Design and formulation of nano-porous controlled porosity osmotic pumps (CPOPs) containing a poorly water soluble drug, glibenclamide

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Abstract: The aim of this study was to design and develop controlled porosity osmotic pumps containing glibenclamide (as an insoluble agent) coated with nano-scale pore formers. Solubility enhancement methods including co-grinding with an anionic surfactant and pH adjustment in core formulation were employed and the prepared cores were coated with nano-suspension coating method. The prepared nano-porous osmotic pump (CPOP) system assessed by comparative parameters including D_{24h} (cumulative release percentage after 24h), t_L (lag time of the drug release from device), drug release rate from device and RSQ_{zero}. Solubility studies of glibenclamide co-ground with an anionic surfactant showed that by increasing the concentration of SLS to 83.33% (ratio of drug: SLS 1:5) in the presence of calcium carbonate, the solubility of glibenclamide was enhanced remarkably. Release study also displayed enhanced D_{24h} and improved kinetic related parameter (RSQ_{zero}) by increasing SLS and calcium carbonate in the core formulation via nano-porous CPOPs. It can be concluded that by employing both co-grinding technology and pH adjustment method in core formulation of glibenclamidenano-suspension coated CPOPs, enhanced D_{24h}, drug release rate and improved kinetic related parameter (RSQ_{zero}) was achieved.

Keywords: Solid dispersion, co-grinding, nano-suspension coating, CPOP, glibenclamide

INTRODUCTION

Osmotic drug delivery systems have gained a great attention among oral novel drug delivery systems (NDDS) due to their unique advantages such as drug release independency in the presence or absence of food, pH changes and other physiological factors (Verma *et al*., 2000, 2002). These systems can be very valuable for delivery of drugs, particularly for drugs with a short biological half-life which requires frequent consumption during 24 hours (Shokri *et al*., 2013; 2008. Numerous systems have been developed based on the principle of osmotic pressure namely elementary osmotic pump (EOP) (Theeuwes 1975; Theeuwes *et al*., 1983; Gong *et al*., 2015), sandwiched osmotic tablet system (SOTS) (Liu *et al*., 2000; Kundawala *et al*., 2016), push-pull osmotic pumps (PPOP) (Malaterre *et al*., 2009; Zhang *et al*., 2011; Liu *et al*., 2014; Tang *et al*., 2013), controlled porosity osmotic pumps (CPOP) (Babu and Ratna 2010; Thakkar *et al*., 2015; Mene *et al*., 2016; Adibkia *et al*., 2014), tablet in tablet (TNT), cores (McKinney *et al*., 2012), asymmetric membrane capsule for osmotic drug delivery (Jain *et al*., 2014; Yang *et al*., 2016; Paraveen *et al*., 2015), osmotic systems made by swellable-core technology (Thombre *et al*., 2004) and swellable elementary osmotic pump (SEOP) (Shokri *et al*., 2008; Malaterre *et al*., 2009; Nokhodchi *et al*., 2008). Due to simplicity and low cost of the production along with reducing the possibility of blocking the pores these systems are becoming more popular. Researchers have incorporated drugs with moderate to high water solubility in controlled porosity osmotic systems (CPOPs) (Adibkia *et al*., 2014; Dasankoppa *et al*., 2003; Pujara *et al*., 2012). Since the majority of drugs has organic structure and in some cases, soluble salts of these drugs have no pharmacological effects or gastrointestinal absorption then formulation of their original form is important. Till now, push-pull osmotic drug delivery systems for insoluble drugs commercially available in the market (nefidipine osmotic pump manufacturing by Pfizer, Procardia XL®) which its manufacture requires very expensive equipment and high technology, such as laser perforation device, tablet layers densitometer using X-ray devices and tableting of two layers with latex in the middle.

