academicJournals

Vol. 13(50), pp. 4568-4576, 10 December, 2014
DOI: 10.5897/AJB2014.13977
Article Number: 0127F1448978
ISSN 1684-5315

http://www.academicjournals.org/AJB

African Journal of Biotechnology

Full Length Research Paper

Novel carrier system for enhancing oral delivery of metformin

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Received 10 June, 2014; Accepted 2 December, 2014

This study was designed to evaluate the potential of PEGylated lipospheres as carriers for improved oral delivery of metformin hydrochloride. Lipospheres were prepared by melt-emulsification method using Phospholipon® 90H in beeswax (30%w/w) as the lipid matrix containing increasing quantities of PEG 4000 and characterized. The *in vitro* and *in vivo* release of the formulations was evaluated. Results show that the particle size and encapsulation efficiency ranged from 33.18±1.75 - 83.23±6.05 µm and 85 to 93%, respectively. Drug release showed a biphasic pattern and was found to follow the Higuchi square root model. Metformin hydrochloride -loaded lipospheres lowered basal blood glucose levels by 60% and sustained antihyperglycemia for over 20 h. This study suggests that encapsulation of metformin hydrochloride into PEGylated lipospheres could reduce its dosing frequency and the associated side effects resulting from high doses of metformin hydrochloride as seen in conventional tablet formulations.

Key words: PEGylated, lipospheres, metformin hydrochloride, anti-diabetic.

INTRODUCTION

The design of an oral controlled drug delivery system should primarily be aimed at achieving more predictable and increased bioavailability of drugs as there are several physiological difficulties, which include restraining/-localizing the drug delivery system within the regions of the gastrointestinal tract and the high variable nature of gastric emptying process (Prajapati et al., 2008). Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentration caused by insulin deficiency, often combined with insulin resistance (Philip et al., 2009). The effective control of blood glucose is the key in preventing or reversing diabetic complications and improving the quality of life for both type I and type II diabetic patients. Although different

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types of oral hypoglycemic agents are commonly employed along with insulin for the treatment of diabetes mellitus, none offers complete glycemic control (Pradeep, et al., 2010).

Metformin HCl is an effective antidiabetic that requires controlled release owing to its short biological half-life (1.5-4 h) (Stepensky et al., 2001; Momoh et al., 2011). It is used as monotherapy as well as an adjunct to diet in the management of type II diabetes in patients whose hyperglycemia cannot be controlled by diet alone. Quite frequently, it causes gastrointestinal problems such as nausea, stomach pain, bloating, and diarrhoea. Metformin hydrochloride is absorbed from the upper intestine within 6 h of administration, so repeated administration is required to maintain effective plasma concentration (Momoh et al., 2013).

Lipospheres were first reported as a particulate dispersion of solid spherical particles between 0.2-100 µm in diameter consisting of solid hydrophobic fat core such as triglycerides or fatty acids derivatives, stabilized by monolayer of phospholipids (Attama et al., 2008, 2009). The internal core contains the drug dissolved or dispersed in solid fat matrix. Lipospheres drug delivery system is an emerging carrier for both hydrophilic and hydrophobic drugs. This carrier system has several advantages over other delivery systems in terms of physical stability, low cost of ingredients, ease of preparation, and scale-up, high dispensability in aqueous medium, high entrapment efficiency, and extended release of entrapped drug (Attama et al., 2009). The novelty of the work lies on the use of beeswax and Phospholipon® 90H (a homo and hetero lipid) in combination with polyvinyl alcohol to improve and enhanced the oral delivery of metformin entrapped lipospheres prepared by fusion method. Recently, lipid-based formulations have been used to control and enhance the release of some drug molecules (Attama et al., 2009; Attama and Nkemnele, 2005). Fusion method enhances the encapsulation of the drug in the core and improves its delivery capacity when in contact with the wall of the gastrointestinal tract (Attama et al., 2009; Philip et al., 2009). The prepared lipospheres were evaluated for production yield, loading efficiency, morphology, particle size, pH analysis, and *in vitro* drug release. The anti-diabetic property of the formulations was also evaluated in alloxan-induced rat model.

The objective of this study was to evaluate metformin hydrochloride-loaded lipospheres prepared by fusion method for possible oral delivery of metformin, in order to achieve a controlled release and enhanced bioavailability.

