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Enhancement of Dissolution of Glipizide from Controlled Porosity Osmotic Pump Using A Wicking Agent And A Solubilizing Agent

Mahalaxmi.R[1*], Phanidhar Sastri[1], Ravikumar[3], Atin Kalra[1], Pritam Kanagale.D[2], Narkhede R[1].

[1]Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal.

[2]Zydus Research Center, Moriya, Ahmedabad.

[3]Department of Pharmaceutics, KLES's College of Pharmacy, Ankola-581314, Karnataka.

Email: mlrcops2002@yahoo.co.in

ABSTRACT: Extended release controlled porosity osmotic pump formulations of model drug glipizide were developed using a wicking agent and a solubilizing agent. Glipizide osmotic tablets were evaluated for their flow properties, weight variation, hardness, friability and content uniformity. The effect of different formulation variables like level of wicking agent, solubilizing agent, level of pore former and membrane weight gain on *in vitro* release were studied. Drug release was found to be affected by the level of wicking agent and solubilizing agent in the core. Glipizide release from controlled porosity osmotic pump was directly proportional to the pore former (sorbitol) and inversely proportional to membrane weight gain. Drug release from the developed formulations was independent of pH and agitational intensity and was dependent on osmotic pressure of the release media. The optimized formulation was also found to stable upon stability studies.

Keywords: Glipizide, Wicking agent, Solubilizing Agent, Osmotic system, Controlled Porosity Osmotic Pump (CPOP).

INTRODUCTION

With the conventional dosage forms it is difficult to achieve and maintain the concentration of the administered drug within therapeutic range, leading to fluctuations in the plasma drug levels[1]. However, significant stride has been made in the development of drug delivery devices that can precisely control the rate of drug release for an extended period of time. In the recent years, pharmaceutical research has led to the development/invention of several novel controlled drug delivery systems of which oral controlled drug delivery system has received greater attention since it is the most popular route of drug administration[2-3]. Several devices for oral drug delivery generally has taken the form of simple tablets, yet have been shown to be quite different functionally[4]**.** One of such an oral drug delivery system is an osmotic controlled drug delivery system. Osmotically controlled oral drug delivery systems utilize osmotic pressure as the energy source for the controlled delivery of drugs. Osmotically controlled drug delivery offers advantages like pH and gastric motility independent drug delivery, delivery of drugs by a zero order. Therefore, it is possible to achieve and sustain a drug plasma concentration within the therapeutic window of drugs, which reduces the side effects and frequency of administration considerably[5-9].

In general delivery of poorly soluble drugs is quiet challenging as they often show difficulties in formulation and drug delivery because of their poor water solubility. They also show erratic dissolution and bioavailability profile[10-11]. Glipizide is one such poorly soluble oral hypoglycemic agent belonging to class 2 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 a rate-determining step (i.e., an effective factor) in its absorption from the gastrointestinal tract[12]. It also has a relatively short elimination half-life of 2-4 h**,** there by requiring twice daily dosing in large number of patients, which often leads to non-compliance. Therefore present work is aimed towards enhancing the solubility,

dissolution there by bioavailability of glipizide using a wicking agent and a solubilizing agent.

MATERIALS AND METHODS

Glipizide, Sodium lauryl sulphate (SLS), Tromethamine, Mannitol, Poly vinyl pyrrolidine (PVP k-30), Magnesium stearate, Aerosil, Cellulose acetate (acetyl content 39.9%), Sorbitol, Poly ethylene glycol (PEG-400) were provided by Zydus research center, Ahmedabad. All the other solvents and chemicals used were of analytical grade.

Analytical method for estimation of glipizide: UV – Spectrophotometric method was chosen for the analysis of glipizide. The wavelength of 276nm was selected as λ max for further studies.

