizide not only reduces the GI irritation, but also give better therapeutic effect. Also by this study the factors responsible for controlling drug release through the elementary osmotic pump tablets were evaluated.

MATERIAL AND METHODS

Material

Metformin HCl was received as a gift sample from Meridian pharma (H.P. INDIA) Glipizide was received as a gift sample from Micro Lab. (Pondicherry, India). Cellulose acetate obtained from Central Drug House, New Delhi, India. PEG-400, PVP K-30, Mannitol, all are also obtained from CDH New Delhi; other chemicals were of analytical grade and used without any further purification.

Identification of both drugs

The content of Metformin HCl was determined at 233 nm by UV. The concentration of Glipizide was determined at 275 nm by HPLC.

Preparing the Tablet Core

The basic tablet formulation and the varying range of all chemicals are listed in Table 1. Core tablets of Metformin HCl and Glipizide were prepared by wet granulation method. Metformin HCl and Glipizide were mixed with all the excipients except, magnesium stearate and talc, all were manually blended, then the blend was granulated with ethanol and resulting wet mass was passed through 16 mesh sieve and dried it in hot air oven at 50-60^{0}C for sufficient time (15-20 min). After this granules were passed through 22 mesh sieve. These granules were then manually blended with magnesium stearate and talc, the resulting granules were then compressed into tablets using calibrated single stroke punching machine.

Coating and drilling of the formulations

The core tablets were coated in a pan coater (laboratory model made of stainless steel). Cellulose acetate (3%w/v) as semi-permeable membrane and PEG 400 as plasticizer were used in coating solution. The core tablets were coated in coating pan and initially pan was rotated at low speed and heated air was passed on the tablet bed. Then the speed of pan coater was increased and coating solution was manually sprayed over the surface of tumbling tablets with a spray gun. The manual coating procedure was done by intermittent spraying and drying. The coated tablets were dried overnight at 50^{0}C to remove solvent. A 0.55 mm orifice was drilled manually by a sharp needle on one side of tablet.

Evaluation of the formulations

The blend was evaluated for flow properties like, % compressibility and angle of repose. The hardness of core tablets were evaluated by Monsanto hardness tester (n=10). Friability of core tablets was carried on a Roche Friabilator for which 20 accurately weighed tablets were used. The core and coated tablets were also evaluated for weight variation, thickness and diameter. The average orifice diameter of the OPT_s was determined microscopically (n=20) using a pre calibrated ocular micrometer (table 3). Effect of various variables like PEG-400 concentration, membrane thickness, orifice size, pH of release media and agitation rate were studied on drug release.

In-vitro release test

Drug release *In vitro* was studied using USP type2 paddle type dissolution apparatus (rotation speed at 50 r/min, 900 ml of phosphate buffer pH 6.8 as the dissolution medium at 37°C ± 0.5°C). During the release test, 5 ml samples were withdrawn at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 9.0 10, 11, 12 and 24 h and filtered through a 0.45 µm filter. An equal volume of fresh dissolution medium at the same temperature was added. The amount of Metformin hydrochloride and Glipizide was determined by measuring the absorbance at 233.0 nm and 275.0 nm using ultraviolet spectrophotometer (Shimadzu 1700, Japan). This study was done in triplicate manner.

Drug content uniformity testing

Metformin HCl and Glipizide content present in osmotic pump tablets were determined by weighing accurately one tablet and crushed it in 100 ml of methanol. The sample was shacked for 30 min and filtered. The solution after filtration was analyzed by UV spectrophotometer at 233 nm, and 275 nm rispectivily after appropriate dilutions with methanol.

Scanning electron microscopy studies

To study the nature of membrane surface of developed osmotic pump tablets, both and after dissolution studies, electron microscopic method was used. The samples for SEM were prepared by placing semi-permeable membrane on a both side adhesive tape stuck to a stub. Gold palladium coating on the prepared stub was carried out by using Sputter coater (POLARON model SC- 76430). The thickness of coating was 189A^0.