MATERIALS AND METHODS

Materials

The following materials were used: Beeswax, Phospholipon® 90H (Nattermann, Germany), Polyvinylalcohol (Sigma-Aldrich, USA), polyethylene glycol 4000 (Cary Roth, Karlsruhe, Germany), Metformin hydrochloride (Farmex, Pharma Ltd, Ikeja, Lagos State, Nigeria), Monobasic potassium phosphate, Sodium hydroxide and Concentrated hydrochloric (BDH, Poole, England), and Distilled water (Lion Water, University of Nigeria, Nsukka, Nigeria). Other reagents were of analytical grade and used without further purification.

Preparation of lipid matrix

The lipid matrix consisting of 4:1 mixture of beeswax and Phospholipon® 90H (P90H) were prepared by fusion method (Attama et al., 2008). Briefly, 80 g quantity of beeswax and 20 g of P90H were weighed using an electronic balance (Mettler H8, Switzerland) and melted together on a crucible at 75°C over a thermo-regulated shaking water bath (Heto, Denmark) and stirred thoroughly to obtain a homogenous mixture. Thereafter, the lipids were allowed to cool and solidify at room temperature to get a lipid matrix.

Preparation of drug loaded and unloaded lipospheres

The melt homogenization technique was adopted (Attama et al., 2008). In each case, the lipid matrix was melted at 70°C, and the aqueous phase containing PEG-4000 and polyvinyl alcohol (PVA) at the same temperature was added to the molten lipid matrix under gentle stirring with a magnetic stirrer (SR 1 UM 52188, Remi Equip., India), and the mixture was further dispersed with a mixer (Ultra-Turrax, Germany) at 8000 rpm for 5 min to produce the hot primary emulsion. The lipospheres suspension obtained after cooling at room temperature was then lyophilized using a freeze-dryer (Amsco GT3, Germany) in order to get water-free lipospheres. Briefly, lyophilisates of the SLMs are obtained by freezing the formulations at a pressure of 2.7 Pa and temperature of 30°C; sublimation and drying were at 15-25°C and all these operations took 6-12 h.

The above procedure was repeated using increasing amount of PEG, (0.5, 1.0, 1.5 and 2.0 g), decreasing amount of lipid matrix; (4.5, 4.0, 3.5 and 3.0 g) and two concentration levels of metformin hydrochloride (250 and 500 mg), to obtain metformin hydrochloride-loaded lipospheres (batches A_1 - A_4 and B_1 - B_4). Unloaded lipospheres (without drug) were similarly prepared (C_1 - C_4). The formulation compositions are shown in Table 1.

Characterization of lipospheres

Particle size analysis and morphological characteristics of lipospheres

The particle size of the lipospheres was determined by computerized image analysis. Approximately, 3.0 mg of the lipospheres from each batch was dispersed in distilled water and smeared on a slide (Marinfield, Germany) using a glass rod. Each of the batches on a slide was mounted and observed under a light photo-microscope (Lieca, Germany). With the aid of the software in the photomicroscope, the projected diameters of the particles corresponding to the particle sizes of the lipospheres were determined and the average calculated. The particle morphologies were also observed and photomicrographs taken. Measurement of particle size of the formulated lipospheres was repeated at intervals of 24 h, one week and four weeks after formulation.

pH stability studies of the formulations

With the aid of a pH meter (Digital pH Meter, Labtech), the pH values of the different batches of the lipospheres formulations

Table 1. Formulation compositions of the lipospheres.

Batch	PEG-4000	Polyvinylalcohol (PVA)	Metformin HCl	Lipid matrix (g)
A_1	0.5	100	500	4.5
A_2	1.0	100	500	4.0
A_3	1.5	100	500	3.5
A_4	2.0	100	500	3.0
B_1	0.5	100	250	4.5
B_2	1.0	100	250	4.0
B_3	1.5	100	250	3.5
B_4	2.0	100	250	3.0
C_1	0.5	100	-	4.5
C_2	1.0	100	-	4.0
C_3	1.5	100	-	3.5
C_4	2.0	100	-	3.0

Batches A_1 - A_4 and B_1 - B_4 contain metformin hydrochloride whereas batches C_1 - C_4 contain no drug.

including those of the control were measured. Measurements were also carried out at one week intervals for one month post-formulation.

