DEVELOPMENT AND CHARACTERIZATION OF ELEMENTARY OSMOTIC PUMP TABLETS FOR SIMULTANEOUS RELEASE OF METFORMIN AND GLIPIZIDE

Bharadwaj P.*, Upaddhyay P. K., Agarwal V, Chaurasia D., Chaurasia H. and Singh R.

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ABSTRACT

The aim of present study was to design and evaluate an elementary osmotic pump-based drug delivery system for controlled release of metformin and glipizide simultaneously for treatment of type II noninsulin dependent diabetes mellitus. Inclusion complex of glipizide with β- cyclodextrin was prepared to enhance its solubility. Core tablets were prepared by wet granulation method. Effects of different variables like amount of plasticizer, osmogen, orifice size and dissolution media were studied on release profile for both drugs. Morphology of semi permeable was studied using electron microscope before and after dissolution test. On increasing the amount of osmogen, the release of both drugs was found to be increased. No significant effect of PVP K 30 was observed on drug release. Optimization results indicated that the release of both drugs was directly proportional to the surface porosity of the membrane. It was concluded that the osmotic pump tablets could provide more prolonged and controlled release that may result in an improved therapeutic efficacy and patient compliance.

Keywords: Elementary osmotic pump, Zero order, Glipizide, Metformin hydrochloride, Controlled release.

INTRODUCTION

Various technologies have been developed for controlled drug delivery. Majority of the oral dosage forms fall in the category of matrix, reservoir, or osmotic systems. Osmotic devices, use technology that delivers the drug at a zero-order rate and minimizes the drug plasma concentration fluctuations, thus reducing the adverse reactions, and improving the patient compliance. Osmotic systems utilize the principles of osmotic pressure for controlled delivery of drugs[1]. Drug release from these systems is independent of pH and other physiological parameters to a large extent [2, 3, 4]. The development of oral osmotic systems has a strong market potential, as evident from the marketed products [5] and number of patents granted in the last few years [6].

*** For correspondence**
Adarsh Vijendra Institute of Pharmaceutical Science-Gangoh, Saharanpur - 24734, U.P
E-mail: meet2peeyush@gmail.com

The osmotic pump tablet system for oral administration has advantages such as-

- It delivers drugs at zero-order release kinetics.
- Constant delivery rate and thereby reduce risk of adverse reactions.
- Delivery of drugs takes place in solution from which it 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.
- The in-vitro release rate for osmotic pumps can be used for drugs having wide range of aqueous solubility [7, 8].

The phenomenon of osmotic pressure difference for delivery of active ingredients was first developed by Rose and Nelson in the 1950s. Further achievement was the development of elementary osmotic pump (EOP) by Theeuwes in the 1970s [7, 9].

Elementary osmotic pumps are systems that deliver the drug in form of solution, at a controlled rate.

The devices are made up of core and semi permeable membrane that coats the core, having an orifice to release the active material. The core contains an active material and an osmotic agent. When the system comes in contact with gastro-intestinal fluid, water enters into the preparation through semi permeable membrane and dissolves the active material in the core, due to generation of osmotic pressure inside the core; drug is released continuously in the form of solution at a slow rate [1, 10, 11].

These systems are suitable for delivery of drugs having high to moderate water solubility. However, by modulating solubility of these drugs within the core, effective release patterns may be obtained for the drugs [1,10,13].

Metformin acts by decreasing hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake. Glipizide lowers glucose concentration by stimulating the release of insulin from pancreatic β- cells. Thus the combination of metformin with glipizide is more effective than individual therapy [14].

Hence this study was aimed to develop controlled release of metformin and glipizide in combination.

MATERIALS AND METHODS

Metformin hydrochloride and glipizide were gifted by Meridian Medicare, Solan (H.P.) and Micro Laboratories, Pondicherry respectively, Cellulose acetate as membrane former obtained from Central Drug House, New Delhi, India. Mannitol as osmotic agent obtained from RFCL- Limited, Delhi. Beta cyclodextrin as solubility enhancer for glipizide was purchased from Himedia laboratories New Delhi. Sodium lauryl sulphate(SLS), Sodium bi-carbonate (SBC), PEG-400, and PVP K-30, all were also purchased from CDH New Delhi; other chemicals were of analytical grade and used without any further purification.

Preparation of osmotic pump tablets

Preparation of inclusion complex of glipizide for solubility enhancement

Solid complex of glipizide and β-cyclodextrin was prepared using kneading method. The molar ratio of 1:10 was taken for glipizide and β-cyclodextrin complex as it was found most suitable. Glipizide and molar quantity of β-cyclodextrin were wetted in a mortar with methanol until a paste was obtained and mixed for 2hr. Then, this prepared paste was left to air dry for one night and finally ground mildly and stored under vacuum in desiccator for 3 days. The product was sieved through 22 mesh sieve [15].

