Available online at www.ijpsdr.com
International Journal of Pharmaceutical Sciences and Drug Research 2013; 5(4): 146-151

Research Article ISSN 0975-248X

Development and Evaluation of Swellable Elementary Osmotic Pump Tablet of Glipizide

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ABSTRACT

A novel type of elementary osmotic pump [EOP] tablet for efficient delivery of poorly water-soluble drug, glipizide has been designed. Drug release from the system, called Swellable Elementary Osmotic Pump [SEOP], is through a delivery orifice in the form of a very fine dispersion, ready for dissolution and absorption. SEOP tablets were prepared by compressing the mixture of micronized drug and excipients into convex tablet. The effect of wetting agent, swelling agent, osmotic agent and hydrophobic plasticizer on the release rate were investigated. The release behavior of glipizide from different formulations of this dosage forms were studied at pH 6.8 for a period of 24 hours. The drug release profile from osmotic devices showed that the type of polymer in the core formulation can markedly affect the drug release. When the amount of HPMC E50-LV was increased from 30 to 60 mg, decrease in drug release was observed. Increasing the amount of wetting agent to an optimum level of 45 mg significantly increased the release rate and improved zero order release pattern of glipizide. Increasing the concentration of Dibutylphthalate [DBP-30%] in the semi permeable membrane of the device retarded the release rate of glipizide but gave best results at the 20% concentration. Based on the SEM studies, optimized orifice diameter was found to be 500µm. Compared with the marketed Glipizide extended release tablet; GF2 gave the best release rate for 24 hours. The bioavailability studies for glipizide SEOP and Glipizide extended release tablet was carried out in albino rabbits and there was a good *in-vivo* and *in-vitro* correlation for GF2 as shown by the higher Cmax and AUC values. Thus a novel SEOP was successfully formulated for glipizide to achieve zero order drug release over a period of 24 hours.

Keywords: Glipizide, HPMC E50LV, Swellable elementary osmotic pump, Zero order release.

INTRODUCTION

Chronic diseases such as diabetes, asthma and heart diseases are often treated using multi-drug therapies, which are vulnerable to incidence of side-effects, poor patient compliance and slow improvement of patients. Though controlled drug delivery systems have been available separately for these drugs, a system that can deliver these drugs at a prolonged rate may ensure improved patient compliance and reduce the problems associated with the multi-drug therapy. In addition to improve patient compliance, as a once-a-daily formulation it could improve the safety profile and activity of drugs exhibiting short biological half life. Controlled release of drug from dosage forms could be achieved by various means, ranging from simple matrix tablets to more technologically sophisticated osmotic controlled drug release systems. [1]

A wide-spectrum of osmotic devices are in existence, out of them osmotic systems are unique, dynamic and widely employed in clinical practice. Osmotic pumps offer many advantages like they are easy to formulate, simple in operation, improved patient compliance with reduced dosing frequency, more consistent and prolonged therapeutic effect is obtained with uniform blood concentration. Moreover they are inexpensive.

Elementary osmotic pump, [EOP] essentially contains an active agent having suitable osmotic pressure, contained into a tablet coated with a semi permeable membrane usually of cellulose acetate [CA]. A small orifice is drilled through the coating by LASER or high-speed mechanical driller. When exposed to an aqueous environment, the soluble drug within the tablet draws through the semi permeable coating, resulting in the formation of a saturated aqueous drug solution within the device. The membrane is non-extensible and increase in volume due to imbibitions of water raises inner hydrostatic pressure, eventually leading to flow of saturated solution of active agent out of the device through the small orifice. [2]

In the present study, we tried to design a new type of EOP like osmotic systems for delivery of an insoluble drug with constant release rate [Zero order release]. This device called

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as Swellable Elementary Osmotic Pump [SEOP], which is structurally similar to EOP's but with different core formulation. In the core of this device, a significant amount of water- swellable and gel-forming polymer as well as suspending agents are used. The membrane is non-extensible and the raise in hydrostatic pressure is mainly due to the osmotic agents and the polymer swelling force which drives the drug out of the system through the orifice. [3]

Glipizide is poorly water-insoluble oral hypoglycemic agent belonging to class-II of biopharmaceutical classification system and is one of the most commonly prescribed drugs for the treatment of patients with type-II Diabetes Mellitus. It is practically water-insoluble, but its absolute bioavailability is close to 1 and its dissolution is considered to be rate limiting step [i.e., an effective factor] in its absorption from gastro intestinal tract. It also has a relatively short elimination half life of 2-4 hours, thereby requiring twice daily dosing in large number of patients, which often leads to non-compliance. The present study was aimed towards the development of swellable elementary osmotic pump tablet of a poorly water insoluble drug, Glipizide with a solubility of 37.2 mg/l. Different formulation variables were studied and optimized to achieve a new formulation for zero order delivery of Glipizide. The bioavailability studies for Glipizide SEOP and commercial extended release tablet was carried out in albino rabbits and there was a good *in vivo-in vitro* correlation. Thus a new SEOP was successfully formulated for Glipizide. [4]