Determination of encapsulation efficiency (EE %)

The encapsulation efficiency of each formulation was determined. A 6 ml volume each of the reconstituted lipospheres was centrifuged for 60 min at an optimized speed of 3000 rpm in order to obtain two phases (aqueous and lipid phases). A 1 ml volume of the aqueous phase was measured out and diluted 1000-fold using distilled water. The absorbance of the solutions at a wavelength of 278 nm, were taken using a UV-spectrometer and the encapsulation efficiency was calculated using the formula below:

$$EE\% = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad (1)$$

Determination of loading capacity (LC)

LC is expressed as the ratio between the entrapped drug by the lipid and the total quantity of lipids used in the formulation and calculated as follows:

$$LC = \frac{\text{Total quantity of drug entrapped by the lipid}}{\text{Total quantity of the lipid in the formulation}} \times 100 \quad (2)$$

***In vitro* drug release studies**

A volume (4.0 ml) of the reconstituted lipospheres from each batch was accurately measured and placed in the donor compartment of a Franz diffusion cell that was separated from the receptor compartment by an artificial membrane (pore size 0.22 µm). The receptor compartment was filled with simulated intestinal fluids (SIF) without pancreatin (pH 7.4) and maintained at a temperature of 37±1°C by means of a thermostatically controlled water bath, with agitation being provided by a magnetic stirring bar at 50 rpm. A 2.0 ml was removed and replaced by an equal volume of the receptor phase at predetermined time intervals. The drug contents were analyzed using a spectrophotometer at a wavelength of 283 nm. The amount of drug released at each time interval was determined with reference to the standard Beer's plot earlier determined for metformin hydrochloride in SIF.

Pharmacodynamic study

Induction of diabetes

The animal experiments in this work complied with the regulations of the Committee on Ethics on the Use of Laboratory Animals of the University of Nigeria and were in compliance with the Federation of European Laboratory Animal Science Association and the European Community Council Directive of November 24, 1986 (86/609/EEC) (EEC, 1986). Rats weighing between 200 - 220 g were purchased from the Department of Biochemistry, University of Nigeria, Nsukka. The rats were all kept in standard and conditioned animal cages and left for one week to acclimatize to the new laboratory environment while being fed with standard laboratory chow diet. Diabetes was induced by intravenous injection of Alloxan dissolved in normal saline through the marginal ear vein at a dose of 120 mg/kg (Builders et al., 2008). After 5-7 days of the Alloxan treatment, rats with frequent urination, loss of weight, and blood glucose levels higher than 220 mg/dL were considered diabetic and selected for the study (Builders et al., 2008). The rats were monitored for persistent blood glucose elevation for 5 days (Sharma et al., 2006). Before testing, animals were fasted overnight with free access to water.

***In vivo* antidiabetic study**

Twenty five (25) Wistar rats (either sex) of an average weight of 200.0±20.0 g were used for the evaluation of the pharmacological effects of metformin hydrochloride-loaded lipospheres after oral administration. In each case, the animals were fasted for 24 h prior to oral administration of the formulations. Rats were divided into five groups of five animals each and the formulations were administered orally. Briefly, the first group received Batch A_1 containing metformin hydrochloride-loaded lipospheres at a dose of 7 mg/kg body weight. The second group received Batch B_1 also containing metformin hydrochloride-loaded lipospheres at a dose of 0.7 mg/kg body weight. Whereas the third group received Batch C_1 (zero-drug loaded liposphere formulation), the fourth group received a