Concerning difficulties in formulation of poorly-water soluble agents, various techniques are developed to overcome the solubility issue. Solubility enhancement techniques can be mainly categorized into chemical, physical modifications of the drug substance, and other methods such as supercritical fluid process and use of adjuvants. Chemical Modifications includes pH Change (use of buffer) (Chaudhary *et al*., 2012), physical modifications consist of particle size reduction (Khadka *et al*., 2014; Savjani *et al*., 2012), crystal engineering

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(Brough and Williams 2013; Thakur *et al*., 2016; Thakuria *et al*., 2013), complex formation-based techniques (Rehman *et al*., 2014; Aiassa *et al*., 2015; Popescu *et al*., 2015; Taupitz *et al*., 2013) and drug dispersion in carriers (Paudel *et al*., 2013; Fong *et al*., 2016; Choudhry and Kumar 2014). It seems that applying these techniques in core formulation of CPOPs can result in improving the solubility and dissolution behaviour of poorly water-soluble agents. The aim of the present study is to develop a controlled nano-porosity osmotic system (CPOP) with a capability for the delivery of poorly-water soluble drugs using the solubility and dissolution rate enhancement techniques such as co-grinding with an anionic surfactant and pH adjustment.

MATERIALS AND METHODS

Materials

Glibenclamide (MahbanChemi Co., Iran), cellulose acetate with 40% acetyl groups (Fluka, Switzerland) as a film former polymer (SPM), hydroxypropyl methylcellulose (HPMC) (E15LV) (Colorcon, England) as a water-swellable polymer and gelling agent, polyethylene glycol (PEG) 200, glycerol and castor oil (Merck, Germany) as a plasticizer and Avicel PH101 (Blanver, Korea) as compressibility and compactibility enhancer were used in the present study. Other materials such as acetone, ethanol, talc, sucrose, lactose and Sodium lauryl sulphate (SLS) were purchased from Merck (Germany). Sucrose was applied as an osmotically active agent in core tablet formulation and as a pore former in SPM structure. Calcium carbonate was purchased from Honeywell (Germany).

Preparation of core tablets of osmotic systems

Core tablet of the base formulation was prepared by mixing all ingredients thoroughly for 10 min using a mortar and pestle. Then the mixture was compressed into convex tablets using a single punch tablet press (Korsch, Germany) with 9 mm diameter oval biconvex punches. Co-grinding formulations were prepared by adding glibenclamide and lactose (1:30) (the amount of lactose was kept constant in all formulations) or SLS (the ratio of drug: SLS was 1:1, 1:2 and 1:5) and grinding them in a ball mill (Retsch® PM100, Germany) in 12.5ml chamber containing 5 balls with 10 mm diameters. The total hours for the grinding were 3h at 350 rpm, but at 10min intervals the ball mill was stopped for 10min to cool the sample down to avoid any stability issue.

Then co-ground powders along with other core ingredients were mixed thoroughly for 10 min by mortar and pestle. Then the mixture was compressed into convex tablets using a single punch tablet press as described above.

The final weight of each tablet was kept constant at 520 mg in order to keep the volume and surface area of tablets constant. All of the core formulations contained 10 mg glibenclamide (Gli). The hardness of all prepared tablets was adjusted in the range of 6-7 Strong Cobb.

Coating of core tablets

Coating suspension containing cellulose acetate, castor oil, glycerol, PEG200 and nano-sized sucrose suspended in acetone/ethanol (90: 10) were mixed in a ball-mill. The mentioned mixture was used for coating of the prepared core tablets employing dip coating technique.

