



FORMULATION AND EVALUATION OF SELF PORE FORMING OSMOTIC TABLETS OF GLIPIZIDE

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ABSTRACT

The purpose of this study was to formulate and evaluate self pore forming osmotically controlled drug delivery system of Glipizide. Glipizide is an oral hypoglycemic agent which belongs to BCS class II with relatively short elimination half life of 2-4 hours. Main objective to formulate this system was to achieve zero order release for Glipizide. The present study was also aimed to develop a system that would reduce the frequency of dosing and thus increases patient compliance. Cellulose acetate was used as a film forming polymer. PEG 400 was used as plasticizer. Potassium chloride was used as pore forming agent. Acetone and methanol were used as solvent. Combinations of Mannitol-Fructose, Mannitol-Sucrose and Lactose-Sucrose were used as osmotic agents. This system was developed in two stages: (a) formulation of core tablet and (b) coating of tablet core. Core tablets were evaluated for content uniformity, hardness and weight variation while coated tablets were evaluated for film thickness and in vitro release study. Effect of varying the concentration of pore forming agent on release rate was studied. Effect of various osmogens differing in osmotic pressure on release rate was also evaluated.

KEY-WORDS: Self pore forming osmotic tablet, Glipizide, Potassium chloride, Mannitol, Lactose, Fructose, Sucrose.

INTRODUCTION

Oral controlled release formulations can provide continuous delivery of drugs at predictable and reproducible kinetics throughout the GI tract¹. In these systems, drug dose and dosing intervals are optimized to maintain the drug concentration within the therapeutic range, thus ensuring efficacy with minimum toxic effects².

Because pharmaceutical agents can be delivered in a controlled manner over a long period by osmotic pressure, there has been increasing interest in the development of osmotic devices in past few decades.

Osmotically controlled drug release formulations deliver drug due to the difference in osmotic pressure within and outside the osmotic pump. The release rate from this system is not affected by gastric pH and other hydrodynamic conditions. Also, release characteristic can be easily adjusted by optimizing the release parameters³.

Elementary osmotic pump (EOP)⁴ was first introduced by Theeuwes, which is simple to prepare and releases drug at an approximate zero order rate. EOP is suitable only for delivery of water soluble drugs. Other historical developments of osmotic pump includes Rose-Nelson pump⁴, Higuchi-leeper pump⁵, ALZET osmotic pump⁶ and push pull osmotic pump⁷. To overcome the limitation for poorly water soluble drugs, two layer push-pull, monolithic osmotic pump, two compartments and sandwiched osmotic pump were developed. All these pumps require a sophisticated laser – drilling technique to make the delivery orifice (a common disadvantage)^{9,10}.

The osmotic pumps suitable for oral administration typically consists of a compressed tablet core coated with a semi permeable membrane that has an orifice drilled into it by means of a laser beam or a mechanical drill. Alternately, coating solution may contain a pore forming agent which solubilizes to form pores in semi permeable membrane. As the core absorbs water, it expands in volume and compresses

drug compartment which pushes the drug solution or suspension out of tablet through one or more delivery orifice¹¹.

Glipizide (second-generation sulfonylurea) is used in NIDDM and acts by increasing the release of endogenous insulin and its peripheral effectiveness^{12,13}. Glipizide belongs to class 2 of Biopharmaceutical Classification System. It has a relatively short elimination half of 2 – 4 hours thereby requiring two to three times daily dosing in large number of patients, which often leads to non-compliance^{14,15}.

In this study, an attempt was made to develop a controlled porosity osmotic pump for a poorly soluble drug (Glipizide) that eliminates the need for complicated and expensive drilling techniques. In this system, osmotic pressure was produced by osmotic agents and polymer swelling force concurrently to drive the drug out of the system through the pores created by the pore-forming agent. Pores are formed as pore forming agents solubilizes after exposure of the system to water^{16,17}.