The coated stubs were randomly scanned under Electron microscope (LEO-430, UK).

RESULTS AND DISCUSSION

Table. 1: Formula for different batches of core formulation.

INGREDIENTS (mg per tablet)	BATCH CODE					
	OPT1	OPT2	OPT3	OPT 4	OPT5	OPT6
Metformin HCl	500	500	500	500	500	500
Glipizide	5	5	5	5	5	5
Mannitol	50	100	150	200	100	100
Lactose	100	100	100	100	50	150
PVP K-30	30	30	30	30	30	30
Magnesium stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3

To study the influences of formulation variables on drugs release, tablets with various formulations (table 1) were prepared. A 0.55 mm orifice diameter was manually drilled on either side of the coated tablet.

- **Influence of amount of Mannitol**

Elementary osmotic pump tablets with different amounts of Mannitol as an osmotic pressure accelerant in the core were prepared. The results are shown in Fig. A significant influence was observed. With an increasing amount of Mannitol, the release rates were accelerated, because the increasing osmotic pressure made more drug release from the core.

- **Influences of coating formulation on drug release**
- **Influence of coating solution concentration**

Cellulose acetate solution of 2%, 3%, and 4% (g/100 ml) with the same quantities of PEG-400 were prepared, respectively. Then, the cores of tablets with the same lot number were coated using the above-mentioned coating solution. It can be observed that the concentration of the coating solution didn't significantly affect drug release. But, in practical use, when the concentration of the coating was above 4%, the viscosity of the coating solution would be too great to finish the coating process. When the concentration of the coating solution is lower than 2%, the coating membrane would be difficult to form. So, 3% cellulose acetate and acetone solution was chosen as the coating solution.

- **Influence of the amount of PEG-400**

In this study PEG-400 was used as a plasticizer. It is commonly used in cellulose acetate semipermeable membranes as a plasticizer. Different amounts of PEG-400 were added to 3% cellulose acetate coating solution to the coat the cores of tablets with the same lot number. The influence of PEG-400 on release was investigated. The results are shown in Fig.

It was observed that PEG-400 had a marked influence on drug release. With the increase in the amount of PEG-400, the drug release rate increased. This may be explained as follows: porous channels in the surface of the coating membrane increased with the increasing amount of PEG-400. Therefore, water could be imbibed into the membrane very quickly, accelerating the release rate of the drug.

- **Influence of amount of plasticizer**

If cellulose acetate solution alone is used for coating, the coating membrane will be easily ruptured over the course of drug release. Plasticizer is good for improving the nature of the coating membrane and plasticity of the coating materials.

Meanwhile, it can improve the membrane's adherence to the core and mechanical character. Therefore, plasticizer is very important in order for the coating film to form.

Influence of different coating weights

The same core tablets were coated with different coating weight (2%, 4%, 6%, and 8%). The influence of different coating weights is shown in Fig. The result shows that the release rate slowed following the increase of the coating membrane thickness. So, the release rate of elementary osmotic pump tablet can be controlled by adjusting the thickness of the coating membrane.

Influence of pH of the medium on release

Three types of medium were chosen to carry out the release test. The results are shown in Fig. The result indicated that the rate was unaffected by pH of the medium. This provided further evidence that the osmotic pump tablets are not affected by the medium's pH.

Influence of release orifice size

Release orifices with different diameters were made in osmotic pump tablets with the same lot number. Fig. shows that within certain ranges, the release results were basically the same. So, in practice, the releasing orifice size could be controlled within a certain range.

Influence of the number of release orifices

The release profiles of elementary osmotic pump tablets with one release orifice and two release orifices are presented in Fig. The results showed that the release rate did not increase significantly with an increasing number of release orifices. The release mechanism of the osmotic pump preparation was also demonstrated: the rate depends on the osmotic pressure across the coating membrane.

