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FORMULATION AND OPTIMIZATION OF EXTENDED RELEASE OF METFORMIN HCL TABLETS BY OSMOTIC TECHNOLOGY

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Abstract

Metformin HCl is an oral anti-diabetic drug from the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function. Metformin is the most popular anti-diabetic drug in the United States and one of the most prescribed drugs in the world.

Metformin Hydrochloride extended release(ER) formulation 1000mg is necessary to achieve a steady state blood level or tissue level for an extended period, which will be therapeutically effective and non-toxic. In this context sustained/controlled drug delivery systems delivers the drug almost at a predetermined rate either systematically or locally for a specified period of time, sustaining the duration of therapeutic activity and reducing adverse effects. Linear and reproducible release similar to that of Fortamet® ER 1000 mg tablets was achieved for optimized formulation (f2 >50) independent of hydrodynamic conditions. The effect of different formulation variables, namely, ratio of drug to osmogent, membrane weight gain, and level of pore former on the in vitro release was studied.

In Osmotic technology systems, osmotic pressure provides the driving force to generate controlled release of drug. In this system a tablet containing a core of drug surrounded by a Semipermeable membrane, which is permeable to water, but not to drug. When this device is exposed to water or any body fluid, water will flow into the tablet owing to the osmotic pressure difference.

The main factors of osmotic technology are drug solubility, Osmotic pressure, Delivery orifice, coating membrane. The water soluble polymers like povidone (PVPK-90) and Sodium lauryl sulfate are mainly used for Osmotic technology in this Elementary Osmotic Pump (EOP).

By observing the pharmacokinetic characteristics and requirements of Metformin HCl, it is clear that ER Osmotic formulation of Metformin HCl is necessary. So this present research is aimed to investigate the possibility of developing ER tablet dosage form for Metformin HCl. The drug release by Metformin HCl ER tablets by osmotic technology is around 85% in 20 hrs. The optimized formulations were subjected to stability studies as per International Conference on Harmonisation (ICH) guidelines and formulations were stable after a 3 month study.

Key Words: Metformin Hydrochloride, Osmotic pump, Elementary Osmotic Pump (EOP), Osmotic technology, Osmogent, Extended release.

Introduction

Metformin HCl is an oral anti-diabetic drug from the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function.

Metformin Hydrochloride extended release(ER) formulation 1000mg is necessary to achieve a steady state blood level or tissue level for an extended period, which will be therapeutically effective and non-toxic.

A detailed review of various types of osmotic pumps has been done by Santus and Baker.[2] Theeuwes introduced the elementary osmotic pump (EOP). [3] In Osmotic technology systems, osmotic pressure provides the driving force to generate controlled release of drug. In this system a tablet containing a core of drug surrounded by a Semipermeable membrane, which is permeable to water, but not to drug. When this device is exposed to water or any body fluid, water will flow into the tablet owing to the osmotic pressure difference. This system contains the drug in solution in an impermeable membrane within device. The electrolyte surrounds the bag. Osmosis is the diffusion of fluid through a semi permeable membrane from a solution with a low solute concentration to a solution with a higher concentration until there is an equal concentration of fluid on both sides of the membrane. Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs.[4] Drug release from these systems is independent of P^H and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system.

Theory of Osmotic Pump

The general expression for the solute delivery rate *(dM/dt)* from an Osmotic pump [3] can be described by the following equation:

$$dM/dt = (A/h)Lp(\sigma\Delta\pi - \Delta\rho) \cdot C$$

Where,

1. A = the membrane area
2. h = the membrane thickness
3. Lp = the mechanical permeability
4. σ = the reflection coefficient

5. π = the osmotic pressure
6. p = the hydrostatic pressure
7. C = the concentration of compound in the dispensed fluid

A simplification of the mentioned equation would lead to the following equation

$$dM/dt = (A/h)K\pi \cdot C$$

Figure 1 is a schematic of elementary *osmotically-controlled delivery device.* Basically, these devices are designed to have a semi-permeable membrane that allows water to move in, but prevents salt and drug molecules from moving out. The drug molecules exit through a small opening due to the increase in pressure brought about by the volumetric increase.