Compression of glipizide osmotic core tablets: Core tablets of glipizide were prepared by wet granulation method and the batch size was kept as 200 tablets. Glipizide previously passed through ASTM sieve no # 40 was mixed with all the excipients which were previously passed through ASTM sieve no # 60 via geometric mixing. The blend was mixed for 10 min in a polybag and later the mixture was granulated with PVP k-30 in isopropyl alcohol (IPA) and the resulting wet mass was passed through ASTM sieve no #14 to obtain granules of uniform size. The granules were then dried at 50 ^{o} (approximately for 15 min) to get a loss on drying (LOD) value between 1% and 1.1%, after which they were passed through ASTM sieve no #30. These sized granules were then blended with magnesium stearate, and aerosil (colloidal silicon dioxide) both ASTM sieve no #60 passed as lubricant and glidant respectively, mixed and were compressed into tablets having an average weight of 300mg using a 27 station tablet punching machine (CDMD4, Cadmach, Ahmedabad, India) fitted with round standard concave punches (12/32''). During the compression run few tablets were taken at random and their weight variation, thickness, diameter, hardness, friability and drug content uniformity were evaluated. The different formulations of glipizide osmotic tablets are given in table 1.

Coating of glipizide osmotic core tablets*:* The core tablets of glipizide were coated in an automated perforated pan coater (GAC-250, Gans coater, India). Various components of the coating solution were added in a sequential manner following the order dichloromethane (DCM) + cellulose acetate + methanol + sorbitol + PEG 400 + water. The component added first was allowed to dissolve before the next component was added. Core tablets of glipizide were placed in the coating pan along with 300 g 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 air temperature reached 35^{o}. The pan rpm was kept in the range of 10–15 and coating solution was sprayed at the rate of 7–9 ml/min. Atomization pressure was kept at 1.2 to 1.9 kg/cm^{2} and the outlet temperature was maintained above 35^{o} by keeping the inlet air temperature in the range of 45–50^{o}. During coating run few tablets were taken randomly and percentage weight gain was determined and coating was continued until desired weight gain was obtained on the tablets. Coated tablets were dried in a tray dryer (BO-6, Bombay Eng. works, Mumbai, India) at 50^{o} over night before further evaluation. The coating compositions for glipizide core formulations are shown in table 2.

Evaluation of glipizide osmotic coated tablets: Prior to the compression, the glipizide powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hausner ratio were calculated. LOD of the granules was determined using a LOD tester .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 was determined by hardness tester and friability of uncoated osmotic tablets was determined by friabilator.

***In vitro* release:** USP I rotating basket dissolution apparatus (Distek, UK.) was used to determine the *in vitro* drug release from the glipizide osmotic tablets. PBS (SIF, pH 6.8,500 ml) maintained at 37 ± 0.5 ^{o} at 75 rpm was utilized as the dissolution medium, under sink conditions ($C<0.15C_s$).

The optimized formulation was then later evaluated for —

Effect of pH: Release studies of the optimized formulation were conducted according to pH change method[13-16]. The release media was simulated gastric fluid (SGF, pH 1.2) for first 2h, acetate buffer (pH 4.5) for next 2h, followed by PBS (SIF pH 6.8) for the remaining 24 h.

Effect of agitational intensity: Release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds[13-16]. Dissolution was carried at 50, 75 and 100 rpm with PBS (SIF, pH 6.8,500 ml) maintained at 37 ± 0.5^{o} as the dissolution medium.

Kinetics and release mechanism studies: In order to confirm the mechanism of drug release, release studies of the optimized formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media, mannitol (osmotically effective solute) was added in PBS (SIF) and the pH was adjusted to 6.8 ± 0.05[14]. Release studies were carried out in 500 ml of media at 75 rpm.

In order to determine the kinetics of drug release first order, zero order and Higuchi plots were drawn and based on the goodness-for-fit (R^2) and sum of squared residuals (SSR), the best model was selected[17].

Stability studies: The optimized formulation of glipizide were packed in strips of aluminum foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40 ^{o} and 75% RH for 3 month (zone III conditions as per ICH Q_1 guidelines). The samples were withdrawn periodically and evaluated for their hardness, content uniformity and for *in vitro* drug release.