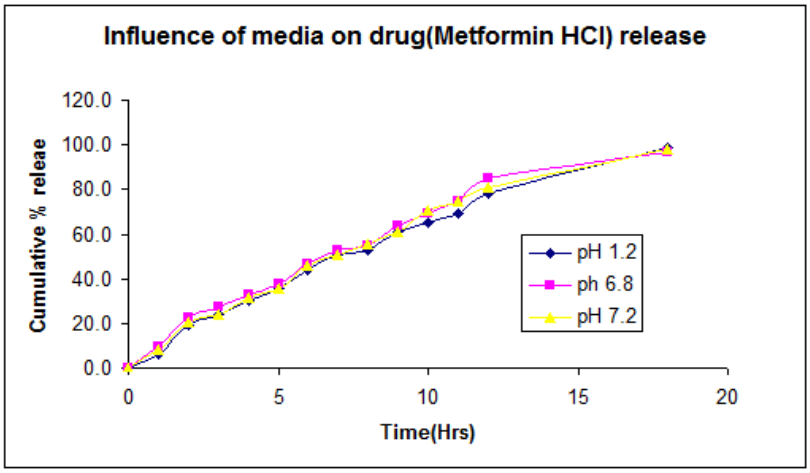

Figure. 1 (a): Effect of media on Metformin HCl release profile.

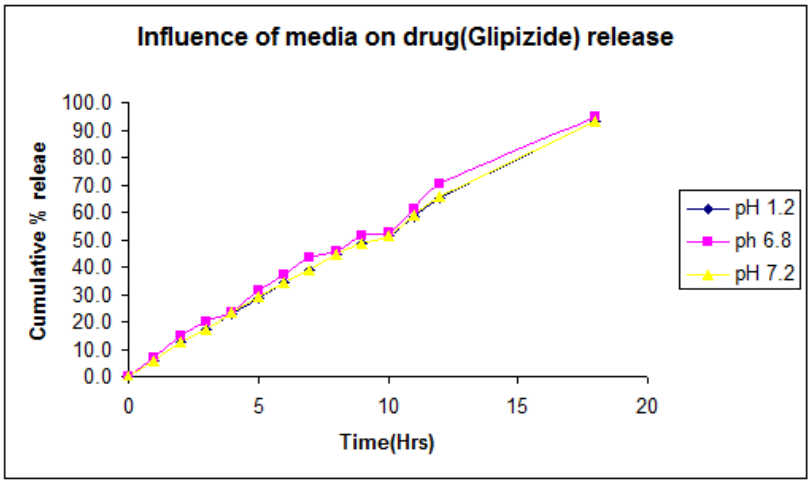

Figure. 1 (b): Effect of media on Glipizide release profile.

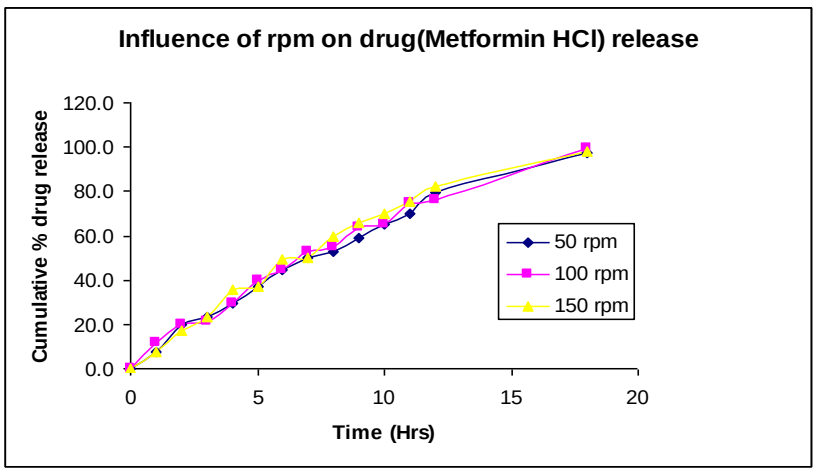

Figure. 2 (a): Influence of agitation rate on Metformin HCl release profile.