MATERIALS AND METHODS

Glipizide was obtained as a gift sample from Aurobindo laboratories, Hyderabad. Cellulose acetate [CA] with 40 % acetyl groups (Loba chemie Pvt. Ltd, Mumbai) was used as a semi permeable membrane. DBP was obtained from Ranbaxy laboratories Pvt Ltd, New Delhi. HPMCE50LV (Dr. Reddy laboratories Pvt. Ltd, Hyd) was used as water swellable and gelling agent. Potassium chloride [KCl], Polyethylene glycol-400 [PEG-400] and Sodium lauryl sulphate [SLS] (finar reagents, Ahmadabad) were applied as osmotically active agent and suspending agent respectively.

Preparation of Core Tablets

Core tablets of Glipizide were prepared by wet granulation [non-aqueous granulation method]. Glipizide was passed through the sieve no. 60 and the other ingredients were passed through the sieve no. 100. All the sieved ingredients (except the lubricant, glidant and binder) were manually blended homogenously by the way of geometric dilution for 10 min. The mixture was granulated using PVP K-30 alcohol system and the resulting wet mass was passed through sieve no. 18. The granules were dried at 50°C (approximately for 10 min) to get a loss on drying [LOD] value between 0.9-1.1 percent, after which they were passed through the sieve no. 22. [4] These sized granules were then blended with magnesium stearate, talc (all passed through sieve no. 60) and compressed into tablets having an average weight of 250 mg using a single stroke tablet punching machine (Cemach, India) fitted with 8mm round standard concave punches. Formulae's of different core formulations of Glipizide are listed in Table 1. During the compression run, few tablets were taken at random and their weight variation, thickness, diameter, hardness, friability and the drug content uniformity were evaluated. [5]

Coating and Drilling of Glipizide Osmotic Core Tablets

The core tablets of Glipizide were coated in a pan coater [VJ instruments, Mumbai]. The composition of coating solution and the different orifice sizes of Glipizide SEOP tablets were given in Table 2. The formulations were coated with coating solution containing DBP-0% [GF14], DBP-20% [GF1-GF13], DBP-30% [GF15], PEG-400 -20% and cellulose acetate 4%. Various components of the coating solution were added in a sequential manner. The component added first was allowed to dissolve before the next component was added. Core tablets of Glipizide SEOP were placed in the coating pan along with 200 grams of filler tablets. Initially, pan was rotated at low speed of 2-5 RPM and heated air was passed through the tablet bed. Coating process was started once the outlet temperature reaches 28°C. The pan RPM was kept in the range of 10-15 and coating solution was sprayed at the rate of 6-9 ml/min. Atomization pressure was kept at 1 kg/cm^2 and the outlet temperature was maintained above 28°C by keeping the inlet air temperature in the range of 50-55°C. Coating was continued until desired weight gain was obtained on the active tablets. The active tablets were dried at 50°C for 16 hours before further evaluation. During coating run, few tablets were taken randomly and percentage weight gain was determined. The membrane thickness of the basic formulation was regulated in the range of 130± 10µm. [5]

Table 1: Formulation with different core related parameters

Formulations	Swelling agent HPMCE50LV(mg)	Wetting agent SLS (mg)	Osmotic agent KCl (mg)
GF1	15	45	100
GF2	30	45	100
GF3	45	45	100
GF4	60	45	100
GF5	30	15	100
GF6	30	30	100
GF7	30	60	100
GF8	30	45	50
GF9	30	45	75
GF10	30	45	120

* Membrane composition was DBP -20%, PEG-400 -20%, orifice size-500µm and cellulose acetate- 4%. The amount of Glipizide was 10 mg for all formulations

Table 2: Formulations with different semi permeable membrane related parameters [CA 4%, PEG-400 20%]

Formulations	Orifice size (µm)	% DBP
GF11	300	20
GF12	400	20
GF13	600	20
GF14	500	0
GF15	500	30

*Core composition for formulations GF11-GF15 was the same as GF2 [Glipizide 10 mg, HPMCE50LV 30 mg, SLS 45 mg, KCl 100 mg]

Table 3: Pharmacokinetic parameters of Glipizide SEOP and Glipizide extended release Tablet (mean±SD, n=3)