Nano-suspension of pore former (sucrose) was prepared by adding 2g sucrose to 10ml ethanol and grinding them in a ball-mill in 25ml chamber containing 8 balls with 10 mm diameter as described above. The cores fixed with micro-drill were floated into coating suspension for 5 s and slowly rotated horizontally followed by drying at room temperature. This step was repeated a number of times until the intended membrane thickness (125±10 μm) was achieved. The same condition was maintained during the coating of all tablets and thickness of the membrane was periodically checked using digital micrometre (Mitotoyo, Japan) with a high accuracy (0.001mm). Cellulose acetate (6 g) and plasticizers namely castor oil (3 %w/v), glycerol (4%w/v) and PEG200 (4 %w/v) were dissolved in 100ml of coating liquid. The nano-suspension of sucrose (4% w/v) was added to the liquid coating as the pore former. During dip coating process the coating suspension was continuously stirred in order to maintain a good uniformity of the particles in the suspension. The core and SPM compositions for different formulations were summarised in table 1.

Particle size analysis

The particle size of un-ground glibenclamide (original drug) and co-ground glibenclamide dispersed in water were measured using laser particle size analyser (SALD-2120, Shimadzu-Japan) and the results are shown in fig. 1.

Solubility studies

In order to measure the solubility of glibenclamide in co-ground formulations, the co-ground formulations containing glibenclamide were added to the buffer where after 24h shaking at 25°C under constant vibration the solid particles of the drug is still visible. The samples were subjected to centrifugation for 20 min at 10000 rpm for UV analysis at a wavelength of 299.8. The experiment was repeated three times to obtain means and standard deviations. The preliminary results showed that 24h shaking was enough to reach an equilibrium condition.

In vitro release test

In vitro release studies were carried out using a dissolution apparatus II paddle method (Erweka DT-6 R, Germany), set at 50±2 rpm (rotating speed) and in 900 mL phosphate buffer at pH 8.5 (6.8g of monobasic

Table 1: Core composition of different formulations (all formulations contained 10 mg glibenclamide)

Formulation code	Core composition (mg)					
	HPMC	Lactose	Sucrose	SLS	Calcium carbonate	Talc
Base formulation	10	300	100	-	-	100
Gli-Lac	10	300	100	-	-	100
SLS1	10	300	100	10	-	90
SLS2	10	300	100	20	-	80
SLS5	10	300	100	50	-	50
SLS1-C	10	300	100	10	50	40
SLS2-C	10	300	100	20	50	30
SLS5-C	10	300	100	50	50	-

Table 2: Size of drug in different formulations

Formulation	Mean Size	D10%	D50%	D90%
Original drug	16.46 µm	3.79µm	20.40 µm	56.78 µm
Gli-Lac	558 nm	367 nm	518 nm	928 nm
SLS1	537 nm	359 nm	497 nm	874 nm
SLS2	511 nm	333 nm	474 nm	875 nm
SLS5	515 nm	341 nm	477 nm	816 nm

Table 3: Obtained results from Glibenclamide solubility tests in buffer (Each sample contained 10 mg glibenclamide in 20ml buffer)

Sample	pH*	Solubility (mg/ml)	Solubility enhancement ratio
Pure glibenclamide (Original Drug)	---	0.053	-
Gli-Lac	---	0.078	1.47
SLS1	7.76	0.073	1.38
SLS2	8.08	0.127	2.40
SLS5	8.90	0.128	2.42
SLS1-C	9.04	0.121	2.28
SLS2-C	9.53	0.154	2.91
SLS5-C	9.91	0.159	3.00
Distilled water	7.41	---	---

* pH value of 20 ml water in presence of co-ground formulations containing 10 mg glibenclamide.

potassium phosphate and 1.99g of sodium hydroxide in 1 L of water, adjusted with diluted phosphoric acid or sodium hydroxide to a pH of 8.5±0.05). The dissolution medium was maintained at 37±0.1°C during the dissolution run. At appropriate time intervals (0.5, 1, 2, 4, 8, 12, 24 hours) the samples were withdrawn and the dissolution medium was replaced by the same volume of a fresh dissolution fluid to maintain the volume of the dissolution constant. The samples after centrifugation for 20 min at 10000 rpm were analyzed at 299 nm using UV/visible spectrophotometer. The mean of three determinations was used to calculate the drug release from each formulation.