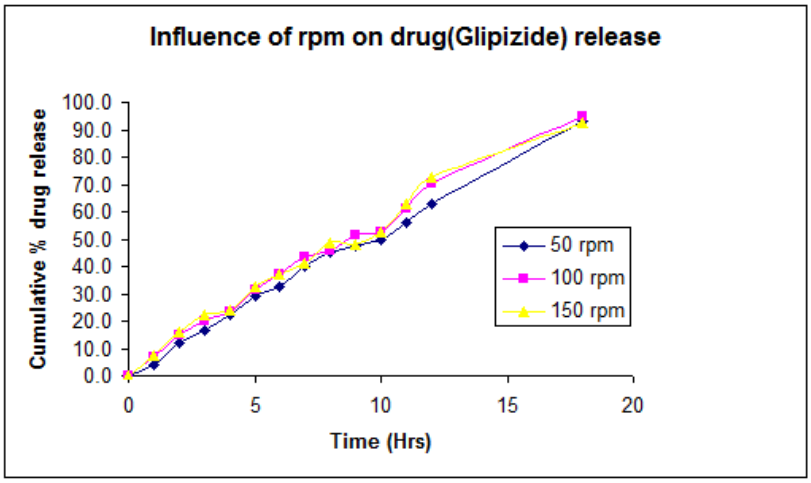

Figure. 2 (b): Influence of agitation rate on Glipizide release profile.

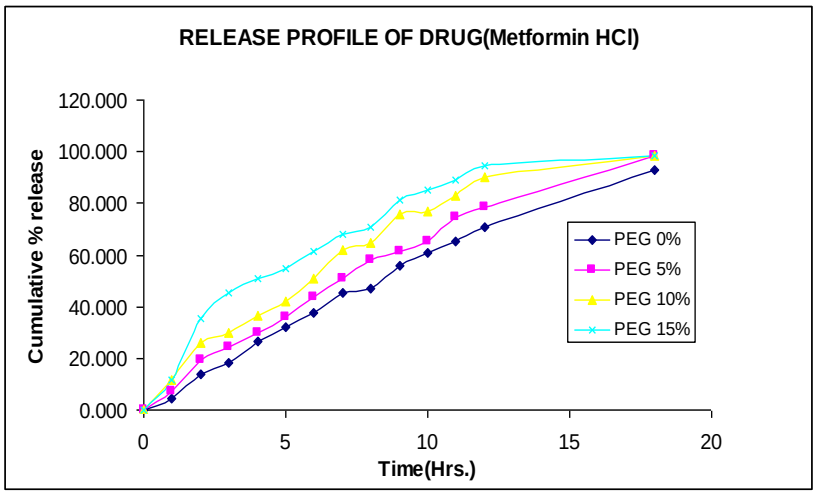

Figure. 3 (a): Effect of PEG400 level on Metformin HCl release profile.

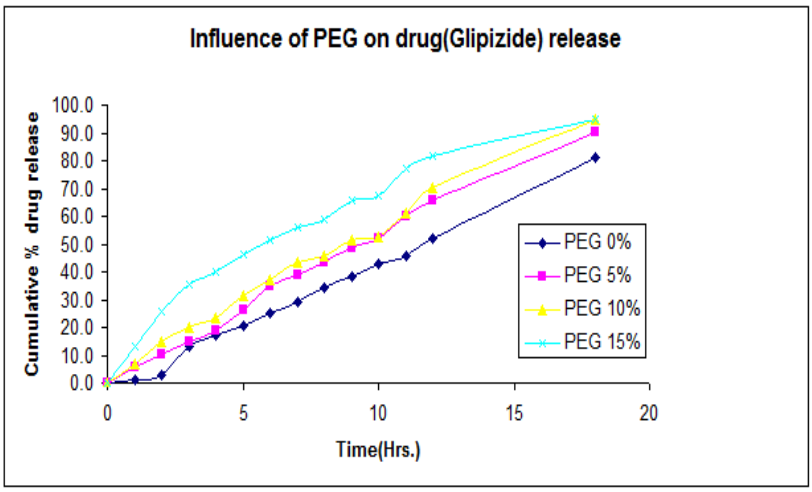

Figure. 3 (b): Effect of PEG400 level on Glipizide release profile.