Preparation of granules of metformin hydrochloride and glipizide [6, 15]

Metformin hydrochloride and inclusion complex of glipizide was mixed with all the excipients except lubricant (magnesium stearate) and glidant (talc); all were manually blended homogeneously in a mortar and pestle through geometric dilution. The blend was mixed for 10-15 minutes. Then the mixture was granulated with ethanol and the resulting wet mass was passed through 18 mesh sieve. The granules were dried in hot air oven at 60°C for sufficient time (10-15 min). These granules were passed through 22 mesh sieve. These sized granules were then blended with magnesium stearate and talc.

Preparation of core tablets [11, 15]

Core tablets of metformin hydrochloride and glipizide were prepared by wet granulation method. Metformin hydrochloride and inclusion complex of glipizide was mixed with all the excipients except lubricant (magnesium stearate) and glidant (talc) all were manually blended homogeneously in a mortar and pestle through geometric dilution. The blend was mixed for 10-15 minutes. Then the mixture was granulated with ethanol and the resulting wet mass was passed through 18 mesh sieve. The granules were dried in hot air oven at 60°C for sufficient time (10-15 min). These granules were passed through 22 mesh sieve. These sized granules were then blended with magnesium stearate and talc. The homogenous

blend was then compressed into tablets having an average weight of 800-950 mg using single stroke tablet punching machine. The formula for different batches of core formulation is shown in Table I.

Coating of core tablets [11,15]

The coating of core tablets was done in coating pan. The composition of coating solution is given in Table II. Cellulose acetate (3% w/V) as semipermeable membrane (SPM) former and PEG 400 as plasticizer were used in coating solution. The core tablets were placed in coating pan which was initially rotated at low speed (2-8 rpm) and heated air was passed on the tablet bed. Later on speed was kept at 15-20 rpm and coating solution was manually sprayed over the surface of the tumbling tablets with a spray gun. The inlet air temperature was kept at 50-55°C and this manual coating procedure was based on intermittent spraying and drying. After coating, the tablets were dried overnight at 60°C to remove residual solvent. The coating composition of tablets is shown in Table II. Orifices of different diameters (0.5, 0.75, & 1.5 mm) were drilled manually on one side of the coated tablet by a sharp needle in different batches.

Evaluation of core and coated tablets

Weight variation [16]

The weight variation test was carried out for 20 randomly selected tablets (core and coated) from each batch and weighed them individually. The average weight was calculated and compared with the individual tablet weights with the average tablet weight. Details are given in Table II.

$$\% \text{ weight variation} = \frac{\text{Individual weight} - \text{average weight}}{\text{Average weight}} \times 100$$

Hardness of core tablets [16, 17]

Tablet hardness is defined as the load required crushing or fracturing a tablet placed on its edge. It is also termed as tablet crushing strength. In this study Pfizer hardness tester was used. The diametrical crushing strength test was observed for 10 tablets from each formulation. The results are shown in Table III.

Percentage friability of core tablets [16, 17]

Percentage friability of core tablet was determined using Roche friabilator. 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min. After removing dusts, tablets were re-weighed. The percentage friability was determined using following formula:

$$\% \text{ Friability} = \text{Loss of weight of tablet/Initial weight} \times 100$$

Thickness of core and coated tablets [16, 19]

Thickness of 20 core and coated tablets from every batch of formulation was measured using a screw gauge and standard deviation was calculated. The results are shown in Table III.

Diameter of core and coated tablets [16]

Diameter of 20 core and coated tablets from each batch was measured using screw gauge and standard deviation was also calculated. The results are shown in Table III.

Morphological study of coated membrane

The surface morphology of the optimized tablet semi permeable coating film was studied by scanning electron microscope before and after dissolution test. The film samples were fixed on a brass stub using double-side adhesive tape. The stubs were then coated with gold to a thickness of about 300 Å using a sputter coater. These samples were than randomly scanned and photomicrographs were taken.

Orifice diameter [19]

The average orifice diameter of the osmotic pump tablets (n=20) was determined microscopically using optical microscope fitted with a pre-calibrated ocular scale.