MATERIALS AND METHODS

Materials

Glipizide was obtained as a gift sample from Ronak Pharmaceuticals pvt Ltd., Patan. Mannitol, Fructose, Sucrose, Lactose, Micro crystalline cellulose (MCC), Poly vinyl pyrrolidone (PVP), Magnesium stearate, Talc, Cellulose acetate, Polyethylene glycol (PEG) 400, Potassium chloride, Acetone and Methanol were purchased from central drug house (P) Ltd., New Delhi.

Method^{10,18,19,27}

Preparation of tablet core: All the ingredients of tablet core except PVP K 30, Talc and magnesium stearate were passed through sieve #85, accurately weighed to the quantities specified in table 1 and thoroughly mixed. Required quantity (as specified in table 1) of PVP K 30 was weighed and dissolved in sufficient quantity of isopropyl alcohol. Wet granulation technique was employed for granulation.

Granules were dried at 50°C for 1 hour and passed through sieve #18. Talc and magnesium stearate were blended with dry granules and compressed into tablets using a rotary compression machine fitted with 10.5mm deep concave punches.

Coating of tablet core: Tablet core formulation F1 was selected to optimize the coating solution formula. Various formulations for coating solutions are as mentioned in table 2. Acetone and Methanol are used as solvents, PEG 400 as plasticizer, Cellulose acetate as polymer and potassium chloride as pore forming agent. Core tablets were coated with coating solution in an automatic perforated coating pan. Initially, pan was rotated at low speed (3-5 rpm) and heated air was passed through tablet bed. Coating process was started only after outlet temperature was reached to 30°C. Coating pan rpm was maintained in the range of 15-20 rpm and coating solution was applied at the rate of 5-7 ml/min. coating process was continued until desired weight was gained on tablet core. For all formulations, coated tablets were dried at 40°C for 3 hours before evaluation.

EVALUATION^{16, 17, 18, 20, 22}

Content uniformity of core tablet

Content uniformity of core tablets was determined for each formulation. 10 tablets (core tablet) were crushed and contents of the crushed tablets equivalent to 10 mg were weighed and 100 ml methanol in a volumetric flask. Flask was sonicated for 30 min. Absorbance was noted in a UV double beam spectrophotometer against methanol as blank after suitable dilutions. Drug content was calculated.

Weight variation test of core tablet

Weight variation test was performed for all the formulations of core tablet. 20 tablets were selected from each formulation and evaluated for weight variation test. Average weight of 20 tablets and deviation in weight of each tablet from average was calculated.

Thickness of the coat

Coat was peeled off from the core tablet and thickness of the film was determined by digital micrometer. Thickness was determined at three different points on the film and average thickness was determined. 5 tablets from each formulation were tested and average was determined.

Hardness of core tablet

Hardness of core tablets from all the formulation was determined by Monsanto hardness tester. 10 tablets from each formulation were selected and hardness test was performed. Average hardness was calculated.

In vitro release studies

A tablet of each formulation was subjected to in vitro release rate studies. The medium used was 900 ml of pH 1.2 buffers for first 2 hour followed by pH 6.8 buffer. Temperature of medium was maintained at 37±0.5°C. Media was stirred at 50 rpm. Samples were withdrawn at 1 hour interval. Graph of time vs. % cumulative drug release was plotted which are shown in figure 1.

RESULTS

Optimization of coating solution

The optimized formula for coating solution is mentioned in table 3. Coating resulted in a weight gain of 2.2% of the core tablet.

Drug content

Drug content of core tablet was uniform within each batch and ranged from 97 – 105%.

Weight variation test

Weight variation test for core tablet was performed for each formulation and average was determined. Individual weights of each tablet for all the formulations were within the range of average weight ± 7.5%.

Thickness of the coating film

Thickness of the coating film was determined by digital micrometer. Thickness of the coating film for optimized formula was found to be 0.067±0.002mm.

Hardness of the core tablets

Average hardness of core tablets for all the formulations were in the range of 4-5 kg/cm².

In vitro release study

In vitro release profile (figure 1, 2 and 3) shows that release from F1, F2, F3, F7, F8, F9 were highly variable. Release from F4 has shown some variation from zero order release pattern. Release of drug from F6 and F5 exhibited zero order release.