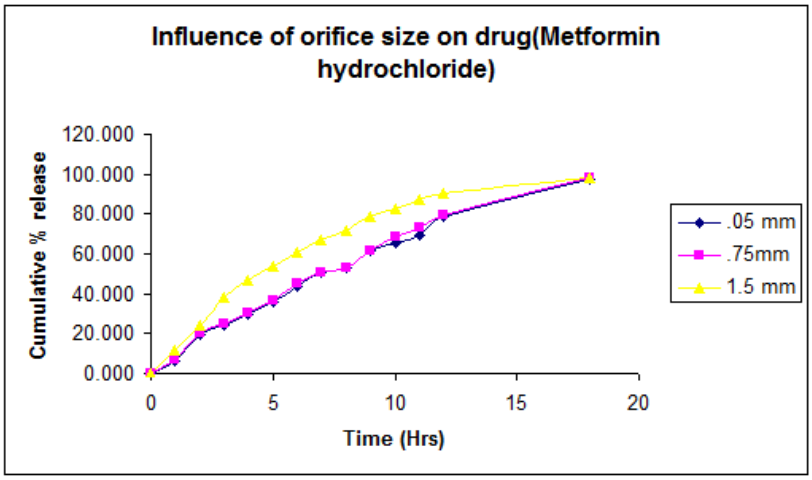

Figure. 4 (a): Influence of orifice diameter on Metformin HCl release profile.

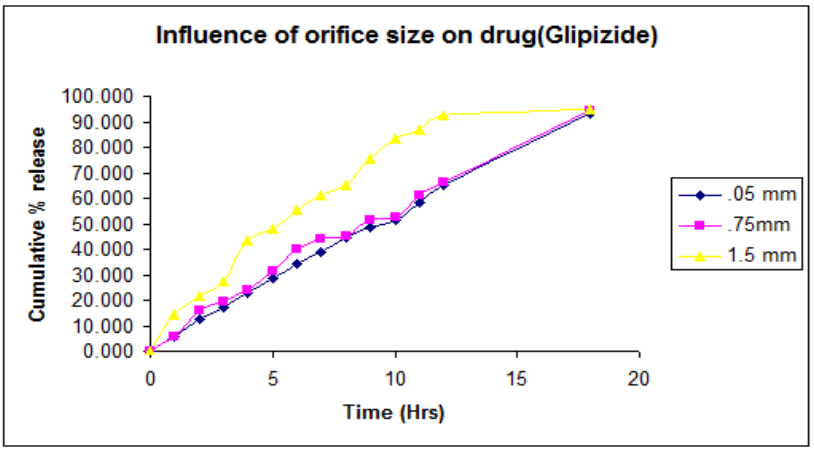

Figure. 4 (b): Influence of orifice diameter on Glipizide release profile.

CONCLUSION

From the results obtained, it can be inferred that the release of Metformin HCl and Glipizide from elementary osmotic pump can be controlled efficiently by the addition of hydrophilic polymer to enhance the solubility in EOPs. The oral osmotic pumps possess many advantages over the simple matrix type of SR/CR oral dosage forms.

The pumps gave better controlled release and time duration for the release can be extended up to 24 h. This can lead to the development of these formulations as potential candidate for once a day dosage form. The optimized formulation was independent of release media and agitation intensity. Hence, the elementary osmotic pump tablets of Metformin HCl and Glipizide may be better candidate for once a day dosage form.

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