Table I: Formula for different batches of core formulation

Formula for different batches of core formulation								
Ingredients (mg per tablet)	**Batch Code**							
	OPT1	**OPT2**	**OPT3**	**OPT 4**	**OPT5**	**OPT6**	**OPT7**	**OPT8**
Metformin HCl	500	500	500	500	500	500	500	500
Glipizide	5	5	5	5	5	5	5	5
β-cyclodextrin	127.4	127.4	127.4	127.4	127.4	127.4	127.4	127.4
Mannitol	50	100	150	200	100	100	100	100
Lactose	100	100	100	100	50	150	100	100
PVP K-30	30	30	30	30	30	30	50	70
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3

Table II: Coating composition of tablets

Coating composition of tablets		
S.NO.	**Coating Formulation Code**	**PEG-400 (%w/w)**
1.	A1	0
2.	A2	5
3.	A3	10
4.	A4	15

**Cellulose acetate (CA)-3%w/v in acetone, in all formulations*

Table III: Physical properties of core tablets and coated tablets

S. No.	**Parameter**	**Formulation code**							
		OPT1	**OPT2**	**OPT3**	**OPT4**	**OPT5**	**OPT6**	**OPT7**	**OPT8**
1	Tablet weight (mg), (n=20)	817.5±.76	867.7± .52	917.7± .54	967.9±.21	817.5±.76	917.4±.65	887.8±.14	908.4±1.7
	Core tablets	834.7±1.7	881.1±1.8	959.5±2.5	979.1±1.8	834.7±1.7	959.5±2.5	899.8±0.4	922.5±.54
	Coated tablets								
2	Highest (%) deviation	0.518	0.478	0.304	0.360	0.387	0.272	0.636	0.562
3	Hardness of core tablets (n=10)	5.16±0.08	5.2±0.12	5.42±0.10	5.1±0.20	5.22±0.17	5.12±0.20	5.16±0.30	5.2±0.25
4	Diameter (mm), n=20	13.23±.02	15.34±.02	13.28±.05	13.35±0.3	13.24±.03	13.19±.04	12.09±0.3	13.28±.03
	Core tablets	13.49±.07	15.65±.06	13.57±.04	13.76±0.7	13.64±.05	13.44±.05	12.48±0.5	13.53±.06
	Coated tablets								
5.	Thickness (mm), n=20	6.05±.28	7.12±.02	6.21±.07	6.07±.04	6.27±.075	6.21±.02	5.23±.11	6.35±0.4
	Core tablets	6.13±.16	7.39±.07	6.43±0.05	6.46±.03	6.38±.17	6.49±.04	5.58±.07	6.51±0.5
	Coated tablets								

6	Friability (%)	0.25	0.067	0.247	0.406	0.304	0.240	0.651	0.541
7.	% Drug content (n=5) Metformin Glipizide	98.3±0.17 97.53±0.2	96.5±0.20 96.3±0.21	98.4±0.18 98.6±0.14	97.9±0.53 99.6±0.77	99.7±0.14 94.7±0.14	96.3±0.08 97.5±0.20	98.5±0.17 99.4±0.16	97.4±0.05 95.5±0.21
8	Orifice diameter (mm) (n=20)	0.53±.016	0.53±.017	0.55±.011	0.52±.01	0.54±.02	0.54±.01	0.54±.01	0.55±.01

Results shown are the mean ± SD. n = 3, OPT = Osmotic pump Tablets

Table IV: Kinetics of *in-vitro* metformin hydrochloride release from different batches of osmotic pump tablets

Batch code	N	Regression coefficient (R)			
		Zero-order	First-order	Higuchi	Hixson-Crowell
OPT1	0.7095	0.8840	0.9872	0.9763	0.9960
OPT2	0.8756	0.9916	0.8979	0.9395	0.9660
OPT3	0.8815	0.9769	0.8763	0.9563	0.9690
OPT4	0.7496	0.9047	0.9755	0.9790	0.9973
OPT5	0.8908	0.9944	0.8993	0.9285	0.9623
OPT6	0.8240	0.9857	0.8986	0.9476	0.9697
OPT7	0.8626	0.9875	0.8956	0.9417	0.9662
OPT8	0.8328	0.9829	0.9263	0.9500	0.9790

Table V: Kinetics of *in-vitro* glipizide release from different batches of osmotic pump tablets

Batch code	N	Regression coefficient (R)			
		Zero-order	First-order	Higuchi	Hixson-Crowell
OPT1	1.0700	0.9984	0.9270	0.8980	0.9638
OPT2	0.9855	0.9987	0.9091	0.9142	0.9617
OPT3	0.9382	0.9960	0.8972	0.9289	0.9609
OPT4	0.8754	0.9601	0.9710	0.9928	0.9967
OPT5	1.0016	0.9957	0.9524	0.9154	0.9809
OPT6	0.9643	0.9983	0.9039	0.9148	0.9594
OPT7	1.0027	0.9986	0.9178	0.9172	0.9672

Development of analytical method for estimation of gilipizide and metformin

A simple, accurate, validated and reproducible UV-spectrophotometric method has been developed for the simultaneous estimation of Glipizide and Metformin in the formulations. Glipizide and Metformin in tablet formulation were estimated by using the multi component mode at 274 nm for Glipizide and 233 nm for Metformin. The Beer's law was obeyed by the concentration ranges of 2-20µg/ml for both Glipizide and Metformin. Mean recovery of 99.90% for Glipizide and 99.99% for Metformin respectively signifies the accuracy of the method.