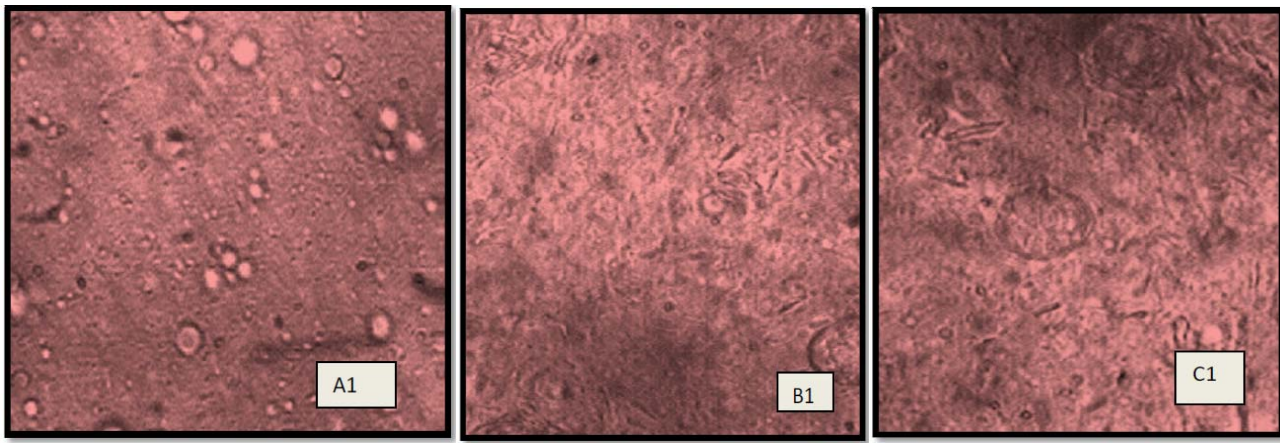

Figure 1. Photomicrographs of representative batches of lipospheres containing 10% w/w PEG 4000 after 1 month. A_1, B_1, and C_1 contain 500, 250 and 0 mg of metformin hydrochloride, respectively.

Table 2. Time-resolved pH-dependent storage study of the lipospheres (Mean±SD, *n* = 3).

Batch	1 week	2 weeks	3 weeks	4 weeks
A_1	4.6±0.1	4.6±0.4	5.0±0.4	5.5±0.3
A_2	4.6±0.2	4.6±0.3	5.0±0.3	5.3±0.3
A_3	4.5±0.1	4.6±0.2	5.5±0.4	5.6±0.4
A_4	4.5±0.3	4.7±0.4	5.2±0.1	5.4±0.2
B_1	4.5±0.2	4.5±0.2	5.3±0.2	5.2±0.1
B_2	4.2±0.1	4.3±0.3	4.7±0.4	4.9±0.0
B_3	4.1±0.1	4.4±0.1	4.8±0.3	5.1±0.4
B_4	4.4±0.3	4.6±0.2	5.2±0.1	5.3±0.3
C_1	4.0±0.4	4.6±0.1	4.7±0.1	4.8±0.2
C_2	3.5±0.2	4.6±0.3	4.6±0.2	4.7±0.2
C_3	3.6±0.2	4.6±0.1	4.7±0.2	4.8±0.1
C_4	3.7±0.2	4.6±0.1	4.7±0.3	4.9±0.1

Batches A_1 - A_4 and B_1 - B_4 contain 500 and 250 mg of metformin hydrochloride respectively, while batches C_1 - C_4 contain no drug.

commercially available metformin hydrochloride preparation (Mephage®) while the last group received metformin hydrochloride dispersed in distilled water (100 mg p.o). The selected formulations (A_1 and B_1) used in the *in vivo* study were based on the results of our preliminary evaluation. Blood samples were taken from the tip of the tail vein at predetermined intervals and blood glucose levels were measured using an Accu-Check Roach, USA). Food and water intake as well as urine output of the animals were measured and monitored in the course of the study (Sharma et al., 2006).

Statistical data analysis

All experiments were performed in replicates (*n*= 3) using SPSS version 18 for validity of statistical analysis. Results were expressed as mean ± SD and differences between means were considered significant at $p< 0.05$ using the analysis of variance (ANOVA).

RESULTS

The particle size and the representatives of the morphology of the formulated batches of the lipospheres are shown in Figures 1 (A_1, B_1 and C_1) and Table 2. There was a slight variation in the particle size of the lipospheres. The drug-loaded lipospheres showed higher particles size compared to drug-loaded batches. Batches in A, B and C showed an irregular shape, sub-batches A had smooth appearance unlike the rest of the batches. However after a period of storage there was slight increase in the particle size of the formulation, although the changes in the size did not altered the shape.

Time-dependent pH analysis

Time-dependent pH analysis was carried out to determine the pH stability of the different batches of the SLMs when stored at room temperature and at different time intervals. Table 2 shows the pH values of the various batches of the metformin hydrochloride-loaded and

Table 3. Physicochemical properties of the lipospheres (Mean±SD, n=3).