Parameters	Glipizide Extended release Tablet	GF2 [optimized formula]
Cmax	2.6 ng/ml	2.3 ng/ml
Tmax	6 h	6.2 h
$AUC_{0-\alpha}$	2754 ng-h /ml	2817.6 ng-h /ml
Ka	0.34 /h	0.29 /h
Ke	0.17 /h	0.16 /h
Vd	13 L	14.5 L
$t_{½}$ (absorption half life)	1.82 h	2.36 h
$t_{½}$ (elimination half life)	4.10 h	9.17 h
CL	11 ml/h	8.1 ml/h

For the coated tablets, a small orifice was drilled through the one side of each coated tablet by standard mechanical driller. The formulations were drilled with different orifice sizes of 300 µm [GF11], 400 µm [GF12] and 500 µm [GF1-GF10,

GF14 and GF15]. After drilling, the orifice size was controlled and measured microscopically [SEM]. [3]

Evaluation of Glipizide Smotic Coated Tablets

Prior to the compression, the Glipizide powder blends were evaluated for their bulk and tapped density. From these values compressibility index and the Hausner ratio were calculated. After compression, Glipizide osmotic tablets both uncoated and coated were evaluated for their weight variation, content uniformity. Thickness and diameter were measured by Vernier calipers. Hardness of the randomly selected tablets were determined by using hardness tester [Monsanto hardness tester, Pharma lab, Ahmadabad] and friability of uncoated osmotic tablets was carried out on a friabilator [Roche friabilator, Mumbai] for which 20 accurately weighed tablets were used.

***In-vitro* Release Test**

USP-II Paddle dissolution apparatus [Electro lab, Mumbai] was used to determine the *in-vitro* drug release from the Glipizide osmotic tablets. Phosphate buffer solution [SIF, pH 6.8], 900 ml maintained at 37± 0.5°C, at 100 RPM was utilized as the dissolution medium, under sink condition. [5] Drug samples of 5 ml [replaced with fresh medium] were taken at distinct time intervals and the drug concentration in the samples were determined spectroscopically [UV-Visible spectroscopy, Schimadzu, Japan] at a wavelength of 274 nm. The release test was performed at least for 3 tablets to obtain average values with standard deviation.

Kinetics and Release Mechanism Studied

In-vitro dissolution data obtained for various formulations were analyzed by various mathematical models [zero order, first order] in order to describe the kinetics of drug release. An osmotic system should release high percentage of its drug content with constant release rate and follow zero order kinetics. Different formulations were compared by using various parameters like t_L [time required for imbibition of water through the semi permeable membrane, gel forming process and its volume enhancement and movement of the formed gel containing drug particles out of the small orifice]. The other important parameter is RSQ_{zero} [R square of release data which was fitted to zero order equation]. Among these different formulations, the formulation with $t_L > 4$ hours were rejected and the other formulations were compared in terms of the RSQ_{zero}. Since the active material in the tablet core doesn't able to induce an osmotic effect due to its poor aqueous solubility, an initial lag time of 1 hr is necessary to moisten the device and the penetration of water into the core. [3]

SEM Studies

In order to elucidate the mechanism of drug release from in-house formulations, surface of the coated tablets both before and after dissolution studies were carried using Scanning Electron Microscope [SEM]. [6]

Pharmacokinetic Study of Glipizide SEOP in Rabbits

Rabbits were used for a pharmacokinetic study based on previous reports. A detailed report on the study was submitted to institutional ethics committee for animals. After having an approval from the ethical committee the study was conducted. The rabbits were divided into two groups, fasted overnight before the experiment. The test animal was not given free access to food and drinking water until 4 hrs after administration. Each rabbit of the different groups was given a Glipizide extended release tablet, 10 mg or a self made Glipizide SEOP [10 mg] respectively. 2 ml of blood samples were taken via ear vein at 0, 3, 6, 9, 12 and 24 hours and collected in heparinized tubes. The blood samples were centrifuged at 4000 RPM for 10 min. Plasma was collected and stored at -20°C until further analysis. 0.05M hydrochloric acid was added to 1ml of plasma samples and vortexed for 30 sec and then the resulting samples were extracted twice with ethyl acetate [3ml once] by ultrasonic vigorously for 3 min. The mixtures were centrifuged at 2000RPM for 10 min, and then the ethyl acetate layers were collected and kept for evaporation to dryness under a stream of air. The residue was dissolved in 50µl of mobile phase by vortexing and an aliquot of 20µl of sample was injected into HPLC for determination of Glipizide. [7]

HPLC Analysis

HPLC system [Shimadzu, Japan] was used for analysis of drug in plasma with column C_{18} [4.8 × 250, 5µm] and the mobile phase consisted of a mixture of acetonitrile - 0.01 M phosphate buffer [pH 3.5] at the ratio of 35:65 at a flow rate of 1 ml/min. The temperature of the column was maintained at 35°C and the wavelength was set at 274nm. [8]

RESULTS AND DISCUSSION

All the formulations were complied with the compendial standards for compressibility index, Hausner ratio, weight variation and the content uniformity. The hardness for all the formulations was found to be in the range of 4-5 kg/cm^2. The percentage weight loss during friability was found to be less than 1% for all the batches. Thus, the Glipizide SEOP's were found to be of good quality, fulfilling all the official requirements. The effect of core parameters, membrane parameters and the orifice diameter were studied.