DISCUSSION

Self pore forming osmotic tablets of Glipizide were successfully formulated and evaluated. Tablet core formulation F5 and F6 coated with F3 coating solution exhibited zero order release. Release rate characteristics were studied by varying the concentration of pore forming agent and varying the osmotic agents in different concentration ratios.

Effect of level of pore former

As the concentration of pore forming agent was increased, release rate was increased and total time to release the drug was decreased.

Effect of osmotic agent

Release of drug is affected by the osmotic pressure of the osmogen. A formulation containing an osmogen with high osmotic pressure showed higher release rates as compared to those containing an osmogen with low osmotic pressure.

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REFERENCES

- Chien YW. Novel drug delivery systems. 2nd ed. New York: Marcel Dekker. 2005. 139-96.
- Sharma S. Osmotic controlled drug delivery system. [Online]. [2008 Oct 20]; [1]. Available from: URL: <http://www.pharmainfo.net/reviews/osmotic-controlleddrug-delivery-system>.
- Higuchi T, Leeper HM. Osmotic dispenser with means for dispensing active agent responsive to osmotic gradient, 1976; US Patent No. 3,995, 631.
- Rose S, Nelson JF. A continuous long-term injector. Aust J Exp Biol Med Sci. 1955; 33: 415-420.
- Theeuwes F, Swanson D, Wong P, Bonson P, Place V, Heimlich K, Kwan KC. Elementary osmotic pump for indomethacin. J Pharm Sci. 1982; 72: 253-258.
- Bittner B, Thelley Th, Isel H, Mountfield RJ. The impact of co-solvents and the composition of experimental formulations on the pump rate of the ALZET osmotic pump. Int J Pharm. 2000; 205: 195-198.
- Higuchi T, Leeper HM. Osmotic dispenser with means for dispensing active agent responsive to osmotic gradient, 1976; US Patent No. 3,995, 631.
- Prabakaran D, Singh P, Kanaujia P, Jaganathan KS, Rawat A, Vyas SP. Modified push-pull osmotic system for simultaneous delivery of theophylline and salbutamol: development and in vitro characterization. Int J Pharm. 2004; 284: 95-108.

