



# Synchronization of swelling, erosion, and release in a novel and robust formulation of glipizide

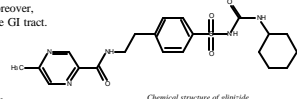
Shahla Jamzad\* and Reza Fassihi  
\* Temple University, School of Pharmacy, 3307 N. Broad St., Philadelphia, PA

## Introduction

Glipizide is an oral antidiabetic agent that belongs to BCS Class II drugs. It is a weak acid (pKa=5.9), with bioavailability of nearly 100%, and t<sub>1/2</sub> of 2-4 hours. The only controlled release glipizide product in the market is Glucotrol XL tablet. It is based on push pull osmotic pump (PPOP) principle which requires a sophisticated and costly technology. Moreover, certain disadvantages have been attributed to oral osmotic pumps such as unpredictable transit in the GI tract.

## Objectives

To develop and evaluate robust direct compression monolithic controlled release matrices for glipizide, matching release profile of push-pull osmotic pump system.



## Methods

Various 10mg glipizide tablets were prepared by dry blending the ingredients followed by direct compression (Table 1).

Dissolution study was conducted in 900ml buffer maintained at 37°C using modified (inset in Fig. 1) USP 27 apparatus II at 75rpm [1]. Release profiles of tablets were compared using  $t_1$ ,  $t_2$ ,  $t_{25\%}$ ,  $t_{50\%}$ , and  $t_{75\%}$  (Table 2).

The capacity for hydration, erosion, and resilience of matrices under conditions similar to the dissolution test, were evaluated gravimetrically according to the following equations with conjunction with textural analysis [3].

$$\% \text{Weight Gain} = 100 \frac{(\text{Wet Weight} - \text{Dry Weight})}{\text{Dry Weight}}$$

$$\% \text{Weight Loss} = 100 \frac{(\text{Original Weight} - \text{Dry Weight})}{\text{Original Weight}}$$

$$W = \int F \cdot dD$$

W: work done by the probe, F: force applied, and dD: total probe displacement.

Table 1. Formulation composition

Ingredients	Amount per tablet in formulation (mg)									
	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10
Glipizide	10	10	10	10	10	10	10	10	10	10
HPMC K100M	90	45				30				
HPMC K15M			45	35	30			38.5	42	31.5
HPMC K100LV		45	45	55	60	60	60	60.5	66	49.5
Epoxy resin	50	50	50	50	50	50	50	50	50	40
Lactose monohydrate										
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Colloidal Silicon dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	152.25	152.25	152.25	152.25	152.25	152.25	152.25	166.25	180.25	138.25

Table 2. Changes in levels of release modifying ingredients and effect on release characteristics

Ingredients	mg/Tab	% Difference relative to H4 formulation								
		H1	H2	H3	H5	H6	H7	H8	H9	H10
Glipizide	10	0	0	0	0	0	0	0	0	0
HPMC K100M				30mg						
HPMC K15M	35	-14.3%	-100%	+10%	+20%	-13%	-20%			
HPMC K100LV	55	+5.1%	+9.1%	+10%	+20%	-13%	-20%			
Epoxy resin	50	0	0	+10%	+20%	-13%	-20%			
Lactose monohydrate										
Magnesium stearate	0.75	0	0	0	0	0	0	0	0	0
Colloidal Silicon dioxide	1.5	0	0	0	0	0	0	0	0	0
$t_1$ (%)	Reference	534	245	4.81	5.79	638	8.85			
$t_2$	Reference	77.07	89.45	76.42	74	7344	65.46			
$t_{25\%}$ (hr)		5.2	4.7	5.4	5.42	4.5	4.7	5.9		
$t_{50\%}$ (hr)		9.5	8.9	8.8	10.7	10.3	9.9	9.2		
$t_{75\%}$ (hr)		15	14.5	15.8	17.0	16.7	16	15.2		

## Results and Discussion

### a. Formulation design and development

In H1 formulation linear release with a maximum of 60% of the drug release in 23 hours (Fig. 1) was achieved.

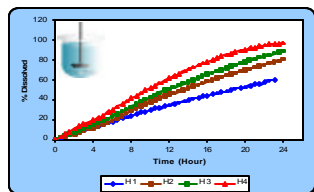


Fig. 1. Dissolution profile of H1-H4 formulations in pH6.8 phosphate buffer at 75rpm

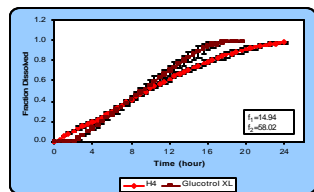


Fig. 2. Comparison of dissolution profile of H4 and Glucotrol XL 10mg tablet in pH6.8 phosphate buffer at 75rpm

## Results and Discussion

Two approaches were examined to increase the release rate and achieve a release profile similar to that of Glucotrol XL:

1. Increase in amount of water soluble excipient, lactose, to accelerate matrix hydration, and facilitate drug diffusion and matrix erosion [4].
2. Reduction in viscosity of matrix by replacing the high molecular weight HPMC (K100M) with lower viscosity grades HPMC (K15M and K100LV) in the H2-H4 formulations (Fig. 1).