Drug content uniformity

For determining the drug (glipizide) content, one accurately weighed tablet was crushed. The powdered sample was dissolved in 100 ml of methanol. The solution was filtered through Whatmann filter paper and after sufficient dilution with the same solvent the samples were analyzed using double beam UV spectrophotometer (Systronic 2202) at 274 nm [11].

And for determining the drug content of another drug (metformin HCl), same procedure was adopted as said above using distilled water as solvent medium and samples were analyzed UV spectrophotometrically (Systronic 2202) at 233 nm.

***In-vitro* dissolution study**

All the developed formulations of Metformin hydrochloride and glipizide were subjected to *in-vitro* release studies using USP-1 basket type dissolution apparatus. The formulated tablet was added to 900 ml of phosphate buffer pH 6.8 at 37± 0.5°C for 18 hrs at 50 rpm. The samples were withdrawn (5ml) at different time interval and replaced with an equivalent amount of fresh medium over 18 hrs. The dissolution samples were filtered to remove particulate matter, after filtration samples were analyzed using UV spectrophotometer (Systronic 2202) at 233 nm for metformin hydrochloride and 274 nm for glipizide. The absorbance of all samples at different time interval was measured. The concentration, amount of drug released and the percentage drug release were calculated.

Influence of different process variables on in-vitro drug release

Influences of osmagents and PVP K-30

Different amount of osmagents (i.e. mannitol, lactose) and PVP K-30 was taken in core tablets. The effect of their presence on release pattern was studied.

Influences of dissolution media on drugs release[11]

To study the effect of dissolution media on drug release and to assure a reliable *in-vitro* performance, release studies tests of the optimal formulation(OPT-3) were performed in 0.1 N hydrochloric acid solution (pH 1.2), phosphate buffer (pH 6.8) and phosphate buffer (pH 7.4) at 37± 2°C. The samples were taken out at predetermined intervals and analyzed after filtration by UV spectroscopic method at 233 nm for metformin hydrochloride and 274 nm for glipizide.

Influences of agitation intensity on drug release [11]

Drug release from osmotic pumps to a large extent is independent of agitation intensity of the release media. To study this parameter, release studies of the optimized formulation was performed at different agitation intensity 50, 100 and 150 rev/min. in USP-1 basket type dissolution apparatus. All samples were withdrawn at predetermined intervals and analyzed after filtration by double beam UV Spectrophotometer (Systronic 2202) at 233 nm for metformin hydrochloride and 274 nm for glipizide.

Influence of the amount of PEG-400 [12,18]

In this study PEG-400 was used as a plasticizer for semipermiable membrane of cellulose acetate. Different amounts of PEG-400 (0%, 5%, 10% and 15%) were added to 3% w/v cellulose acetate coating solution to coat the cores of tablets with the same lot number. The influence of PEG-400 on release was investigated.

Influence of orifice size and membrane thickness [12]

The elementary osmotic pump (EOP) systems contain at least one delivery orifice in the membrane for drug release. It was suggested that the size of delivery orifice must be in appropriate range; this must be smaller, than the maximum limit to minimize the diffusion of drug and also must be larger than the minimum size to minimize hydrostatic pressure inside the system. Similarly EOP systems must also have optimum thickness of for better release of drug.

Kinetics of drugs release

Dissolution data of the prepared formulations of metformin hydrochloride and glipizide osmotic pump tablet was fitted to various mathematical models (zero-order, first order, Higuchi and Hixson-crowell) in order to describe the kinetics of drug release.

RESULTS AND DISCUSSION

To study the influence of tablets formulation variables on drug release, tablets with various compositions were prepared, subsequently coated with composition code A2. The data revealed that formulation OPT3 containing mannitol and lactose have higher drug release rate than formulation OPT1 having lesser amount of lactose and mannitol. The higher release rate from OPT3 may be due the presence of mannitol which acts as osmagent and hence increases the osmotic pressure and results more drug release from the core. The release rate was also increased because metformin hydrochloride generates its own osmotic pressure and thus helps in increasing the total osmotic pressure of the formulation. A significant influence of mannitol was also observed. With an increasing amount of mannitol, the release rates were increased, because the increasing osmotic pressure made more drugs release. (Fig. 1a and 1b)

Further, the effect of lactose on drug release rate was studied. The formulation OPT6 showed higher release rate than OPT5. More lactose incorporated into the tablets causes liquefaction of core formulation hence increase the release. (Fig. 2a and 2b)