BC	EE(%)	DL%	YD%	Particles size (µm)		
				24 h	1 week	4 weeks
A_1	92.46	39.31	88.00	53.11±1.1	61.11±0.15	73.00±0.12
A_2	90.14	30.13	79.10	49.01±0.2	57.42±0.12	69.80±1.11
A_3	86.60	31.02	86.11	54.19±0.11	61.10±0.15	65.20±1.15
A_4	85.50	32.47	88.20	51.87±3.01	53.01±1.15	67.22±0.00
B_1	84.93	24.51	90.10	52.12±0.13	53.17±1.22	59.21±0.05
B_2	83.19	24.91	79.00	55.11±3.75	60.21±1.00	63.23±1.11
B_3	68.70	24.68	74.10	62.08±3.75	65.20±0.00	74.00±3.75
B_4	65.22	25.15	80.01	56.01±3.75	61.11±0.15	62.23±0.30
C_1	-	-	89.13	54.03±5.65	57.00±1.43	63.27±2.63
C_2	-	-	86.21	33.18±1.75	59.20±3.75	73.21±0.15
C_3	-	-	88.81	43.23±0.12	63.02±0.25	81.21±5.25
C_4	-	-	82.03	52.22±1.85	72.11±2.15	83.23±6.05

BC = Batch code; EE = % encapsulation efficiency; D L = % drug loading and % yield value. Batches A_1 - A_4 and B_1 - B_4 contain 500 and 250 mg of metformin hydrochloride while batches C_1 - C_4 contain no drug (0 mg).

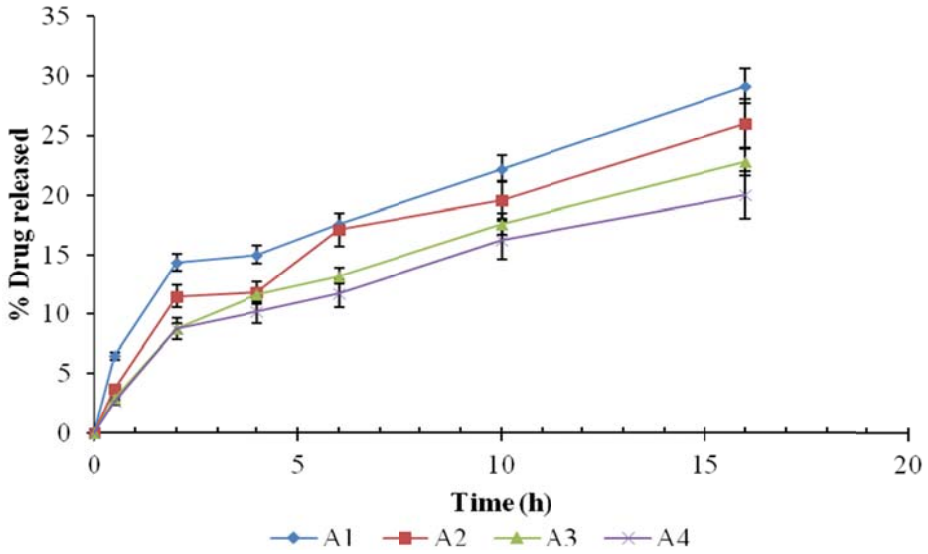

Figure 2. Release profile of metformin HCl from the lipospheres (Batch A) in SIF. (A_1-A_4= batches of the formulation contain 500 mg of metformin hydrochloride.

unloaded lipospheres. The pH varied from between 3.5 to 4.6 after one week of preparation to between 4.7 and 5.6 after four weeks of preparation, while the unloaded lipospheres (C_1-C_4) recorded the highest variation in pH after four weeks of formulation. Results revealed that the EE % decreased as the amount of polymer (PEG-4000) in the lipid matrix increased.

In other words, EE % decreased as the lipid base decreased (Table 3) but increased with increase in the concentration of the drug such that the maximum EE % was 92.58% for lipospheres (batches A) containing 500 mg of metformin hydrochloride, as compared to 84.93% recorded for lipospheres (batches B) containing 250 mg of the drug (Table 3).

In vitro drug release studies

Figures 2 and 3 show the *in vitro* release profiles of different batches of the metformin hydrochloride-loaded lipospheres in SIF. There was an initial release of about 15-20% of drug from the metformin hydrochloride-loaded lipospheres within the first 0.5 to 1 h. Drug release from the formulations was sustained for up to 20 h with only