9. Longxiao L and Xiangning X: Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet. *International Journal of Pharmaceutics*. 2008; 352: 225–230.
10. Thakor R, Majmudar F, Patel J, Rajput G: Osmotic Drug Delivery Systems Current Scenario: Review. *Journal of pharmacy research*. 2010; 3(4).
11. Thombre AG, Appel LE, Chidlaw MB, Daugherty PD, Dumont F, Evans LAF, Sutton SC. Osmotic drug delivery using swellable-core technology. *J Cont Rel*. 2004; 94: 75-89.
12. Patel Chirag J, Mangukia Dhruv K, Asija Rajesh, Asija Sanjeeta, Kataria Sandeep, and Patel Pinkesh: Formulation and evaluation of matrix diffusion controlled transdermal drug delivery system of glipizide. *Journal of Drug Delivery & Therapeutics*. 2012; 2(1): 41-48.
13. Tripathi KD. *Essential of Medical Pharmacology*, 4th ed. Jaypee Brothers Medical Publishers, New Delhi. 2004; 266-274.
14. Chun-Yu Wang, Hsiu-O Ho, Ling-Hong Lin, Ying-Ku Lin, Ming-Thau Sheu, *International Journal of Pharmaceutics*. 2005; 297: 89–97
15. Goodman and Gilman's "The Pharmacological Basis of Therapeutics" 10th edition, 1701- 1703.
16. Sudeesh edavalath, Shivanand k, Kalyani prakasam, B prakash rao and Goli divakar: formulation development and optimization of controlled porosity osmotic pump tablets of diclofenac sodium. *International journal of pharmacy and pharmaceutical sciences*. 2011; 3(1): 80 – 87.
17. B. Prakash rao, m. Geetha, n. Purushothama, utpal sanki: Optimization and development of swellable controlled porosity osmotic pump tablet for theophylline. *Tropical journal of pharmaceutical research*. june 2009; 8 (3): 247-255.
18. Shivanand Pandey and Paridhi Shukla: Formulation and Evaluation of Osmotic Pump Delivery of Oxybutynin. *IJPRIF*. oct-dec 2009; 1(4): 1638-1643.
19. Rajeshri wakode and Amrita bajaj: Formulation and in vivo evaluation of once a day push-pull osmotic tablet. *International journal of pharma and bio sciences*. oct-dec 2010; 1(4), 44-56.
20. ShokriJ, AhmadiP, RashidiP, ShahsavariM, Rajabi- Siahboomi A, NokhodchiA: Swellable elementary osmotic pump (SEOP): an effective device for delivery of poorly water-soluble drugs. *Eur. J. Pharm. iopharm*. 2008; 2: 289–297.
21. Lindstedt B, Ragnarsson G, Hjartstam J: Osmotic pumping as a release mechanism for membrane coated drug formulations. *Int. J. Pahrm*. 1989; 56: 261-268.
22. Okimoto K, Ohike A, Ibuki R, Aoki O, Rajewski RA: Design and evaluation of an osmotic pump tablet (OPT) for chlorpromazine using (SBE). *Pharm. Res*. 1999; 5549-554.
23. Javad Shokari, Parinaz ahmadi, Parisa Rashidi, Swellable elementary osmotic pump (SEOP): An effective device for delivery of poorly watersoluble drugs. *European J. of Pharm. and Biopharm*. 2008; 68(2):289-297.
24. Biliote Anne Martine, Osmotic delivery system, European Patent No. EP 1469826 B1, 2006.
25. Kenneth C., Waterman E LT Osmotic delivery system. US Patent 0161882 A1, 2003.
26. Liu X, Chen D., Zhang R, Evaluation of monolithic osmotic tablet system for nifedipine delivery in vitro and in vivo. *Drug Dev. Ind. Pharm*. 2003; 7: 813–819.
27. Afifa Bathool, Gowda D V, Mohammed S. Khan, Vikas K Gupta and Rohitash Kumar: Development and Evaluation of Microporous Osmotic tablets of Diltiazem hydrochloride. *The Pharma Research Journal* 2011; 6(1), 112-119.
28. Mothilal M, Damodharan N, Lakshmi KS, Sharanya VB, Srikrishna T. Fomulation and in vitro evaluation of osmotic drug delivery system of metoprolol succinate. *Int J Pharm & Pharm Sci*, 2010; 2(2).
29. Rose S, Nelson JF. A continuous long term injector, *Aust. J. Exp. Biol*. 1955; 33:415-420.
30. Bindschaedler C, Gurny R, Doelker E. Osmotically controlled drug delivery systems produced from organic solutions and aqueous dispersions of cellulose acetate. *J Cont Release*. 1986; 4: 203–212.

Table 1: Composition of tablet core

Ingredients	Quantity/tab								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glipizide (mg)	10	10	10	10	10	10	10	10	10
Mannitol (mg)	30	50	40	30	50	40	30	50	40
Fructose (mg)	50	30	40	50	30	40	50	30	40
MCC (mg)	70	70	70	70	70	70	70	70	70
PVP K 30 (mg)	15	15	15	15	15	15	15	15	15
Mg stearate (mg)	2	2	2	2	2	2	2	2	2
Talc (mg)	2	2	2	2	2	2	2	2	2

Table 2: composition of coating solution

Ingredients	F1	F2	F3	F4	F5
Cellulose acetate (mg)	3	3	3	3	3
PEG 400 (ml)	2.5	2.5	2.5	2.5	2.5
Potassium chloride (mg)	0.2	0.4	0.6	0.8	1.0
Acetone (ml)	80	80	80	80	80
Methanol (ml)	20	20	20	20	20