Influence of Swelling Agent on the Release Profile

Apart from osmotic pressure, the swelling of polymer is very important in controlling the amount of drug release from osmotic devices. The mechanism of drug release from these devices is not a simple osmotic mechanism but swelling of polymer is another driving force for the release of drug. So, swellable polymer was utilized for osmotic delivery of drug [Glipizide] which is having poor aqueous solubility. Uniform rate of swelling of polymer ensures that the drug is released at a relatively constant rate. Also the pressure produced during swelling does not lead to rupture of the device. Different formulations were prepared using different concentrations of HPMC E50 LV [15 mg, 30 mg, 45 mg and 60 mg] which were incorporated into the core of the osmotic devices. The release profiles of these formulations were shown in Fig. 1. When the amount of HPMC E50 LV was 15 mg [GF1], only 61% of the drug was released within 24 hours. But when the amount of HPMCE50LV was slightly increased to 30 mg [GF2], 93.2 % of the drug was released within 24 hours. However, when the amount of HPMCE50LV was increased from 30 mg to 45 mg [GF3] and 60 mg [GF4], no significant amount of the drug was released. This effect may be due to the high viscosity of HPMCE50LV, which made it difficult to release the drug from the system through the orifice of the semi permeable coating. The selection of a suitable concentration of polymer is crucial step for designing the osmotic pump. High concentration polymer will burst the osmotic device and very little concentration will provide low viscosity inside the device. All the release data were subjected to kinetic analysis, and the results [GF1 (0.980), GF2 (0.987), GF3 (0.965) and GF4 (0.981)] showed that the core formulations

containing 30 mg of HPMCE50LV [GF2] showed higher correlation coefficient for zero order release. Therefore, GF2 formulation was adopted for further investigation.

Influence of Wetting Agent on the Release Profile

It has been reported that in case of water insoluble drugs, meaningful release rates may not be obtained from elementary osmotic pump and controlled porosity osmotic pump. This is because of the kinetics of osmotic drug release is directly related to the solubility of drug within the core. As Glipizide is practically water insoluble drug, SLS was added as a solubility modifier to increase the release rate of the drug. Generally, SLS acts as a wicking agent that is dispersed throughout the composition and enhances the contact surface area of the drug with incoming aqueous fluid. Thus, the drug might be released predominantly in a soluble form through the delivery orifice in the membrane. [9] Different formulations were prepared with different concentrations of SLS [15 mg, 30 mg, 45 mg and 60 mg] and dissolution profiles were shown in the Fig. 2. Only small amount of the drug was released, 49.8% with 15 mg [GF5] of the SLS within 24 hours. When the amount was slightly increased from 15 mg to 30 mg and 45 mg, 73.2% and 93.2% of the drug was released within 24 hours respectively, this shows a huge increase in the drug release rate. But when the amount was increased to 60mg [GF7, 88.6%], it could not improve the release rate and correlation coefficient. Comparing the correlation coefficient of these formulations, it revealed that an increase in the amount of SLS from 45 mg to 60 mg could not improve the correlation coefficient and GF2 formulation has the best correlation coefficient [RSQzero were 0.932, 0.968, 0.987 and 0.972 for GF5, GF6, GF2 and GF7 respectively]. Based on the above results, GF2 formulation containing SLS 45 mg was considered as a suitable concentration.