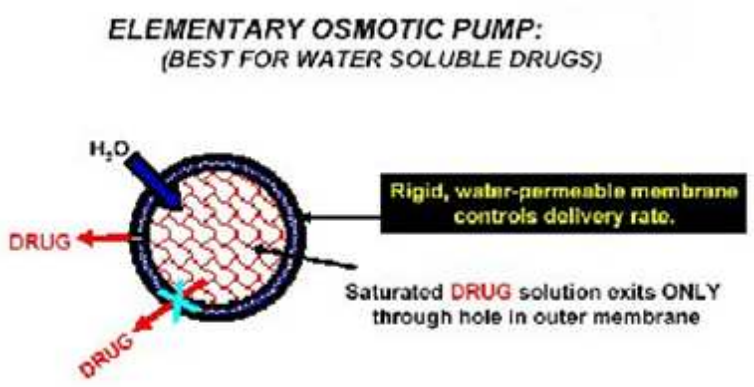


Fig 1 Elementary Osmotic Pump (EOP)

Types of Osmotic pump delivery systems. [5-6]

1) Elementary osmotic pump (EOP)
2) Push pull osmotic pump (PPOP)
3) Liquid Oral Release Osmotic Systems (L-OROS)
4) Controlled porosity osmotic pumps(CPOP)
5) Sandwiched osmotic tablet (SOTS)

Elementary osmotic pump (EOP)[7-8]

The basic concept of Elementary osmotic pump (EOP) is as follows:

a) EOP consists of an osmotic core (containing drug with or without an osmotic agent) coated with a semi permeable membrane (SPM).

b) The dosage form, after coming in contact with the aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation.

c) This osmotic imbibition of water results in formation of a saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice in the membrane.

d) Though 60–80% of drug is released at a constant rate from EOP, a lag time of 30–60 min is observed in most of the cases as the system hydrates before zero-order deliver from the system begins. These systems are suitable for delivery of drugs having moderate water solubility.

The use of an elementary osmotic pump system was chosen for the formulation. The factors which affect the drug release from osmotic pumps are as follows:

Factor	Affect on drug release
Drug Solubility	1) Release rate directly proportional to solubility of drug within core. 2) Both highly and poorly water soluble drugs are not good candidates for osmotic delivery.
Osmotic Pressure [9-10]	1) Release rate is directly proportional to the osmotic pressure of core formulation. 2) Additional osmagents required if drug does not possess suitable osmotic pressure

Delivery orifice [11-13]	1) Should be within desired range to control the drug release.
Coating membrane	1) Release rate affected by the type and nature of membrane forming polymer, thickness of the membrane and presence of other additives (ex: plasticizer, flux enhancers etc.

So, in present work Elementary osmotic Pump (EOP) was selected for preparation and evaluation of Metformin HCl ER tablets.

Materials and methods

Metformin Hydrochloride was obtained from Matrix laboratories, Hyderabad, Andhra Pradesh, India. PVPK-90 (Kollidon30, BASF, Ludwigshafen, Germany), Sodium lauryl sulphate Stepanol WA 100), Magnesium stearate (Ferro) were procured from Matrix laboratories, Hyderabad, India. Cellulose acetate was obtained from Eastman Chemical Inc, Kingsport, TN, PEG 400 (S.D. Fine Chemicals Ltd, Mumbai, India). Triethyl citrate, Acetone procured from Yarrow Chemicals, Mumbai, India. All other solvents and reagents used were of analytical grade. Fortamet ER 1000mg tablets were procured from retail pharmacy, USA.

Preparation of ER Tablets using osmotic technology

Metformin Hydrochloride ER Tablets by Osmotic Technology were prepared by optimizing the following four critical steps:

1. Optimizing the core tablet formulation.
2. Optimizing coating ingredients and parameters.
3. Optimizing the % weight build up of coating material.
4. Optimizing the orifice Size on drug release.