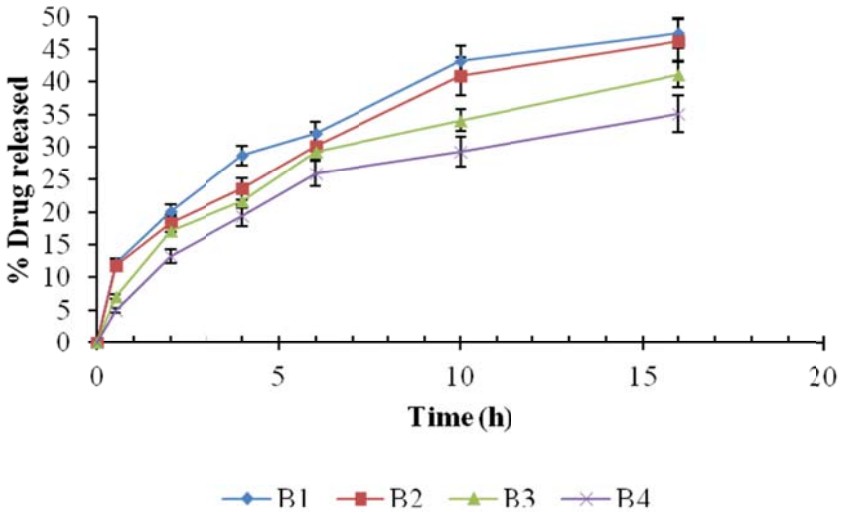

Figure 3. Release profile of metformin HCl from the lipospheres (Batch B) in SIF. (B_1-B_4= batches of the formulation contain 250 mg of metformin hydrochloride.

Table 4. Release kinetics of the lipospheres.

Formulation code	Higuchi's plot	Korsmeyer-Peppas plot		
	r^2	r^2	(n)	Mechanism of release
A_1	0.947	0.896	0.605	Non-fickian
A_2	0.963	0.880	0.438	Fickian
A_3	0.963	0.898	0.618	Non-fickian
A_4	0.956	0.865	0.603	Non-Fickian
B_1	0.762	0.966	0.475	Fickian
B_2	0.672	0.989	0.451	Fickian
B_3	0.762	0.926	0.578	Non-fickian
B_4	0.779	0.920	0.647	Non-fickian

A_1 - A_4 and B_1 - B_4 = batches of the formulation contain 500 and 250 mg, respectively of metformin hydrochloride.

50% of the metformin hydrochloride being released after 16 h.

Modeling of *in vitro* drug release

The release mechanism for metformin hydrochloride-loaded lipospheres is shown in Table 4. The *in vitro* release profile of metformin hydrochloride from the lipospheres was fitted into the Higuchi equation and the plots showed high linearity ($r^2 > 0.999$).

Pharmacodynamic studies

Figure 4 shows the changes in blood glucose levels after the formulations were administered to diabetic rats. At 7.0 mg/kg body weight, orally delivered metformin hydrochloride-loaded lipospheres lowered basal blood glucose levels in diabetic rats by 60% and sustained hypoglycemia for over 20 h. No reduction in blood glucose levels was observed in rats that received no treatment. Reduction in blood glucose levels was similarly observed in rats that received pure sample of metformin hydrochloride and the commercially available metformin hydrochloride marketed sample (Mephage®). Although, there was sustained antihyperglycemia in all cases, for about 10 h, the hypoglycemic effect was greater in rats that received the PEGylated microscopic lipospheres than those that received the latter (pure sample of metformin hydrochloride and Mephage®). The result here further suggests that the release of metformin hydrochloride from the lipospheres stimulated the release of insulin from the production cell or stimulated the tissue uptake of glucose or both in a controlled manner as was observed in the glucose lowering effect.