RESULTS

Evaluation of Glipizide osmotic tablets: The glipizide powder blends were free flowing as indicated by the values of bulk density (0.512-0.609 gm/cm^3), tapped density (0.542-0.625 gm/cm^3), compressibility index (less than15) and Hausner ratio (less than1.25). LOD of granules was with in limits between 1 to 1.1%. Weight variation was with in the USP limits (±7.5%). Thickness and diameter was kept constant. Hardness was kept constant (6-8kp) for uncoated tablets and friability of uncoated tablets was less than 1% indicating mechanical stability with content uniformity between 95-105%.

Effect of level of wicking agent and solubility modifier

The core tablets of glipizide GLPF01 coated with coating solution 1 has shown incomplete drug release after 24 h. In order to enhance the solubility, *in vitro* release of the glipizide a wicking agent SLS (12mg/tablet) was added into the core formulation GLPF02 and was coated with the coating solution 1. In this case also incomplete drug release was achieved but %CDR after 24 h was more than the GLPF01. In order to achieve complete drug release, tromethamine was added as a solubility modifier to increase the micro environmental pH of the core above the pK_a of glipizide. Tromethamine has been used as a buffering agent to increase the dissolution rate. Four batches were prepared in which the concentration of SLS was kept constant and the concentration of tromethamine was varied in order to optimize its concentration so as to achieve the desired *in vitro* release. Batches GLPF03, GLPF04, GLPF05 and GLPF06 were prepared with 25% w/w, 16%w/w, 10%w/w and 5 %w/w of tromethamine respectively and were subsequently coated with different coating solutions containing different amounts of sorbitol.

Initially GLPF03 and GLPF04 were coated with coating solution 1,2,3,4 to achieve a weight gain of 7%w/w and 9%w/w of total solid contents in the coating respectively (figure 1). In both the formulations GLPF03 & GLPF04 coated with coating solutions 1,2,3 there was initial faster release but complete drug release was achieved, where as in formulations coated with coating solution 4 there was initial fast release but the drug release was incomplete . In order to reduce the initial fast release GLPF05 and GLPF06 were formulated with 10%w/w and 5% w/w of tromethamine and coated with coating solution 3 with a weight gain 6%w/w. Their *in vitro* release indicates that the reduction in the concentration of tromethamine has direct effect on drug release and incomplete drug release was observed in GLPF06. In case of GLPF05 complete drug release was achieved with initial faster release. Therefore, in order to reduce the initial drug release, GLPF05 was again coated with coating solution 3 with a weight gain of 8%w/w and 10%w/wand GLPF05 with 10% weight gain had given the desired *in vitro* profile and was taken as the optimized formulation (figure 2).

Effect of level of pore former: To study the effect of level of pore former sorbitol, core formulations of glipizide GLPF03 and GLPF04 were coated with different coating solutions of various compositions containing 0% and 50% w/w of sorbitol in the formulatory trials. Their *in vitro* release was shown in figure 1. It was clearly evident that, the level of sorbitol had a direct effect on drug release. As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release. The results are consistent with other reports[13-16].

Effect of weight gain: To study the effect of weight gain of the coating on drug release, in the formulatory trials core tablets of glipizide GLPF05 were coated with coating solution 3 in order to achieve a weight gain of 6,8,10% w/w of the total solid contents in coating. The *in vitro* release was shown in figure 2. It was evident that drug release decreases with an increase in weight gain of the membrane. No bursting of the systems was observed during any of the dissolution run in any of the formulations which assures that the formulations will remain intact in GIT without any incidence of dose dumping. The results are consistent with other reports[13-16].

Effect of pH: In order to study the effect of pH on drug release, release studies of the optimized formulation GLPF05 coated with coating solution 3 were conducted according to pH change method. Figure 3 show the release profile of Glipizide from GLPF05 and it was clearly evident that the release profile was similar in both the media. The results are consistent with other reports[13-16].

Effect of agitational intensity: Drug release from osmotic pumps, to a large extent, is independent of agitational intensity of the release media[13-16,22]. Release studies of GLPF05 were carried out in USP I rotating basket dissolution apparatus at varying rotational speed (50, 75and 100 rpm). Figure 3 show that the release profile of glipizide from the GLPF05 formulation which was fairly independent of the agitational intensity of the release media and hence it can be expected that the release will be independent of the hydrodynamic conditions of the body.