1. Optimizing the core tablet formulation.

As the Metformin Hydrochloride API flow and compressibility index are poor, wet granulation procedure was followed for preparation of core tablet using Povidone (PVPK-90) as binder solution. SLS is used as a wetting agent and osmagent/absorption enhancer. Magnesium stearate used in this formulation functions as lubricant.

Ingredients	**Formulation code**		
	F1	**F2**	**F3**
	% Tablets		
Metformin Hydrochloride	91.9	89.8	87
Povidone (PVPK 90)	3.0	6.0	8.0
Sodium lauryl Sulphate	4.6	4.6	4.6
Magnesium stearate	0.5	0.5	0.5
Purified Water	q.s	q.s	q.s
Isopropyl alcohol	q.s	q.s	q.s

Table 1 Core tablet composition

Povidone in this formulation acts as a binder as well as an osmagent. The release of the drug is directly proportional to the osmotic pressure built up in the formulation. To control the drug release the osmotic pressure gradient between the compartment and the external environment must be optimized. Hence the concentration of povidone in the core is optimized.

The tablets were prepared by wet granulation technique using fluid bed equipment. Metformin Hydrochloride, Povidone (PVPK 90) (50%) were mixed together through mesh #40. SLS and 50% of Povidone were dissolved in the required amount of isopropyl alcohol (IPA) used as binder solution. This blend was granulated by using a Fluid Bed Equipment (FBE) fitted with a top spray gun with nozzle size of 1.5 mm. The blend was granulated with the binder solution by using Fluid Bed Equipment (FBE) (Make: GPCG 1.1 P+AM) fitted with a top spray gun with nozzle size of 1.5 mm. The parameters of FBE are as follows: Inlet temperature: 60°C-65°C,

Product Temperature:42°C-45°C, Exhaust Temperature: 42°C-45°C,Blower speed- 20-35%, Atomization air: 1-1.45 Mpa. Spray rate: 3-5 gm/min. The granules obtained from FBE were then milled using a 1.5 mm screen through multimill (Make: Coromandal Engineering, Hyderabad) and then passed completely through mesh # 18. The milled granules was then lubricated with magnesium stearate and compressed using a tooling of 12.7mm round standard concave punch using 10 station mini press (Make: Rimek).

The blends prepared had good flow property and tablets were made without any problems. The friability and hardness of tablets prepared from F2 blend were as satisfactory compared to the other blends. Therefore the PVPK 90 was chosen as the final grade and the amount maintained at 6% w/w of the tablet. Different core formulations are given in Table 1.The tablets of F2 were then taken further to optimize the coating parameters.

(II) Optimizing Coating ingredients & parameters

Since the membrane in osmotic systems must be semi permeable in nature, any polymer which is permeable to water but impermeable to solute can be selected. Cellulose acetate has been widely used to form a rate controlling membrane for osmotic systems. Higher release rate were observed with Tri ethyl citrate since hydrophilic plasticizers were found to increase the drug release. In this composition PEG 400 acts a flux enhancer there by increasing the osmotic pressure in the compartment. By choosing proper contents in coating composition the drug release can be controlled to desired levels.

Ingredients	**Formulation code**		
	C1	**C2**	**C3**
	% / tablets		
Cellulose Acetate	75.0	65.0	45.0
Polyethylene glycol (PEG 400)	10.0	20.0	40.0
Tri ethyl citrate	15.0	15.0	15
Acetone	q.s	q.s	q.s
Purified Water	q.s	q.s	q.s

Table 2: Coating composition

The tablets of F2 with maximum hardness were chosen from the above prepared batches. The coating solution was prepared by dissolving Cellulose acetate in Acetone. The PEG 4000 was dissolved in water and poured in the Cellulose acetate and Acetone Solution and solution stirred until a clear solution was obtained. To this tri ethyl citrate was added and stirred until equally dispersed. The coating equipment used was manufactured by Freund. Weight build up was set from 5-6 %. The parameters for coating were as follows: Inlet Temperature: 40°C-45°C, Exhaust Temperature: 32°C-35°C, Spray Rate: 2-5 gm/min, RPM of Pan: 12-14. Atomization air: 0.1 Mpa.