Table 3: optimized formula

Ingredients	Coating solution	Tablet core	
Cellulose acetate	3	-	-
Peg 400	2.5	-	-
Potassium chloride	0.6	-	-
Acetone	80	-	-
Methanol	20	-	-
Glipizide	-	10	10
Mannitol	-	50	40
Sucrose	-	30	40
MCC	-	70	70
PVP K 30	-	15	15
Mg stearate	-	4	4
Talc	-	4	4

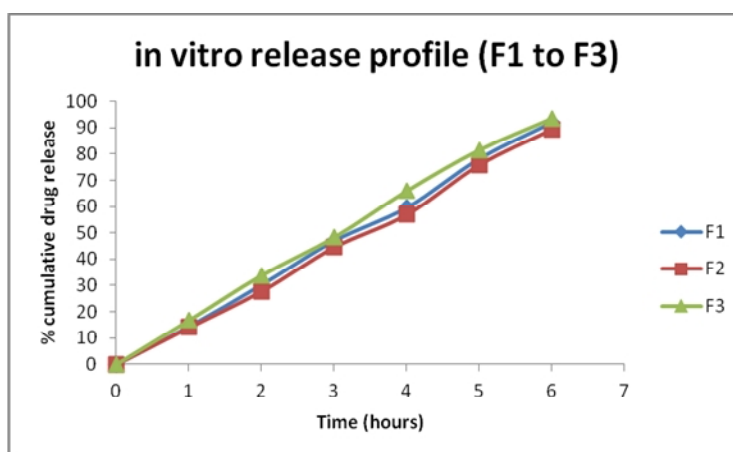


Figure 1: in vitro release profile (F1 to F3):

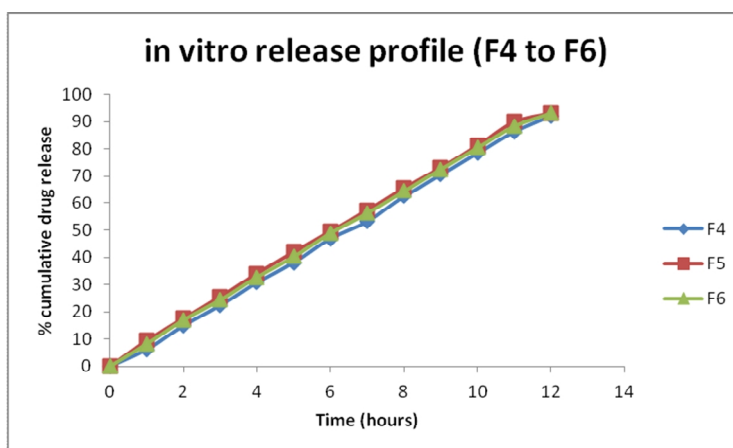


Figure 2: in vitro release profile (F4 to F6):

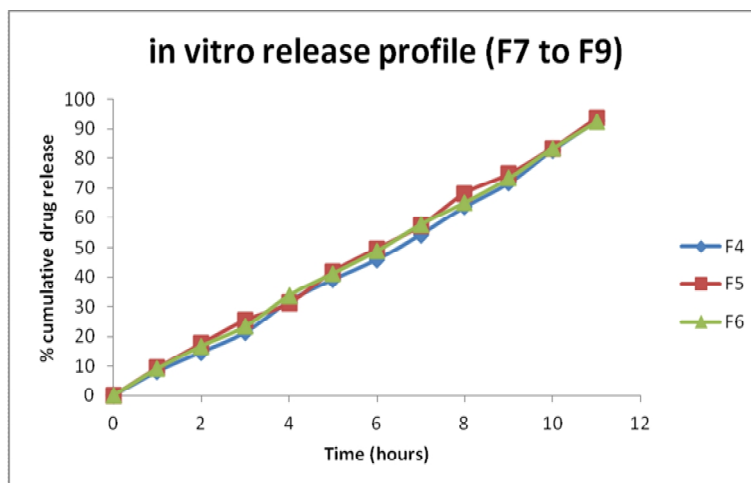


Figure 3: in vitro release profile (F7 to F9)

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