Effect of osmotic pressure: To study the effect of osmotic pressure, release studies of the optimized formulation GLPF05 was conducted in the media of different osmotic pressure by the addition of osmotically effective solute mannitol (osmotic pressure of the core formulation was determined to be 61.1 atm). Table 3 indicates that the drug release was highly dependent on the osmotic pressure of the release media. Glipizide release from the formulations decreased as the osmotic pressure of the media increased. It was concluded that osmotic pumping is the major mechanism governing drug release from the developed formulations.

Kinetics and mechanism of drug release: *In vitro* dissolution data of the optimized formulation was fitted into various mathematical models (zero order, first order, and Higuchi) in order to describe the kinetics of drug release. Drug release from GLPF05 formulation fitted well into first order kinetics as shown in table 3, while

the second best model describing the release was zero order model. The reason for first order release could be because of the presence of wicking agent and solubility modifier in the core formulation, which was necessary to modulate the solubility of glipizide. Since no attempts were made to control the release of wicking agent and solubility modifier from the formulations, majority of it must be releasing before the entire drug release took place and thus, drug release showed first-order release[25, 26].

Stability studies: The accelerated stability studies were carried out according to ICH guidelines. Optimized formulation GLPF05 was packed in strips of aluminum foil laminated with PVC by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40 ^{o} and 75% RH (zone III conditions as per ICH Q_1 guidelines) for 3 mo. The tablets were withdrawn periodically and evaluated for their drug content, hardness and *in vitro* release. The similarity factor (F_2) was calculated by taking initial sample i.e. 0 mo sample as reference and was found to be with in limits (50-100)[17]. For calculation of fit factor only one time point $t_{80\%}$ i.e. time taken for the release of 80% of glipizide was taken. The formulation GLPF05 was found to be stable in terms of drug content and *in vitro* release as shown in table 4 & figure 4.

DISCUSSION

The dosage form developed was designed as a tablet core coated with a rate controlling membrane. The tablet core consists of a wicking agent and a solubility modifier, osmagent and other conventional excipients. Wicking agents in the formulations are those agents which are capable of drawing water inside the core compartment by forming channels in the core there by creating necessary osmotic pressure for the release of the drug. They also will increase the solubility of the drug because of their surfactant property thereby enhancing the drug release[18,19]. Solubility modifier used in the formulations are alkalinizing agents that are in immediate contact with the drug and capable of modifying the micro environmental pH of the core above the pK_a of drug. The core compartment is surrounded by a membrane consisting of a semipermeable membrane forming polymer, a water soluble additive as the pore former, and a 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. After coming into contact with the aqueous fluids, the wicking agent and solubility modifier dissolves and elevates the micro environmental pH of the tablet core above the pK_a of the drug, thus increasing its solubility. The dissolved drug is released through the pores created after leaching of water-soluble additive in the membrane.

SLS and tromethamine were used as wicking and solubilizing agents respectively. Cellulose acetate (acetyl content 39.9%) and sorbitol were used as water insoluble semi permeable polymer and water soluble pore former and PEG-400 was used as water-soluble plasticizer.This phenomenon could be expected because osmotic pumps are suitable for delivery of drugs having intermediate water solubility[20,21]**.** It was reported that in case of water insoluble drugs, meaningful release rates might not be obtained using EOP or CPOP as the kinetics of osmotic drug release is directly related to the solubility of drug within the core[14]. Glipizide is a weakly acidic drug that is practically insoluble in water and buffer media of acidic pH[12,21] . It was inferred that as the core in the formulation GLPF01 only contains an osmagent without any solubility enhancing agent, incomplete drug release was observed.

Hence it was inferred that wicking agent SLS can enhance the solubility of glipizide to some extent but other solubilizing agents are required in order to achieve complete drug release from the osmotic pump[22]. Initial faster drug release was attributed to higher concentration of buffering agent tromethamine in the core, which was attributed to lack of pore former sorbitol in the coating.