Different concentrations of the coating ingredients are given in Table 2. The dissolution studies of the coated with a 0.5mm drilling using manual drilling machine were carried out using UV Spectrophotometric method (Make: Shimadzu UV-3600) at 233nm. It was found that the dissolution profile of coating done with C2 was comparable to the marketed formulation (Fortamet ER). Therefore C2 was the composition chosen for further optimization of coating parameter. The dissolution profiles of C2 & C3 over a period of 12hrs are given in Fig 2).

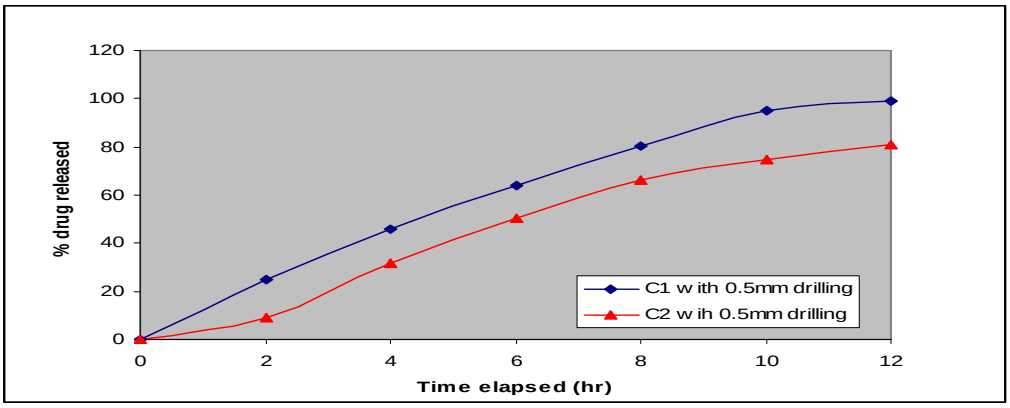


Fig 2: Dissolution profiles of C1 & C2

3) Optimizing the % weight build up of coating material

The thickness of membrane has a profound effect on the drug release from osmotic systems. The release rate from the osmotic systems is inversely proportional to membrane thickness. The membrane thickness is directly proportional to the % w/w build up during coating. In case of elementary osmotic pumps the release rates were found to decrease with increase in membrane thickness from 85-340 µm. This is due to the increased resistance of membrane to water diffusion.

coating weight buildup/Tablets (% w/w)	Formulation code
4.0	C4
6.0	C5
8.0	C6
10.0	C7

Table 3: %w/w builds up

Tablets of F2 were taken with the optimized coating formula of C2. The different % weight buildups are given in Table 3. The dissolution profiles for all the batches given in fig 3:

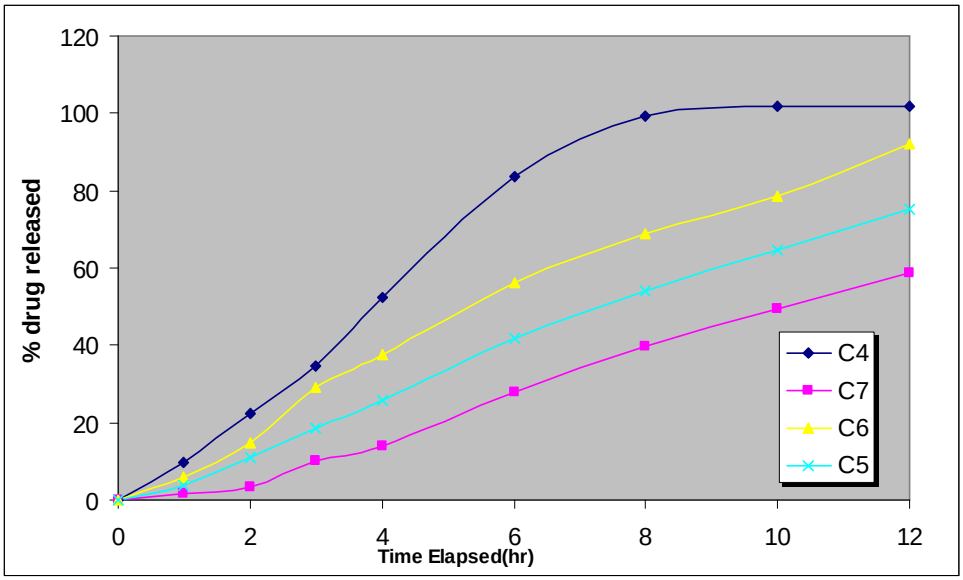


Fig 3: Dissolution profiles of C4, C5, C6 & C7

From the dissolution profiles it was observed that Batch No: C5 and C6 show zero order kinetics and C5 is similar to that of the marketed formulation. The % w/w coating build up is then maintained between C5 & C6 for all further trials.

3) *Optimizing the orifice Size on drug release.*

Osmotic delivery systems contain at least one delivery orifice in the membrane for drug release. The size of the orifice must be optimized in order to control the drug release from osmotic systems. If the orifice is too small zero order delivery will be affected due to the development of hydrostatic pressure within the core and eventually lead to deformation of system. If the orifice is too large then solute diffusion might take place and lead to a non –zero order release of drug. Drug release from osmotic pumps is not affected by the size of orifice within certain limits. Beyond these limits the orifice diameter has a significant effect on the release rate.

Orifice size (% w/w)	Formulation code
0.25	D1
0.5	D2
0.9	D3

Table 4: Drill sizes used

A mechanical drill fitted with the drill sizes mentioned in table 4 was taken and drilling done by hand. The dissolution profile of different drill sizes are given in fig 4:

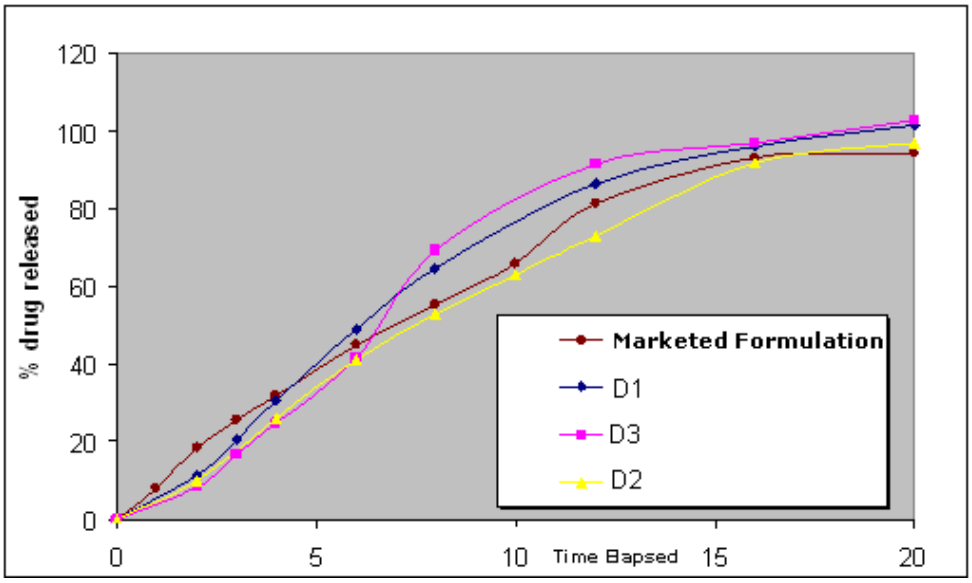


Fig 4: Dissolution profiles of D1, D2 & D3.