Mathematical treatments

As the main aim of the formulations was achieving zero-order kinetics and the ability to release most of the drug within the specified time, therefore, to this end, D_{24h} (percent of the drug released within 24 h), t_L (lag time of the drug release from device), RSQ_{zero} (R square of release data fitted to zero order equation) and release rate were calculated and used to evaluate the performance of the formulations. The lag time is the required time to reach steady state drug release from osmotic devices. Negative lag time is considered as burst release of the drug from the system.

RESULTS

As the particle size is important in the design of COPO, the particle size distribution of the components was determined and shown in Figure 1. In addition, their D10, D50 and D90% were also calculated and listed in Table 2. The table shows that the average particle size was around 500 nm.

Table 3 shows the effect of SLS concentration (20, 40 and 100 mg of SLS in 20 ml distilled water) in solid dispersion formulations in the absence or presence of 100 mg calcium carbonate (SLS1-C, SLS2-C and SLS3-C) on pH of distilled water. The results showed that generally, high pH enhanced the solubility of glibenclamide.

Table 4: Comparative parameters of formulations

Core formulation	RSQ_{zero}	D_{24h} (%)	t_L (h)	Release rate (mg/h)
Base Formulation	0.77	15.69	-8.68	0.65
Gli-Lactose	0.72	18.10	-9.35	0.75
SLS1	0.75	17.81	-10.28	0.73
SLS2	0.83	28.98	-6.86	1.21
SLS5	0.96	49.04	-4.52	2.04
SLS1-C	0.83	20.30	-7.89	0.85
SLS2-C	0.88	36.71	-1.76	1.53
SLS5-C	0.95	68.15	-3.1	2.84