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Table 1: Different Formulations of Glipizide Osmotic Tablets.

Ingredients in mg	GLPF01	GLPF02	GLPF03	GLPF04	GLPF05	GLPF06
Glipizide	10	10	10	10	10	10
SLS	----	12	12	12	12	12
Trimethamine	----	----	84 (28%w/w)	48 (16%w/w)	30 (10%w/w)	15 (5%w/w)
Mannitol	272	260	176	212	230	245
PVP K-30	12	12	12	12	12	12
IPA*	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	3	3	3	3	3	3
Aerosil	3	3	3	3	3	3
Tablet weight	300	300	300	300	300	300

* Quantity sufficient in ml

Table2: Coating Compositions for Glipizide Core Formulations.

S N		Coating solutions			
		1	**2**	**3**	**4**
1	Cellulose acetate	60g	60g	60g	60g
2	Sorbitol	30g (50%w/w)	18g (30%w/w)	6g (10%w/w)	---
3	PEG-400	6g	6g	6g	6g
4	Water*	58ml	58ml	58ml	58ml
5	DCM*	870ml	870ml	870ml	870ml
6	Methanol*	580ml	580ml	580ml	580ml

*Ratio of DCM: methanol: water is 15:10:1.

Table 3: Release Kinetics For optimised (GLP F05) Formulation

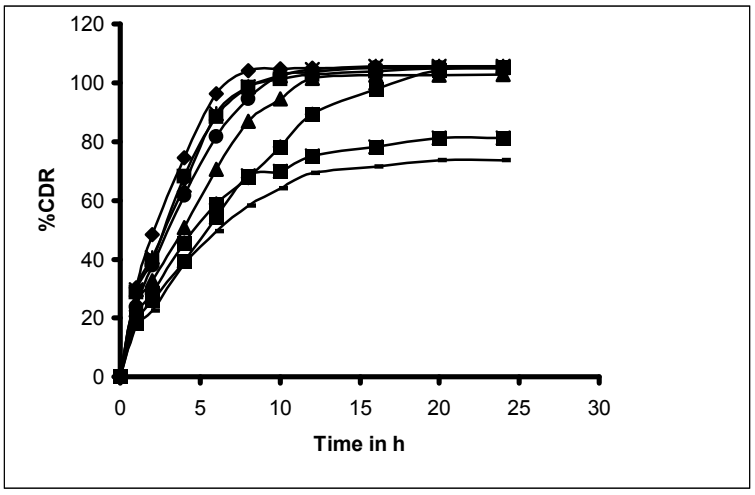
Model	**R^2**	**SSR**
Zero order	0.9713	159.29
First order	0.9926	68.9
Higuchi	0.9234	625.3

R^2- goodness for fit; SSR- sum of squared residuals

Table 4: Stability Studies of GLPF05 Formulation

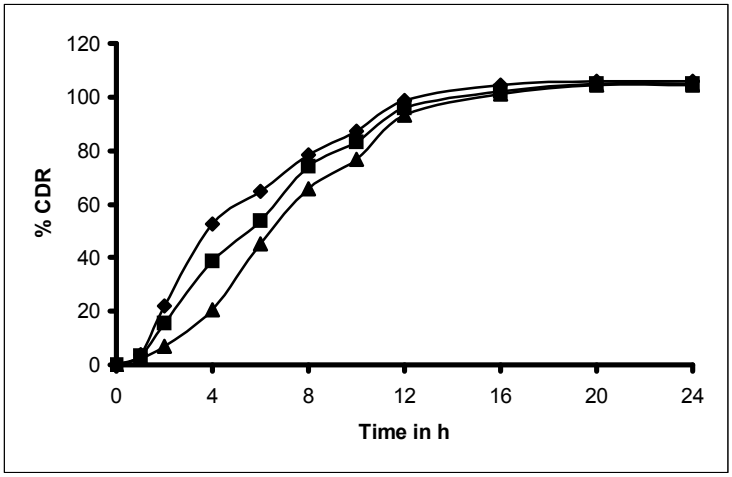
Parameter	**0 month**	**1 month**	**2 month**	**3 month**
Hardness	15.6±2.34	17±1.24	17±2.61	18±2.32
Drug content	103.60±2.44	104.20±2.95	101.60±1.64	100.40±2.10
Similarity factor (F_2)	-----	65.12	74.32	61.76

Figure 1: *In vitro* release of GLPF03 and GLPF04 formulation coated with coating solution 1,2,3,4 in PBS 6.8 pH.