From the dissolution profiles of the above batches the profile of D2 is optimized and matched to that of the marketed formulation. The optimized formula is given in Table 5. Hence the present formula is linear and reproducible release similar to that of Fortamet® ER 1000 mg tablets was achieved for optimized formulation D2 (f2 >50) independent of hydrodynamic conditions.

Ingredients	**% w/w**
Tablet Core Composition	
Metformin Hydrochloride	89.8
Povidone (PVPK 90)	6.0
Sodium lauryl Sulphate	4.6
Magnesium searate	0.5
Purified Water	q.s
Isopropyl alcohol	q.s
Coating composition & Parameters	
Cellulose Acetate	65.0
Polyethylene glycol (PEG 400)	20.0
Tri ethyl citrate	15.0
Acetone	q.s
Purified Water	q.s
Weight Build up (%w/w)	6-7 %
Drill size	0.53 mm

In Vitro Drug Release

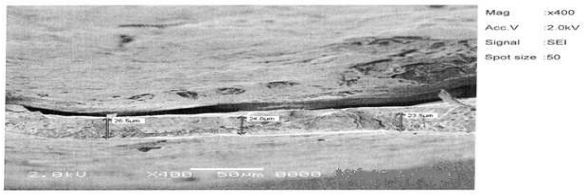
In vitro drug release of the formulations was performed using United States Pharmacopeia (USP) type I apparatus (Electrolab, Mumbai, India) attached with auto-sampler, at 100 rpm. The dissolution medium consisted of 1000 ml of pH 6.8 phosphate buffer at 37°C ± 0.5°C. The drug release at different time intervals was analyzed by Ultraviolet Spectroscopy (UV) at 233 nm using 0.2 cm cuvettes. The release studies were conducted in triplicate and parameters such as percentage cumulative drug release and drug release rate were calculated.

Scanning Electron Microscopy (SEM)

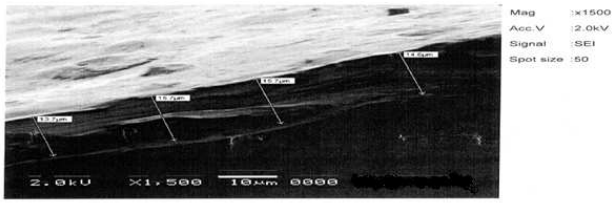
Coating membranes of formulation obtained before and after soaking of the tablet in water for about 48 hours were examined for their porous morphology by scanning electron microscope (XL30 ESEM TMP+EDAX, Philips, Eindhoven, The Netherlands). Membranes were dried at 50-C for 2 hours and stored between sheets of wax paper in a dessicator until examination. To know the thickness of the coating layer, thickness of the Semipermeable membrane, Depth and

diameter of the laser drilled hole of the formulation SEM studies are performed. The results are shown in Fig 5:

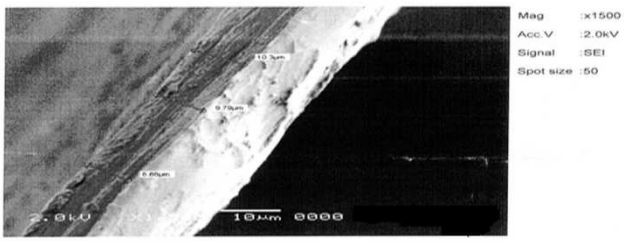
Coating Layer thickness of Intact tablet (Initial).



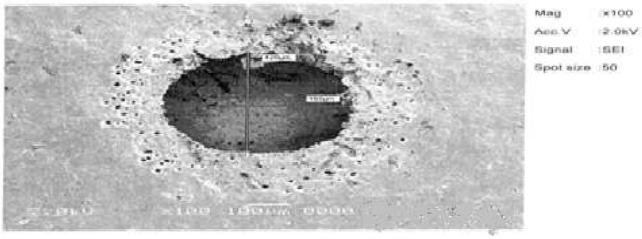
Thickness of Semipermeable Membrane. (After 2 days in Water)