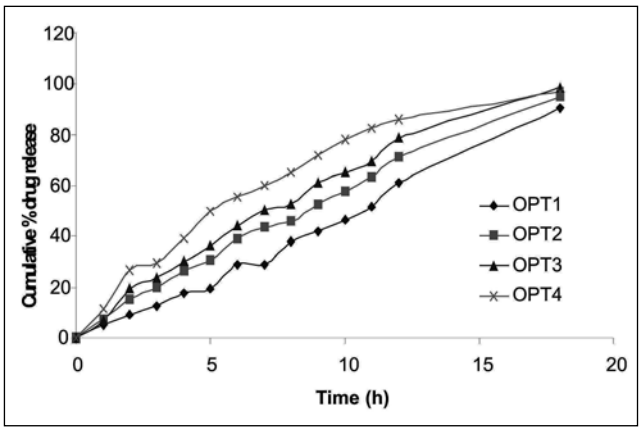

Fig. 1a: Effect of Mannitol on release of Metformin HCl

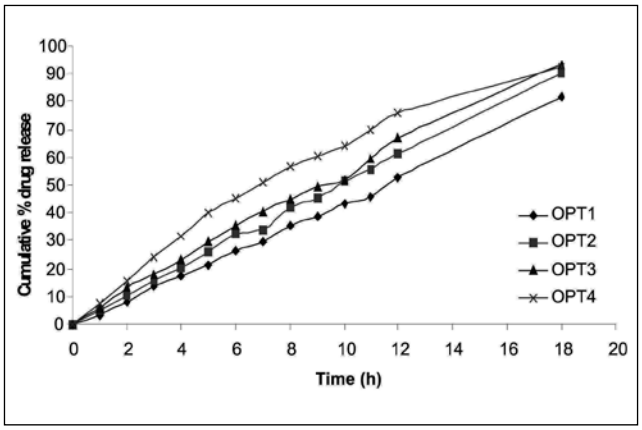

Fig. 1b: Effect of Mannitol on release of Glipizide

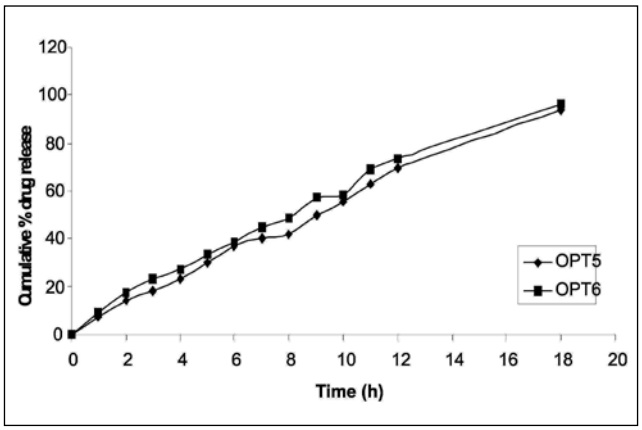

Fig. 2a: Effect of Lactose on release of Metformin HCl

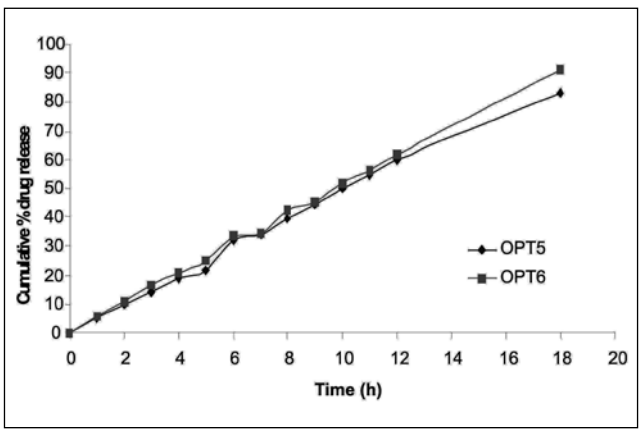

Fig: 2b: Effect of Lactose on release of Glipizide

Further, the effect of PVP K-30 on drug release rate was studied. It was observed that in formulation OPT7 and OPT8, there was no significant change on release rate of metformin hydrochloride and glipizide. (Fig. 3a and 3b)