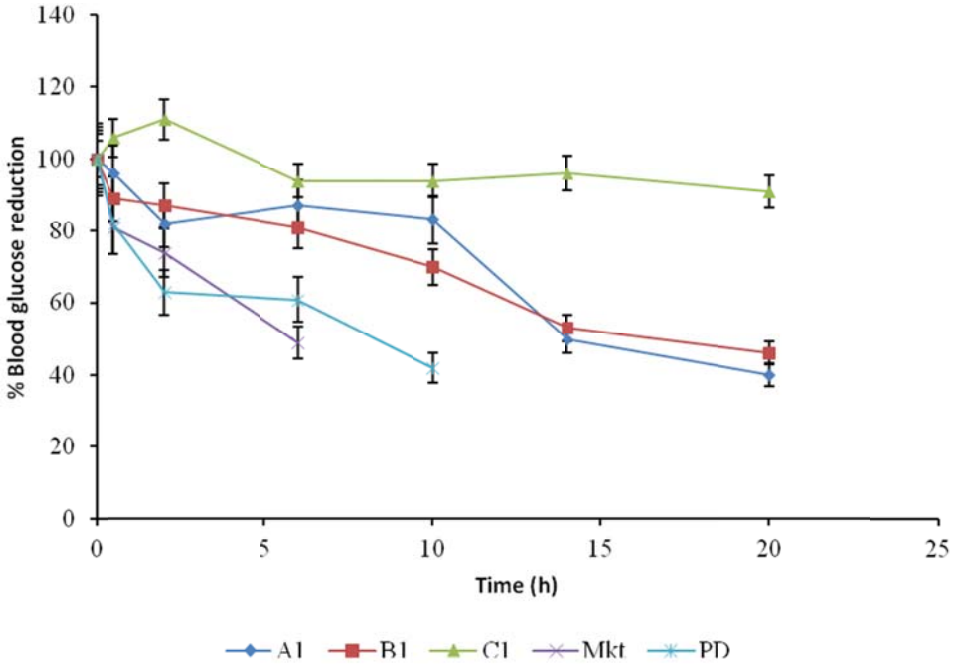

Figure 4. Percentage reduction in blood glucose level in diabetes rats after oral administration of metformin hydrochloride lipospheres formulations (A_1, B_1 and C_1 contain 500, 250 and 0 mg of metformin hydrochloride), Mkt = market sample and PD= Pure drug.

DISCUSSION

In this study, a PEGylated microscopic lipospheres delivery system of metformin hydrochloride was developed and evaluated for enhanced oral delivery of metformin hydrochloride. The lipospheres formed were fairly smooth and spherical in shape, and showed some consistency according to the drug incorporated into the formulation (Figure 1). There were no signs of sedimentation after the formulations stood for a period of 8 weeks. There was a slight increase in the particle sizes after four weeks. The increase in the particle size was directly proportional to the amount of drug entrapped in the formulation. This increase may be due to crystallization of the formerly molten matrices or it may be due to aggregation and subsequent growth by Ostwald ripening or sintering (Attama et al., 2008; Attama et al., 2009). The increase in particle size was not significant ($p>0.05$).

The pH of the different batches of lipospheres was measured at one week intervals up to one month after preparation to ascertain the variation of pH with time, which could be a function of degradation of the drug or lipid component or both. In pharmaceutical formulations, the initial preparation may be stable, but as time goes on, degradation of either the components or the drug or both may set in on storage through generation of unfavorable pH (increase or decrease) or reactive species from the drug.

It is therefore of paramount importance to determine the pH of maximum stability for formulations and utilize the knowledge in designing a suitable formulation for the drug (Sepici, et al., 2004). This will serve as a guide for the formulator on the need of adding a preservative or stabilizer to ensure that a stable product is achieved and maintained throughout the shelf-life of the product. The slight increase in the pH values in all the lipospheres (Table 2) may not be attributable to drug degradation since there was also a rise in the pH of the unloaded lipospheres.

Degradation of the lipidic excipients, common to all the formulated lipospheres, to free fatty acids could occur, causing a fall in the pH of the formulation rather than a rise in pH as was observed in the present study, which is consistent with earlier report (Attama and Nkemnele, 2005), suggesting that it is neither the drug nor the excipients that caused the rise in pH. It would, therefore, be reasonable to infer that the rise in pH is due either to a rise in the particle surface pH or the likely interaction of the ions present in the medium with the components of the formulations (Gao, et al., 2004).

The function of the formulated lipospheres is to deliver the active pharmaceutical ingredient (API) for further absorption into the biological system (Attama et al., 2009; Nnamani et al., 2007). This can be expressed or determined by the EE % and LC. Encapsulation efficiency is a function of the amount of drug entrapped in lipid base to the total weight of drug while the loading capacity expresses the ratio between the entrapped drug and the total weight of lipid used as a carrier (Attama et al., 2009; Nnamani et al., 2007).

Results reveal that the EE % decreased as the amount of polymer (PEG-4000) in the lipid matrix increased. In other words, EE % decreased as the lipid base decreased (Table 3) but increased with increase in the concentration of the drug (Table 3). This showed that the polymer (PEG-4000) together with the lipid matrix promoted drug solubilization in a concentration-dependent manner. The lipid matrix accommodated more drugs at higher drug loadings possibly due to the low crystalline nature of the excipients. The variation in the EE % as shown in Table 3 is a clear indication that both the lipid and PEG contents are critical variables in the amount of drug that could be entrapped by the formulated lipospheres.