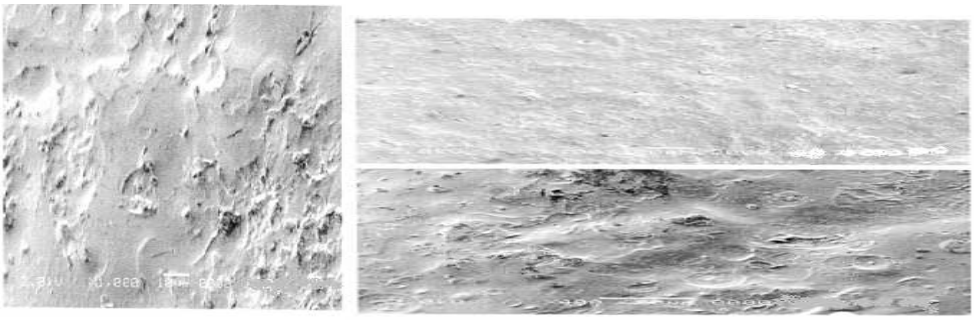
Thickness of Semipermeable Membrane (Initial)



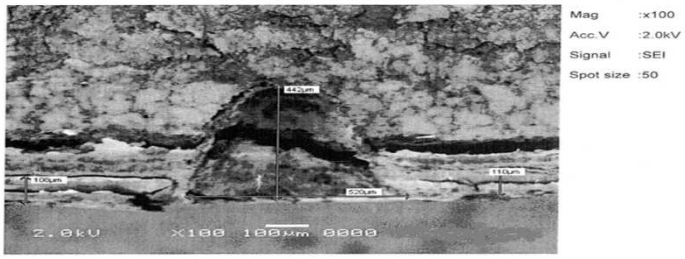
Diameter of Lesser Drilled Hole (After 2 days in Water)



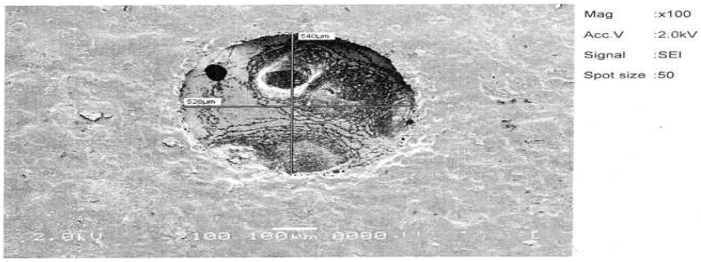
Surface of Semipermeable Membrane (After 2 Days)



Diameter and Depth of Lesser Drilled Hole (Initial)



Diameter of Lesser Drilled Hole (After 2 days in Water)



Thickness of Semipermeable Membrane.(After 2 days in Water)

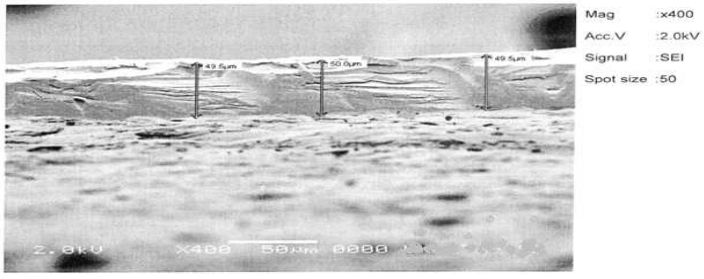


Fig 5: Scanning electron microscopy of membranes optimized formulation initial and after 2 days in water.

Kinetics of Drug Release

The cumulative amount of drugs released from the optimized system at different time intervals were fitted to zero order kinetics using least squares method of analysis to find out whether the drug release from the systems provides a constant drug release pattern.[9] The correlation coefficient between the time and the cumulative amount of drug released was also calculated to find the fitness of the data to zero-order kinetics.