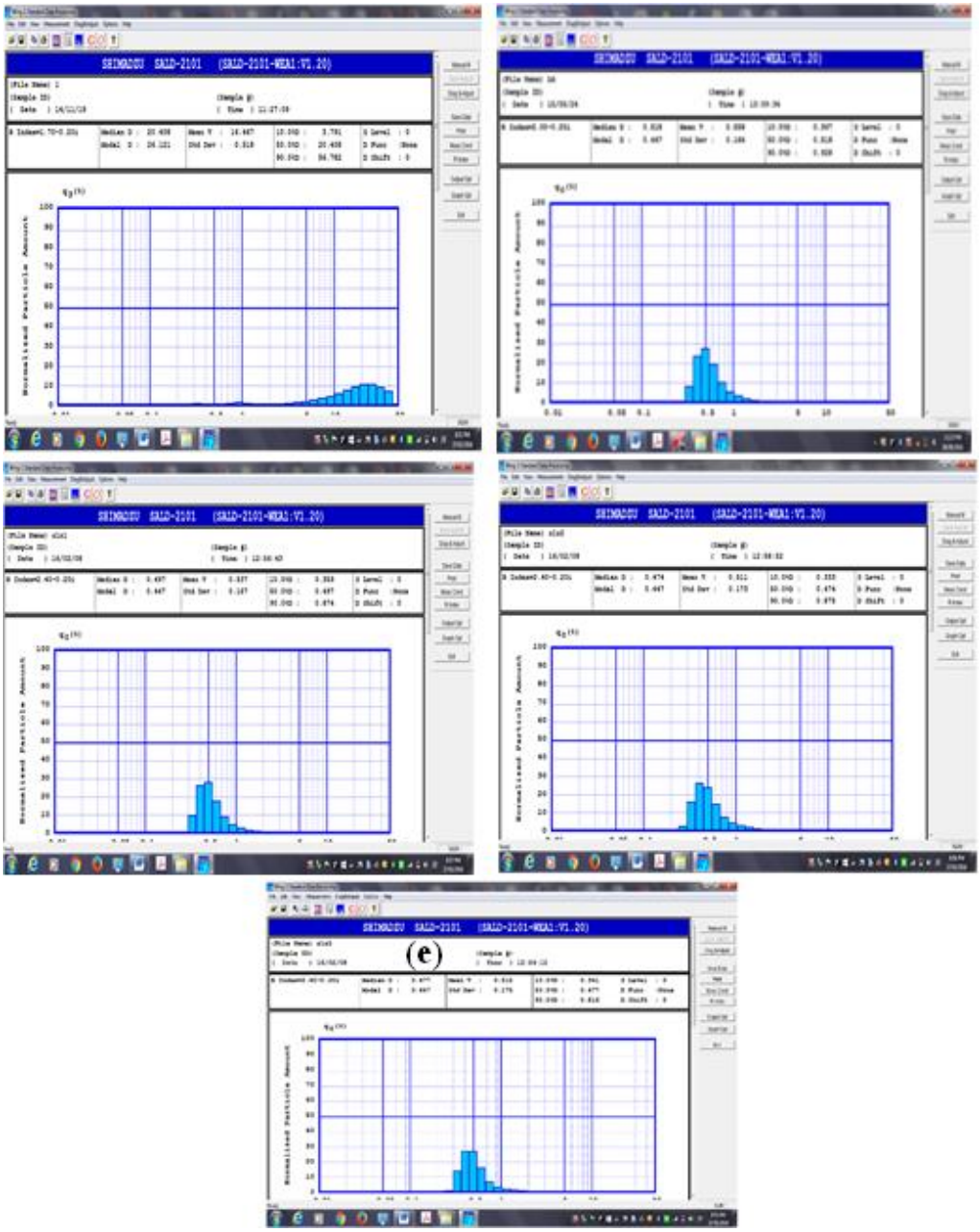

Fig. 1: a) size of pure glibenclamide (original drug), b: size of glibenclamide in Gli-Lac co-grinding, c: size of glibenclamide in SLS1 Co-grinding, d: size of glibenclamide in SLS2 co-grinding and e: size of glibenclamide in SLS5 co-grinding.

Figure 2 shows that the dissolution profiles of co-ground of glibenclamide-lactose used in the core formulation improved dissolution rate compared to the base formulation. As shown in fig. 3, by adding SLS to the core formulation the dissolution rate was further enhanced compared to the base formulation. The present research also investigated the effect of an alkaline agent (calcium carbonate) on glibenclamide release profile (Figure 5). It shows that the presence of calcium carbonate changed the release profiles (fig. 3) and also the solubility of the API (table 3).

DISCUSSION

Particle size analysis

Based on the particle size results, co-grinding of the drug in ball-mill resulted in glibenclamide size reduction from micronized range to nano-scale (fig. 1). The results of particle size analysis exhibited that there was no significant difference in the size of particles between all ground formulations and the average particle size was around 500 nanometers (table 2).

On the basis of the Ostwald-Freundlich (equation 1), size reduction can have a positive effect on the solubility of the particles when it falls below 1 micron (Muller and Peter 1998). Therefore, it is expected the higher amount of drug solubility and dissolution rate from glibenclamide-lactose co-ground containing nano-sized drug compared to the base formulation containing micronized glibenclamide (around 16 micrometres).

According to the Ostwald- Freundlich equation:

logCs/C= 2sV/2.303RTrr (eq. 1)

where:

Cs = solubility

C = solubility of the solid consisting of large particles

S = interfacial tension substance

V_= molar volume of the particle material

R = gas constant

T = absolute temperature

R = density of the solid

R = radius.

Effect of pH and solubility studies

The pH results showed that both SLS and calcium carbonate have alkaline property and they were able to increase the pH value of water leads to a better solubility of glibenclamide in these media compared to acidic condition. Glibenclamide as a weak acid with a pKa of 5.3 is expected to have pH-dependent solubility (Wei and Lobenberg 2006). Therefore, it is important to investigate the effect of pH on the solubility of the drug.