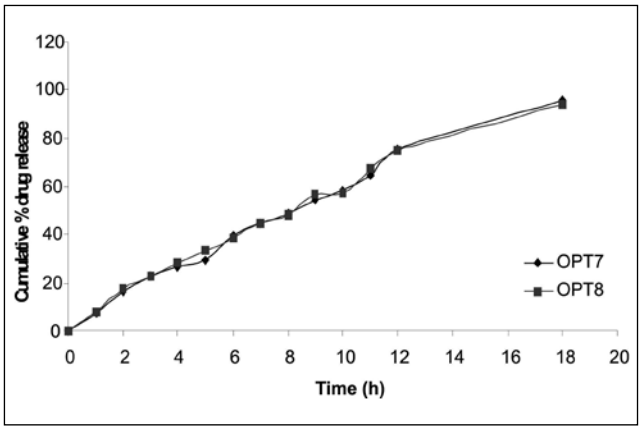

Fig. 3a: Effect of PVP K30 on release of Metformin HCl

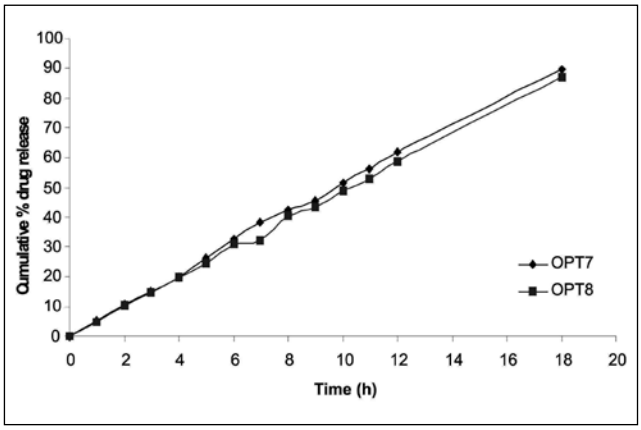

Fig. 3b: Effect of PVP K30 on release of Glipizide

Based on the above results the optimized amounts of mannitol 150mg and lactose 100mg were used in formulation OPT3, this formulation was used for further studies.

Since PEG 400 is a hydrophilic plasticizer, the more PEG incorporated into CA membrane, the more void space formed after leaching. Thereby on increasing the membrane permeability resulted, higher drug release rate was obtained. The formulation with no PEG 400 showed some lag period, releasing the drug at zero-order rate. On increasing concentration of PEG 400 (5%, 10%, and 15%) release rate was found to be increased, but 15% PEG 400 level showed more non-linear release profile. (Fig. 4a and 4b)

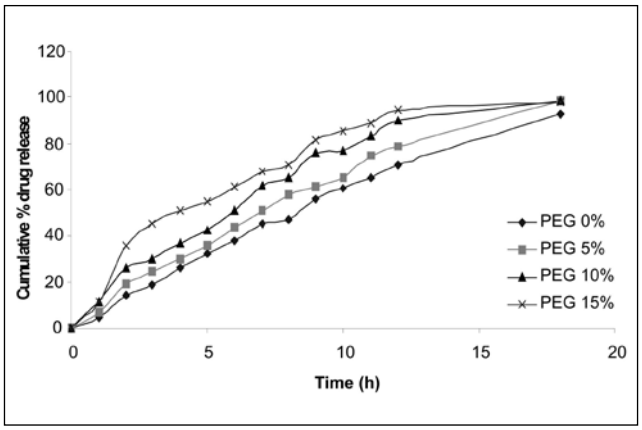

Fig. 4a: Effect of PEG on release of Metformin HCl

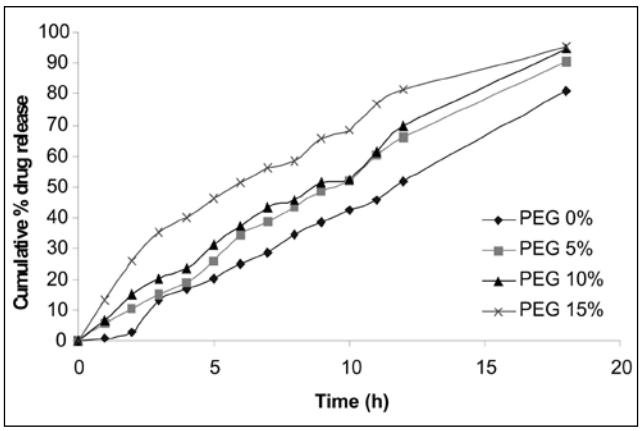

Fig. 4b: Effect of PEG on release of Glipizide

Cellulose acetate (CA) coating membranes of the formulation OPT3, obtained before and after dissolution were studied by SEM. Membranes obtained before dissolution showed nonporous region. After 18 hrs dissolution, the membrane clearly showed pores owing to dissolution of PEG400. The leaching of PEG400 from the membranes leads to formation of pores, and thus the release of drug took place. It was found that membrane was porous and intact without any cracks even after dissolution. (Fig. 5a and 5b)

The formulation OPT3 was coated with A2 coating solution and the drug release profile was recorded for