Influence of Osmotic Agent on the Release Rate

Osmotic agent is the main factor that must be optimized to control the release rate of the drug between the inside compartment and the external environment. The drug release from SEOP takes place only after sufficient buildup of osmotic pressure in the core tablet. The difference in osmotic pressure between inside and outside of SEOP causes water penetration into the core; the drug will get solubilized and then released from the orifice due to increased hydrostatic pressure. This process will be continued until the osmotic pressure between inside and outside environment becomes equal. This pressure causes the expulsion of the drug along with the osmotic agent from the core to the outside of SEOP. Different concentrations of KCl [50 mg, 75 mg, 100 mg and 120 mg] were incorporated into the osmotic core and their influence was shown in the Fig. 3. From the results, it is clear that the KCl concentration had a remarkable effect on the release rate of Glipizide SEOP. At the low osmogen concentration of KCl [50 mg], GF8 formulation released only 52.6% of the drug within 24 hours. As the concentration of KCl was increased from 50 mg to 75 mg [GF9, 76.5%] and 100 mg [GF2, 93.2%], there was an enhancement in the release rate. But, when the concentration was increased beyond 100 mg, burst and rapid drug release was observed in the formulation, GF10 containing 120 mg of KCl and the integrity of the membrane was completely lost. Also, this formulation released 91.6% of drug within 16 hours [t_L > 4 h] and followed non zero order kinetics. So, this formulation was not taken into consideration. Kinetic related parameters also improved by increasing the KCl concentration up to 100 mg [RSQ zero for GF8 [0.937], GF9 [0.972], GF2 [0.987]] and the formulation GF10, does not followed zero order kinetics, which also showed burst release within 16 hours. Based on the above results, the formulation containing KCl 100 mg [GF2] was considered for further studies.

Influence of Coating Solution and Plasticizer on the Release Rate

DBP and PEG-400 were used as a lipophilic and hydrophilic plasticizer in the cellulose acetate coating solution respectively. As PEG-400 is a hydrophilic plasticizer, it could be leached out easily and leave behind an entirely porous structure which increases the permeability and drug release rate. In contrast, as DBP is insoluble in water, it is difficult to leach because of its hydrophobic character, and the residual DBP would resist water diffusion and as a consequence, the drug release rate was decreased. Different concentrations of DBP were incorporated into the coating solution and the release profiles of this formulation were illustrated in the Fig. 4. The formulations GF14, GF2 and GF15 containing same concentrations of PEG-400 [20% w/w] and CA-4% but with varying concentrations of hydrophobic plasticizer, DBP [0% w/w, 20% w/w and 30% w/w] in the respective formulations. From the results, the highest release rate [93.4%] was observed for the sample containing 0% w/w [GF14] of DBP within 16 hours, this may be due to the presence of only hydrophilic plasticizer in the tablet. When the concentration of DBP was increased from 0% w/w [GF14] to 20% w/w [GF2], 93.2% of drug was released within 24hrs and no crack was found in the osmotic device and retained its integrity during the release process. From the results, it also showed that as the concentration of DBP was increased from 20% w/w to 30% w/w, because of its hydrophobic nature led to the reduction in the drug release rate, 80.9% [GF15]. The more DBP was incorporated, the more difficult to leach and in turn, lower the permeability and release rate. It can be concluded from the results, that a good hydrophilic and lipophilic balance in SPM is required to achieve desired release profile with zero order kinetics. [10] Comparing the results, it was concluded that the coating solution [CA-4% w/w] containing DBP 20% w/w and PEG-400 20% w/w are the optimum percentages in the SPM to obtain zero order release device.

Influence of Orifice Size on Release Rate

Different formulations were drilled with the orifice sizes of 300µm [GF11], 400µm [GF12], 500µm [GF2] and 600µm [GF13] respectively. Fig. 5 represents the effect of orifice size on the drug release rate and shows that an increase in the orifice size resulted in an increase in the rate of release of Glipizide from SEOP. The percentage release for the tablets with orifice size of 300µm, 400µm and 500µm after 24 hours was 52.6%, 76.5% and 93.2% respectively. But the formulation GF13, which was drilled with the orifice size of 600 µm released 85.6% of the drug within 16 hours [t_L >4 h] and showed burst effect. Kinetics of release data for zero order showed that as the size of orifices increased, the RSQ_{zero} values for zero order kinetics got better [RSQ_{zero} for tablets with orifice size of 300µm, 400µm and 500µm were 0.937,0.972 and 0.987 respectively]. But the RSQ_{zero} for the formulation, GF13 with the orifice size of 600 µm followed non-zero order kinetics [RSQ_{zero} 0.860]. Based on the results obtained, formulation with the orifice size of 500µm was considered as the optimum orifice size for the formulations.