As shown in table 3, the solubility of glibenclamide before and after co-grinding by lactose increased from 0.053 to 0.078 mg/ml. When SLS was incorporated with different concentrations the solubility of the drug was further improved reaching 0.128mg/ml (solubility enhancement ratio around 2.5) at the highest concentration of SLS (ratio of drug: SLS 1: 5). These results are expected as SLS is able to increase the pH of the medium leading to a better solubility at higher pH. As the drug is a weak acid it was decided to incorporate a basic agent such as calcium carbonate for further improvement in the solubility. The data showed that the solubility of glibenclamide increased in the presence of calcium carbonate particularly when the ratio of drug: calcium carbonate was 1:5 showing the highest solubility enhancement (3-fold) compared to other formulations. The highest enhancement ratio was obtained for the formulation ground with calcium carbonate with a ratio of drug: calcium carbonate 1:5 (SLS5-C).

Effect of core formulation on drug release from osmotic systems

The improvement in the dissolution of API-lactose could be attributed to the size reduction of glibenclamide from 16.46 µm (in the base formulation) to 558 nanometers (in the co-ground formulation) which led to the higher solubility based on Ostwald-Freundlich equation (see table 3 for the solubility data). This, in turn, led to the enhanced dissolution according to Noyes & Whitney equation (Noyes and Whitney 1897). Table 3 also shows that the Improvement in D_{24h} was greater than SLS1 formulation but less than other formulations.

In the core formulations, SLS acts as a solubilising agent leads to solubility enhancement of the drug. By increasing the amount of SLS in the formulation more SLS micelles are formed in the dissolution medium around the drug particles. These micelles are able to dissolve more drugs leading to solubility enhancement. The dissolution profile revealed that lower D_{24h} belonged to SLS1 formulation among other SLS co-ground formulations. By increasing the SLS level to 2 and 5 folds, D_{24h} increased from 17.81% to 28.98% and 49.04% respectively, whereas the enhancement in D_{24h} in SLS5 was greater than SLS2 in spite of approximately showing similar solubility enhancement ratios. This can be described by other properties of SLS such as wettability. SLS, as an anionic surfactant, possess high wetting ability which can prevent the particle agglomeration and decrease the surface tension between drug particles and the dissolution medium .Therefore, undissolved nanocrystals can also release via nanopores and dissolve in the dissolution medium. The other reasons for the higher drug release by adding further SLS in the core formulation can be related to its ionisation ability when it contacts with water and producing an additional internal osmotic pressure. SLS as an osmotic agent was also employed in the design of swellable controlled porosity osmotic pump by Rao and coworkers (Rao *et al.,* 2009). This additional pressure pushes more drug out of the system. The final reason to enhance the drug release is the alkaline nature of SLS in

water which enhanced the solubility of glibenclamide inside the system by increasing pH of the surrounding area of the drug based on table 3.

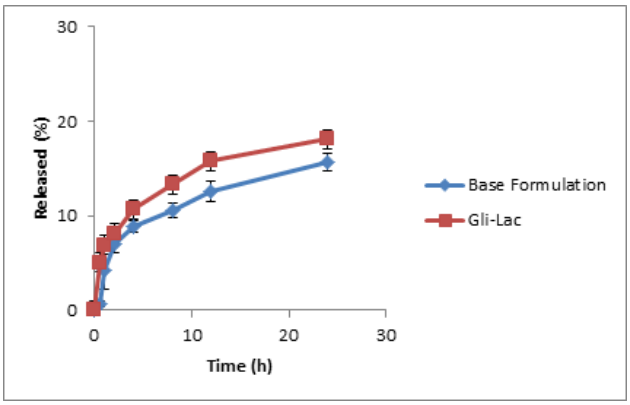

Fig. 2: Effect of size reduction on glibenclamide release profile from base and formulations containing lactose.