Loading capacity, however, increased as the amount of polymer (PEG-4000) increased and as the amount of the lipid matrix decreased. Batches A lipospheres recorded greater loading capacity than Batches in B lipospheres (Table 3). The presence of PEG-4000 in the lipospheres batches A_1-A_4, B_1-B_4 and C_1-C_4 was found to be essential in obtaining spherical particles (Figures not shown). The yields of the lipospheres suggested that the processing parameters and the fusion method employed in the preparation of the liposphere did not affect the yield, thus making the process up scalable and this could be of commercial interest.

The particle size of lipospheres (C_1-C_4) containing no API but formulated with 10 % of PEG were slightly larger than those formulated with 30% PEG-4000. The particle size and morphology of metformin hydrochloride - loaded lipospheres are shown in Table 3 and Figures1, respectively.

Drug release is affected by the nature or design of the delivery system and the medium used in the release study. Factors such as pH are among the most important factors affecting drug release. Other factors such as viscosity and gastro intestinal motility affect the *in vivo* release of drugs while *in vitro* release is affected by agitation, viscosity and temperature of the medium, stirring speed of the apparatus used in the release study. Figures 2 and 3 show the *in vitro* release profiles of different batches of the metformin hydrochloride-loaded lipospheres in SIF. There was an initial release of about 15-20% of drug from the metformin hydrochloride-loaded lipospheres within the first 0.5 to 1 h, which could be attributed to drug desorption from the surface of the lipospheres, of drug particles that were not encapsulated in the lipid core.

Loosely or poorly bound drug is released rapidly while drug entrapped within the polymer matrix (core) is released in a more gradual fashion either through erosion or diffusion. The initial drug release which was observed may be due to unbound drug (Defang et al., 2005; Wang, 2006). Clinically, however, burst release may not always be undesirable especially in conditions such as hyperglycemia where there is urgent need for lowering of blood glucose levels. In such cases, the initial amount of of drug released can serve as a loading dose and the remaining amounts of drug released slowly over time will serve as the maintenance dose. Drug release from the formulations was sustained for up to 20 h with only 50% of the metformin hydrochloride being released after 16 h. This slow phase of drug release is attributable to gradual drug release from the core of the lipid matrices via diffusion-controlled processes (Luan, 2006).

Various kinetics models were used to describe the release of metformin hydrochloride from the liposphere formulations. The criterion for selecting the most appropriate model was chosen on the basis of goodness-of-fit test. The results (Table 4) revealed that diffusion is the likely mechanism of release of metformin hydrochloride from the lipospheres. To confirm that release of the loaded drug occurred through diffusion, the release data were fitted into the Korsmeyer-Peppas equation from which n values ranging between 0.438 and 0.647 were obtained. These values show that release of metformin hydrochloride from batches A_1, B_1 and B_2 followed Fickian diffusion mechanism whereas the mechanism of release in batches A_2, A_3, A_4, B_3 and B_4 was non-Fickian (Ofokansi et al., 2007).

Results of the *in vivo* pharmacodynamic study show that percentage reduction of basal blood glucose levels of 47 and 49% respectively was achieved by the pure sample of metformin hydrochloride dispersed in distilled water and the commercial product (Mephage®). The order of hypoglycemic activity of formulated metformin hydrochloride -loaded lipospheres are batch A_1 > batch B_1 > PD > MK > batch C_1. This shows that batches A1 and B1 possessed greater antihyperglycemic effect than commercially available metformin HCl formulation and pur sample of metformin hydrochloride, an indication that entrapment of metformin hydrochloride into PEGylated lipospheres not only improved its therapeutic effectiveness but also extended its therapeutic action, consistent with a similar reported study (Attama et al., 2009; Nnamani et al., 2007).

Conclusion

In designing a drug delivery device such as those based on polymers or lipids or combinations thereof, the choice as well as the combination ratio of the polymers or lipids or other excipients should be considered based on the desired pattern, route of administration, stability, and other physicochemical considerations. In this research work, metformin hydrochloride-loaded lipospheres were successfully prepared and optimized and evaluated in a diabetic animal model.

Majority of the formulated lipospheres of metformin hydrochloride exhibited better *in vivo* performance than commercially available MT formulation. In the light of the importance of metformin hydrochloride in the management of type II diabetes mellitus, the formulated lipospheres

could further be exploited as an alternative dosage form for metformin hydrochloride. In view of the sustained hypoglycemic effect that was observed in metformin hydrochloride-loaded PEGylated lipospheres, the studied formulation would be a necessary intervention in reducing the dosing frequency of metformin hydrochloride with concomitant reduction in the side effects associated with it.

Conflict of Interests

The author(s) have not declared any conflict of interests.

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