RESULTS AND DISCUSSION

Metformin Hydrochloride ER tablets containing different concentrations of povidone in core along with other additives such as osmogent were prepared by wet granulation and subjected to quality control tests such as Hardness, Thickness, drug content and invivo drug release studies. The dosage form developed was designed as a tablet core coated with a rate-controlling membrane. The core compartment is surrounded by a membrane consisting of a Semipermeable membrane-forming polymer, water-soluble pore-forming additives, and at least one plasticizer capable of improving film forming properties of the polymers. The Semipermeable membrane-forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug. The dissolved drug is released through the pores created after leaching of water-soluble additive(s) in the membrane. Cellulose acetate was used as water-insoluble polymer. PEG-400, Tri ethyl citrate were used as plasticizers/flux enhancer.

Drug-Excipient Interaction Studies

Compatibility studies for Metformin Hydrochloride conducted at 40°/75 % RH (open and sealed) and at 50° (open and sealed) are satisfactory as there are no significant changes observed

physically in the samples. It was clear that no specific interaction between the drug and excipients used in the present formulation.

Assay and Physical Evaluation

Core tablet weights varied between 1100 mg and 1140 mg (mean 1120 mg), thickness of the core tablets was found to be in the range of 8.30 and 8.90 mm (mean 8.65 mm). The hardness of core tablets was found to be between 18 and 22 Kilopascal (kP) (mean 20 kP).The assay of drug in various formulations varied between 98±5% (mean 101.20%) which was assayed by UV Spectrophotometric method (Make: Shimadzu UV-3600) at 233nm. Thus, all the physical parameters of the compressed tablets were practically within limits.

Stability Data of the finalized formulation:

Optimized Formulation tablets were packed in HDPE container with Child Resistance Cap (CRC) sealed and loaded in stability chamber at 40°C/75 % Relative humidity for 3 months. The tablets were withdrawn periodically and evaluated for drug content, hardness, and release studies. The formulations were found to be stable in term of drug content and dissolution stability (Fig 6:).

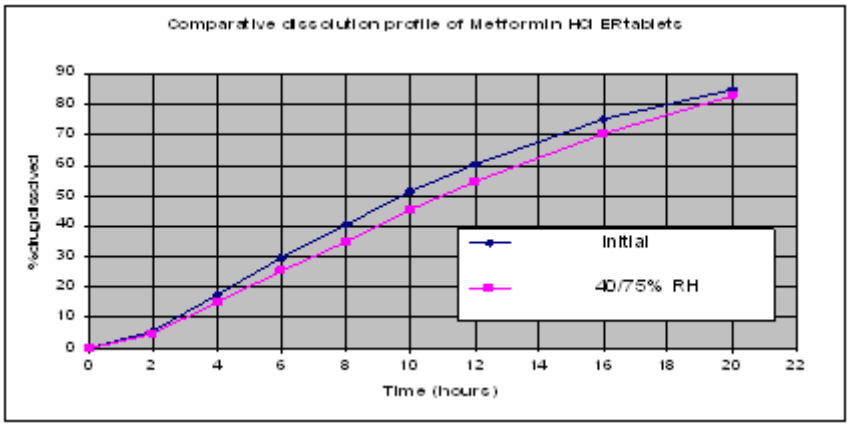


Fig 6: Release profile of Optimized formulation Initial and 40°C/75 % RH (3 months)

CONCLUSION

Metformin HCl ER release tablets 1000 mg can be designed using a porous osmotic pump–based drug delivery system (EOP). Metformin HCl. It is evident from the results that the rate of drug release can be controlled through osmotic pressure of the core, level of pore former, and membrane weight with release to be fairly independent of pH and hydrodynamic conditions of the body. Metformin HCl release from the developed formulations was inversely proportional to the osmotic pressure of the release media, confirming osmotic pumping to be the major mechanism of drug release. Results of SEM studies confirmed the formation of pores in the membranes after coming into contact with the aqueous environment. Compatibility studies for Metformin Hydrochloride at 40°/75 % RH (open and sealed) and at 50° (open and sealed) stations are satisfactory as there are no significant changes observed physically in the samples.

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