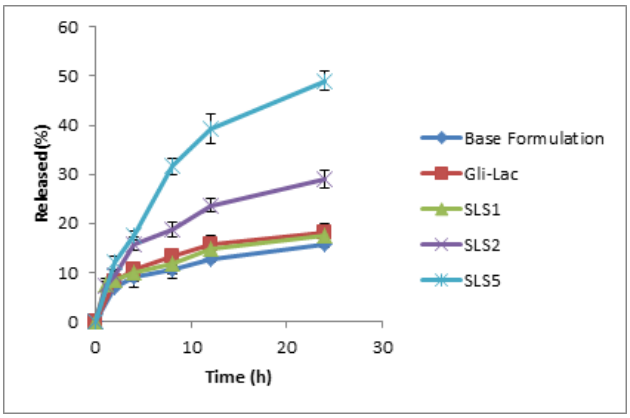

Fig. 3: Effect of co-grinding on the dissolution of glibenclamide containing different concentrations of SLS.

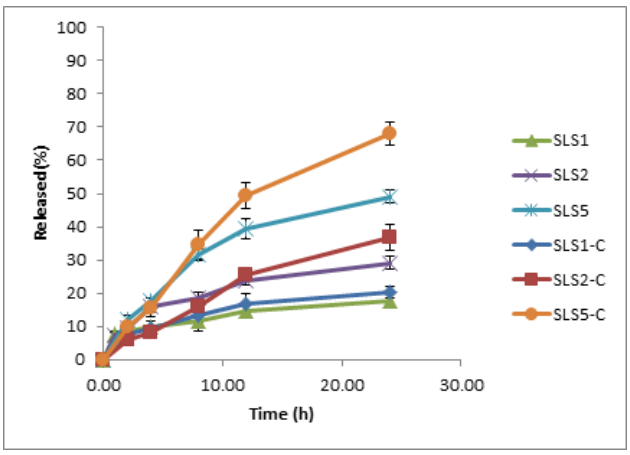

Fig. 4: Effect of the alkaline agent (calcium carbonate) on glibenclamide release profile.

In next step, the effect of another alkaline agent (calcium carbonate) in core formulation was evaluated. pH results showed that calcium carbonate can increase the pH value of the formulations up to 9.91 (table 3). It was shown that the solubility values of the formulations containing calcium carbonate increased up to 3 times (table 3) leading to an increase in D_{24h} for SLS2-C and SLS5-C (3-fold, see table 4) compared to formulations without calcium carbonate (SLS2 and SLS5). Apart from the solubility enhancement, the reason for such a big enhancement in D_{24h} could be contributed to higher internal pressure in these systems resulted by calcium carbonate as osmotic agent leading to higher drug release rate. This effect is more obvious in SLS5-C.

Among all formulations, SLS5-C exhibited higher D_{24h}. Although the acceptable D_{24h} is considered higher than 75% in osmotic systems, in the case of glibenclamide which is a poorly water-soluble drug, achieving 68% release is a great success in novel nano-porous CPOP, whereas this was not possible in conventional osmotic pumps when a poorly water-soluble drug was used. All formulations had negative lag time which indicates the burst release of glibenclamide from Designed CPOPs (table 4).

Table 4 also shows that SLS5-C shows near zero-order release pattern compared to the other formulations in the present study. This is interesting to see that not only SLS5-C shows faster release but also showing zero-order release pattern compared to the base formulation.

CONCLUSION

Solubility mediated core formulation in nano-porous CPOPs for the water-insoluble agent was developed and the effect of various formulations was evaluated. The results revealed that using novel CPOP it was possible to increase D_{24h} and achieved zero-order release pattern if the concentration of SLS and calcium carbonate in the core formulation was optimised. The improved release parameters can be achieved by implementation of various strategies including size reduction to nanoscale, pH adjustment inside the system, the presence of different concentrations of SLS and calcium carbonate. The latter two factors can increase the wettability and the solubility of the drug in the core formulations during the dissolution process.

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