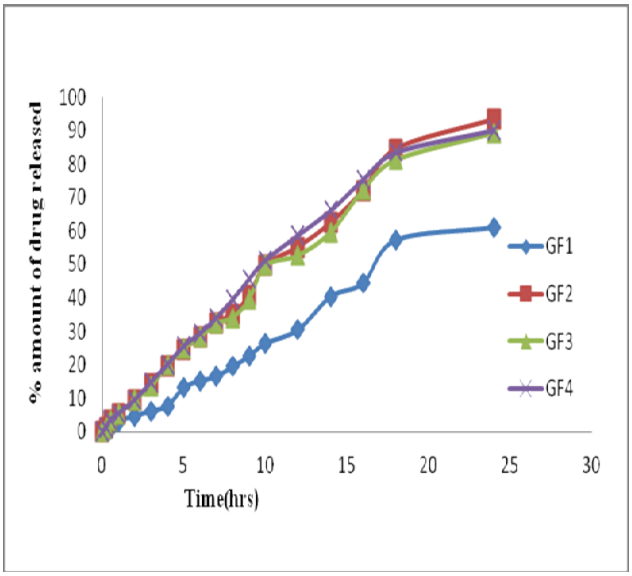

Fig. 1: Influence of swelling agent on the release profile of GF1-GF4

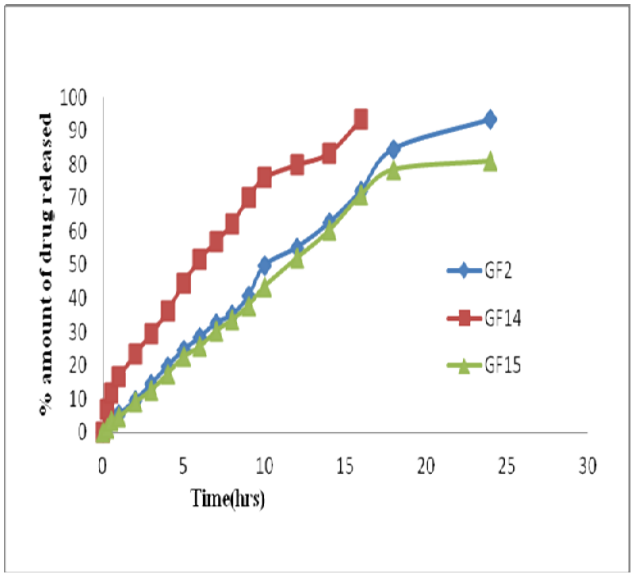

Fig. 4: Influence of % DBP on the release rate of GF2, GF14 & GF15

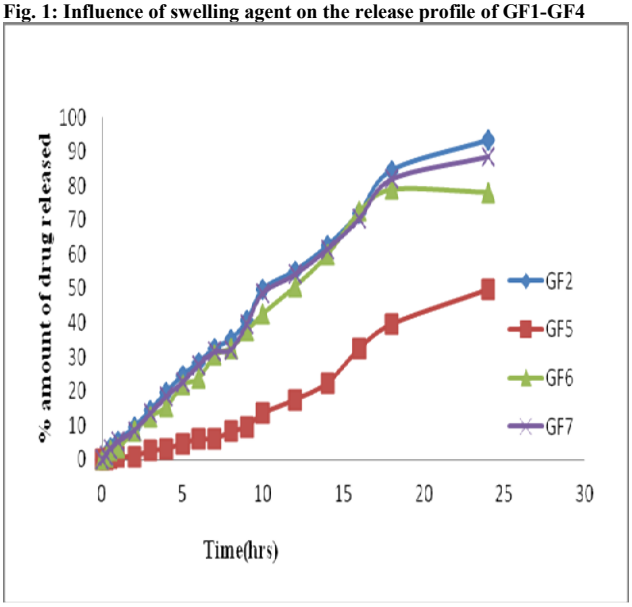

Fig. 2: Influence of wetting agent on the release profile of GF2&GF5-GF7

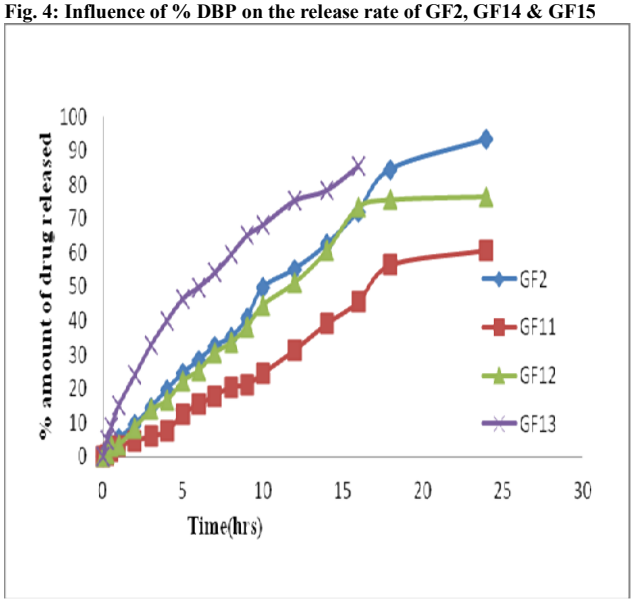

Fig. 5: Influence of orifice size on the release profile of GF2& GF11-GF13

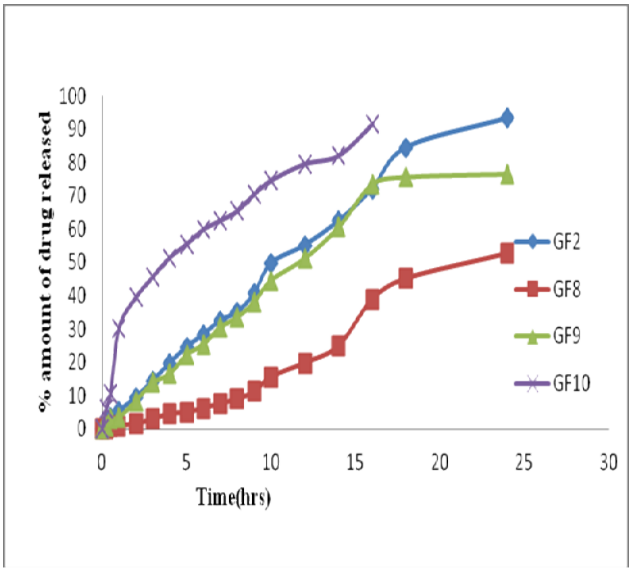

Fig. 3: Influence of osmotic agent on the release profile of GF2&GF8-GF10

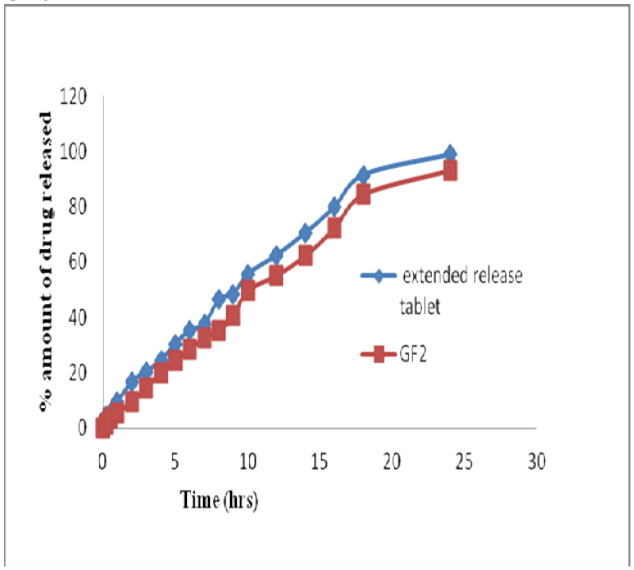

Fig. 6: Drug release kinetics of glipizide SEOP and commercial extended release Tablet

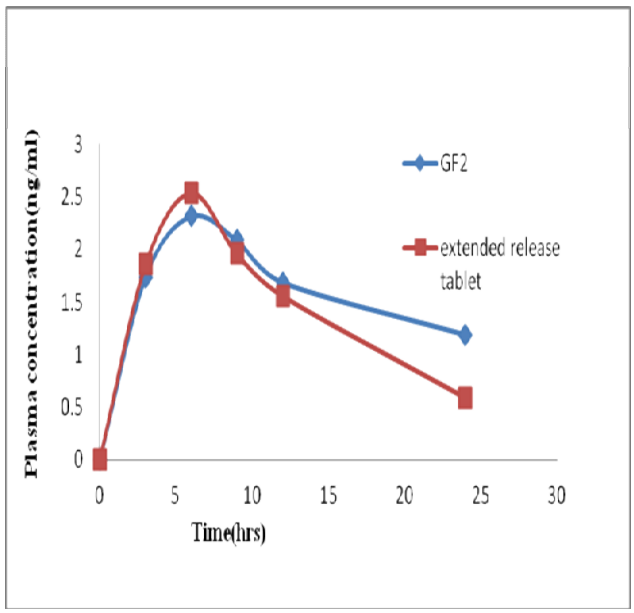

Fig. 7: Plasma concentration time profile of commercial extended release Tablet and GF2 [optimized formula]

Scanning Electron Microscopy [SEM]

In order to elucidate the mechanism of drug release from in-house formulations, the surface of coated tablet and orifice size was studied using SEM for the promising formulation [GF2] and the optimum orifice size was found to be 500µm.

Drug Release Kinetics of Glipizide Seop

With the marketed Glipizide extended release tablet as the control, the characteristic of Glipizide SEOP was verified and both release profiles are shown in Fig. 6. In order to establish the mechanism of drug release, the experimental data was fitted into mathematical models. The RSQ_{zero} values of the zero order release model were found to be [0.932-0987] higher when compared to those of first order release models [0.891-0.977] for Glipizide SEOP tablets. But in case formulations containing KCl 120 mg, RSQ_{zero} values were more for first order release kinetics compared to zero order release because of higher buildup of osmotic pressure inside the core. The zero order rate constant [K_o] for both the promising formulation [GF2] and commercial extended tablet was found to be 4.205 but the RSQ_{zero} value of GF2 [0.987] which was slightly higher than the marketed formulation [0.977]. So this formulation [GF2] was considered for further study.