With H4 formulation linear release profile ( $R^2=0.9984$  for up to 80% release) similar to the reference product Glucotrol XL ( $t_2=58$ ) was achieved (Fig. 2). In this case, drug release was complete and the matrix was fully dissolved at the end of the experiment.

In design of the low solubility / low dose drug matrix systems with desirable release kinetics, the critical point is to find an appropriate ratio between polymers and release modifying ingredients to correctly balance interrelationship between swelling front and diffusion and erosion boundaries throughout the dissolution process.

In H4 formulation the weight gain and mass loss proceeded throughout the entire course of the dissolution (Fig. 8). The high capacity of HPMC matrix for water retention and the osmotic pressure generated by lactose are largely responsible for such behavior. Fig. 8 clearly demonstrates that in the case of low solubility/low dose drugs, synchronization of swelling, erosion, and drug release is the key parameter to provide zero order release kinetics.

### b. System endurance

Effect of hydrodynamics and pH on drug release from H4 formulation is depicted in Fig. 5. Lower dissolution rate in acidic pHs is attributed to low solubility of glipizide in acid media and the lack of sink condition in pH 2 and 4.4.

Robustness of H4 formulation was studied through changes in viscosity grade of HPMC and amount of release modifying ingredients as shown in Table 1 and 2. The dissolution profiles (Fig. 6) and the calculated  $t_1$ ,  $t_2$ ,  $t_{25\%}$ ,  $t_{50\%}$ , and  $t_{75\%}$  (Table 2) suggest similarity of the entire release profiles relative to the reference formulation H4.

The rate of hydration in all formulations was similar as shown in Fig. 7, although erosion pattern showed more variation. In all formulations release was in accordance with dynamics of hydration suggesting the dominant role of swelling and associated diffusion mechanism (Fig. 8). Similarity of hydration patterns (Fig. 7) and consequent similarity of release profiles (Fig. 6) are attributed to the constant ratio of lactose to polymer content (0.56).

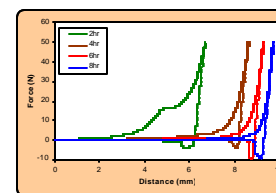


Fig. 3. Textural profiles of H4 formulation at different time points

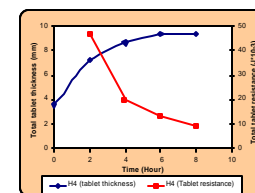


Fig. 4. Change in the hydrated tablet's thickness and strength

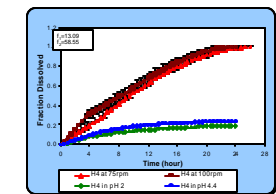


Fig. 5. Dissolution profile of H4 in pH2, 4.4, and 6.8 buffer at 75rpm

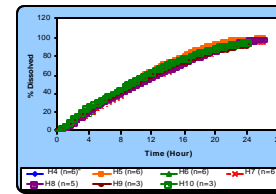


Fig. 6. Dissolution profiles of H4-H10 formulations in pH6.8 phosphate buffer at 75rpm

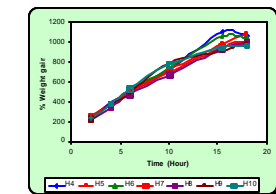


Fig. 7. Comparison of degree of hydration in developed formulations

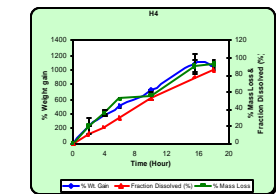


Fig. 8. Comparison of degree of hydration, mass loss and drug release for H4 formulation

## Conclusions

Monolithic HPMC matrix formulations were developed for a low solubility/low dose drug, glipizide. Drug release was similar to that of the commercial product Glucotrol XL ( $t_2=58$  for H4). The kinetics of drug release was in accordance with the kinetics of hydration/swelling. Simplicity of formulation, ease of manufacture, complete disintegration/dissolution, reproducibility of release profile, strong physical structure of the gel, insensitivity to hydrodynamics and pH condition, and robustness of formulation are among the advantages of the developed formulation.

## References

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4. S. Jamzad, R. Fassihi, Poster presented in AAPS annual meeting, Baltimore, MD, 2004.