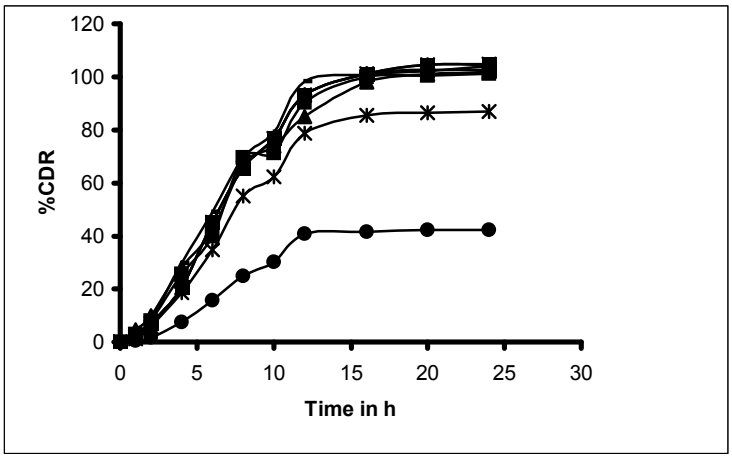
♦ GLPF03 coated with coating solution 1; ■ GLPF03 coated with coating solution 2; ▲ GLPF03 coated with coating solution 3; x GLPF03 coated with coating solution 4;
* GLPF04 coated with coating solution 1; ● GLPF04 coated with coating solution 2;
′GLPF04 coated with coating solution 3;-GLPF04 coated with coating solution.

Figure 2: *In vitro* release of GLPF05 formulation coated with coating solution 3 in PBS 6.8 pH.



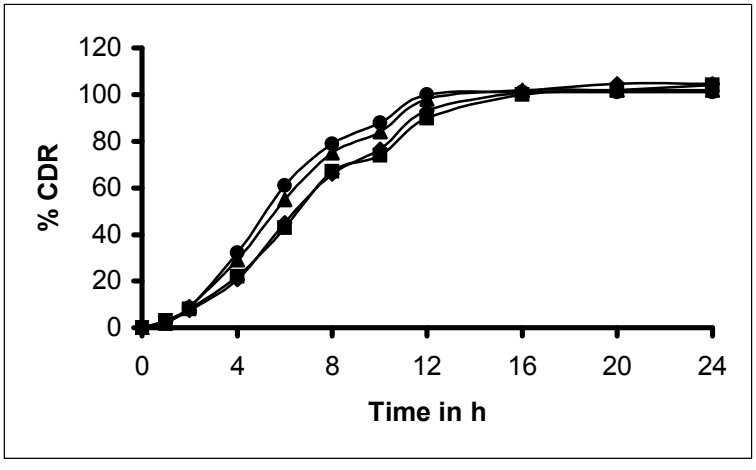
■ 8% w/w weight gain;▲10 % w/w weight gain; ♦ 6% w/w weight gain

Figure 3: Effect of pH, agitational intensity and osmotic pressure of media on the *in vitro* release of GLPF05 formulation.



♦ GLPF05 in PBS pH 6.8; ■ GLPF05 pH change method;▲ GLPF05 at 50 rpm;
x GLPF05 at 75 rpm; * GLPF05 at 100 rpm; ● GLPF05 at 0 atm; ′ GLPF05 at 25 atm;
- GLPF05 at 50 atm.

Figure 4: Effect of Ageing on the *in-vitro* Release of GLPF05 Formulation.



♦ 0 month; ■ 1 month;▲2 month;● 3 month

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