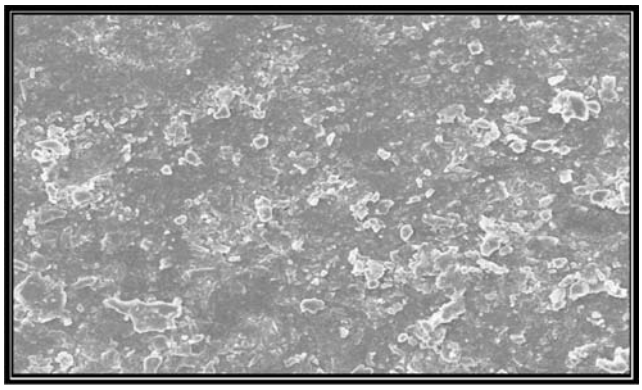

Fig. 5a: SEM micrograph of coating membrane before dissolution

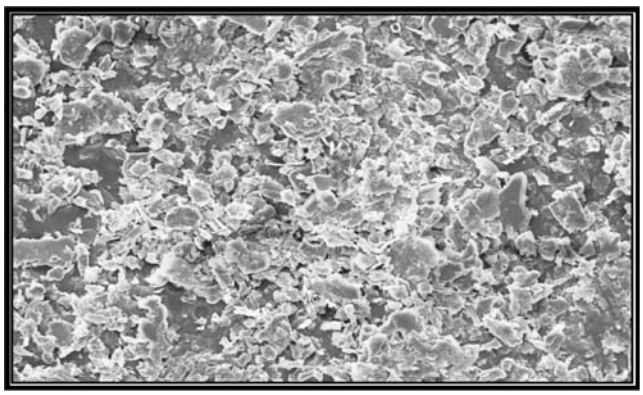

Fig. 5b: SEM micrograph of coating membrane after dissolution

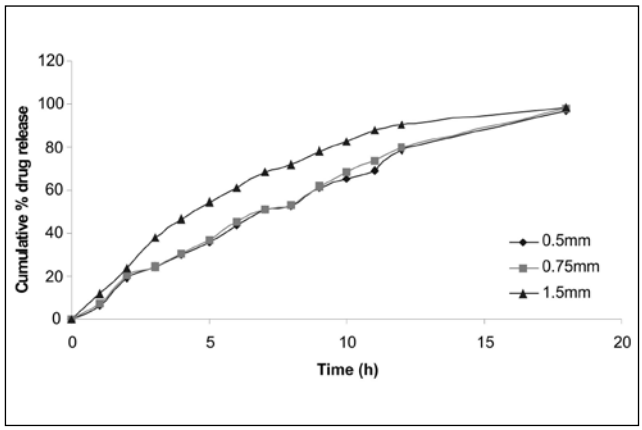

Fig. 6a: Effect of thickness of membrane on release of metformin HCl

different orifice size 0.5 mm, 0.75 mm and 1.5 mm. Results of release study indicated that there was no significant difference ($p>0.05$) in release profiles however with orifice size 1.5 mm somewhat rapid release was noted. This may be due to diffusion of drug from the larger orifice. For further study 0.5 mm orifice diameter was adopted. Further it was also observed that the tablet with the membrane thickness of 0.5 mm showed the maximum and rapid drug release. No significant difference in release of drug was observed in the tablets with membrane thickness of 0.75mm and 1.5 mm. (Fig. 6a and 6b)

The release profiles of optimal formulation

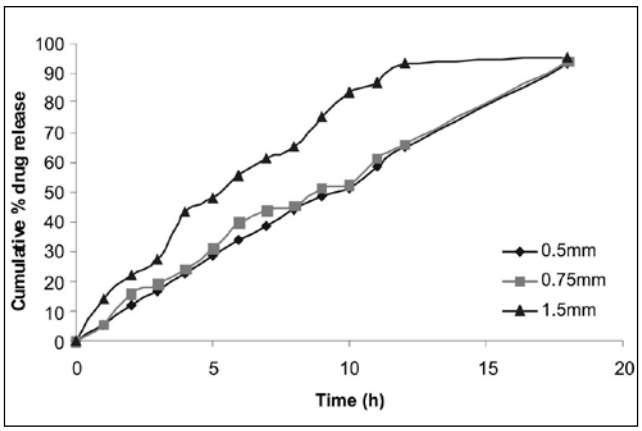

Fig. 6b: Effect of thickness of membrane on release of glipizide

OPT3 in different dissolution media were recorded. Release pattern in all media was found almost to be similar. This can be explained as the CA act as semipermeable membrane since, ions are not readily exchanged through it. Therefore the release of the drug from these systems is independent of pH of the surrounding medium. (Fig. 7a and 7b)