Pharmacokinetic Study

The profiles of the mean plasma concentration verses time for the Glipizide SEOP and commercial extended release tablet were shown in Fig. 7, could follow by a single compartment model. The mean pharmacokinetic parameters are shown in Table 3. The relative bioavailability of Glipizide SEOP was 102.3% compared to marketed extended formulation. The Ka of SEOP [0.29 h^{-1}] was smaller than that of commercial extended tablet [0.34 h^{-1}], while T_{max} shown peak concentration of SEOP [6.2 h] than commercial extended tablet [6hr] and the maximum concentration [C_{max}] in blood was 2.3 ng/ml for SEOP while 2.6 ng/ml for commercial extended release tablet. These results indicated Glipizide obtained in blood was more constant due to zero-model release of Glipizide from SEOP compared with Glipizide extended release tablet and SEOP could supply a safer therapeutic window relative to the commercial extended release tablet. The clearance [CL] for SEOP 8.1 ml/h was smaller than that of commercial extended release tablet [11 ml/h], indicating the retention time of SEOP *in-vivo* was longer and the clinical effect could last for a longer time with those of commercial extended tablet as control.

The current research investigates the formulation of Swellable Elementary Osmotic Pump [SEOP] tablets of Glipizide using HPMC E50LV as swelling agent, KCl as osmotic agent, sodium lauryl sulphate as wetting agent, and DBP as hydrophobic plasticizer coated with a cellulose acetate membrane with orifice drilled on one side of tablet. The SEOP was simple to prepare because there was no need for a push compartment. The SEOP was optimized by changing the concentrations of the ingredients and the orifice size to achieve zero-order release kinetics for the delivery of the model drug Glipizide. The optimized system was able to release Glipizide at zero order kinetics for 24 hour when tested in pH 6.8 medium. The relative bioavailability of Glipizide SEOP was 102.3% compared to marketed extended formulation, which showed the formulation, GF2 might have good pharmacological activity *in-vivo*. These data collectively support the recommendation that SEOP is expected to be a delivery system for water insoluble drug such as Glipizide.

REFERENCES

1. Ouyang D, Nie S, Liluai, Guo H, Liu H, Pan W. *In vitro- in vivo* evaluation of two extended release preparations of combination metformin and glipizide. Drug Development and Industrial Pharmacy 2005; 31: 677-685.
2. Suresh PV, Prabhakaran D, Paramjit S, Parijat K. Effect of hydrophilic polymers on release of diltiazem hydrochloride from elementary osmotic pump. International Journal of Pharmaceutics 2003; 259: 173-179.
3. Nokhodchi A, Mohammed NM, Javad S, Mahbobah S, Parinaz A, Parise R. Factors affecting the release of nifedipine from a swellable elementary osmotic pump. Drug Delivery 2008; 15: 43-48.
4. Sanjay G, Rajan KV. Development and evaluation of osmotically controlled oral drug delivery system of glipizide. European Journal of Pharmaceutics and Biopharmaceutics 2004; 57: 513-525.
5. Mahalaxmi R, Phanidhar S, Ravikumar, Atin K, Pritam KD, Narhede R. Enhancement of dissolution of glipizide from controlled porosity osmotic pump using a wicking agent and a solubilizing agent. International Journal of Pharmatech Research 2009; 1(3): 705-711.
6. Charulatha R, Kumaravel RR. Design and evaluation of swellable delivery of anti hypersensitive drugs by swellable elementary osmotic pump (SEOP). Journal of Pharmacy Research 2012; 5(4): 2141-2145.
7. Xiong KC, Minsua, Yan G, Fengliang C, Guangxi Z. Design and evaluation of osmotic pump based controlled release system of ambroxol hydrochloride. Pharmaceutical Development and Technology 2010; 1-8.
8. Hakan E. High performance liquid chromatographic determination of glipizide in human plasma and urine. Journal of Chromatography 1987; 421: 319-326.
9. Sanjay G, Rajan KV, Divi MK. Formulation aspects in the development of osmotically controlled oral drug delivery systems. Drug Development and Industrial Pharmacy 2000; 26(7): 695-708.
10. Ali N, Javad S, Parinaz A, Parise R, Mahbobah S, Ali RS. Swellable elementary osmotic pump (SEOP): An effective device for delivery for poorly water soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics 2008; 68: 289-297.