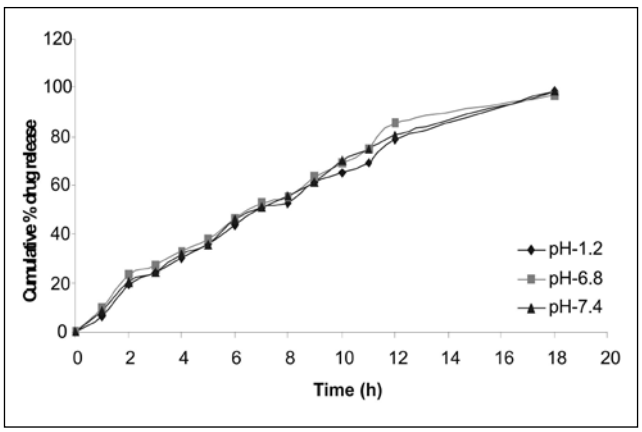

Fig. 7a: Effect of mediaon release of metformin HCl

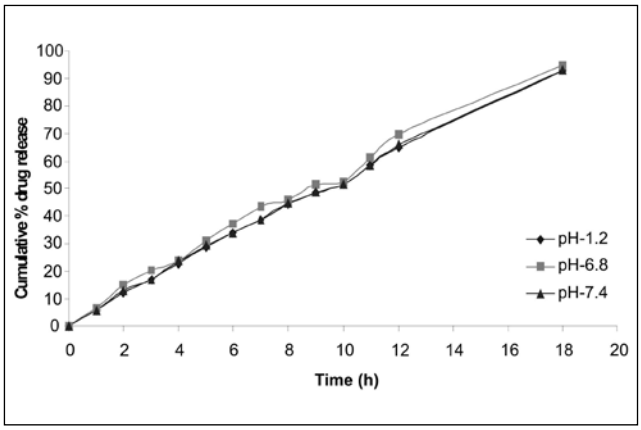

Fig. 7b: Effect of mediaon release of Glipizide

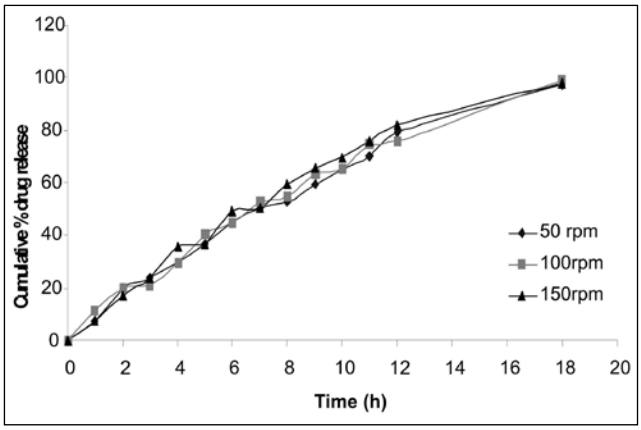

Fig. 8a: Effect of agitation rate on release of Metformin HCl

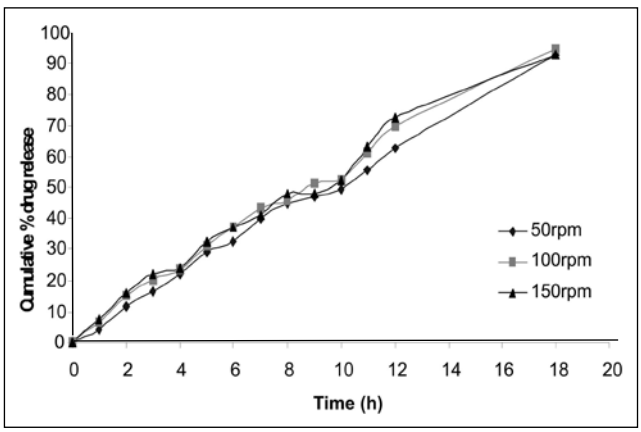

Fig. 8b: Effect of agitation rate on release of Glipizide

The release rate at 50 rpm, 100 rpm, and 150 rpm were analyzed by PCP Disso-V2-08. Thus it could be predicted that the mobility of gastrointestinal tract may not affect the drug release of the osmotic pump tablets OPT3.

Since, it can be concluded that as drug release was independent of agitation rate from OPT system, and osmotic tablet might exhibit a comparable *in-vitro* and *in-vivo* release rates. (Fig. 8a and 8b)

All release kinetic models were applied on the formulation OPT3, OPT4, OPT6 and OPT7 because of their satisfactory release behaviour. The best-fit model was found to be zero order (for OPT3, OPT6 and OPT7), and Hixson-crowell (for OPT4). The selection criteria for the best model were based on goodness of fit of the data and residual sum of squares. The formulation OPT3, OPT4, OPT6 and OPT7 have the value ($0.5<n<1.0$) suggest that the release of metformin hydrochloride and glipizide from osmotic pump tablets followed non-Fickian mechanism. (Table IV and V)

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