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Research paper

Floating lipid beads for the improvement of bioavailability of poorly soluble basic drugs: *In-vitro* optimization and *in-vivo* performance in humans

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ABSTRACT

The challenge in developing oral drug delivery systems of poorly soluble basic drugs is primarily due to their pH dependent solubility. Cinnarizine (CNZ), a model for a poorly soluble basic drug, has pH dependent solubility; where it dissolves readily at low pH in the stomach and exhibits a very low solubility at pH values greater than 4. It is also characterized by a short half life of 3–6 h, which requires frequent daily administration resulting in poor patient compliance. In an attempt to solve these problems, extended release floating lipid beads were formulated. A 2^4 full factorial design was utilized for optimization of the effects of various independent variables; lipid:drug ratio, % Pluronic F-127, % Sterotex, and Gelucire 43/01:Gelucire 50/13 ratio, on the loading efficiency and release of CNZ from the lipid beads. *In-vivo* pharmacokinetic study of the optimized CNZ-lipid beads compared to Stugeron® (reference standard) was performed in healthy human volunteers. A promising approach for enhancing the bioavailability of the poorly soluble basic drug, CNZ, utilizing novel and simple floating lipid beads was successfully developed. Zero order release profile of CNZ was achieved for 12 h. Mean AUC_{0-24} and $AUC_{0-\infty}$ of the optimized CNZ-loaded lipid beads were 4.23 and 6.04 times that of Stugeron® tablets respectively.

1. Introduction

The development of oral drug delivery systems for poorly soluble basic drugs is problematic because of their pH dependent solubility. Poorly water soluble basic drugs are very sensitive to pH changes, and following oral administration and dissolution in the acidic stomach environment, they tend to precipitate upon gastric emptying to higher pH medium in the intestine, leading to compromised or erratic oral bioavailability [1,2].

Cinnarizine (CNZ) is a lipophilic drug with partition coefficient of $\log P = 5.8$. It is a weak base with $pK_{a1} = 2$ and $pK_{a2} = 7.5$ having pH-dependent solubility. It exhibits higher solubility at low pH values (0.29 mg/ml in 0.1 N HCl) and lower solubility at higher pH (0.002 mg/ml in phosphate buffer pH 7.2) [3]. CNZ was chosen as a model compound representing poorly soluble basic drugs.

CNZ is a piperazine derivative with antihistaminic, sedative and calcium channel blocker. It is used in the treatment of nausea and vertigo caused by Meniere disease and other vestibular disorders and for prevention and treatment of motion sickness. CNZ has a short half-life of 3–6 h [4]. The usual dose for vertigo and vestibular disorders is 25 or 30 mg three times daily [5,6] and the only commercially available dosage forms are immediate release tablets and capsules, hence frequent daily administration is required resulting in poor patient compliance.

Aiming to solve these problems, extended release floating drug delivery system for continuous delivery of CNZ in the stomach was proposed [7]. Not only for reducing frequency of drug administration, but also it was suggested that prolonged gastric retention with slow continuous drug release, could result in the enhancement of CNZ bioavailability, through reducing the expected drug

Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; C_{max}, peak concentration; CNZ, Cinnarizine; DSC, differential scanning calorimetry; Gel, Gelucire; h, hour; IS, internal standard; LC-MS/MS, liquid chromatography mass spectroscopy; SEM, scanning electron microscope; T_{max}, time of peak concentration; XRD, X-ray diffraction.

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precipitation from its acidic solution upon gastric emptying and its contact with higher pH environment in the intestine.

Green technologies, which offer freedom from organic solvents, are preferred due to stringent global environmental concerns. Lipid-based sustained release matrix systems have emerged as promising and efficacious agents with wide spectrum of desired characteristics for effective drug delivery. They are characterized by low melt viscosity, thereby obviating the need of organic solvents for dissolving the drug, the absence of toxic impurities such as residual monomers catalyst and initiators, the potential biocompatibility and biodegradability, and prevention of gastric irritation by forming a coat around the drug were considered as the main advantages of lipid carriers compared to polymers [8,9].

The aim of this work was to statistically optimize a novel, simple approach utilizing floating, gastro-retentive, controlled release lipid beads, potentially suitable for once daily administration aiming to improve the low and erratic bioavailability for poorly soluble basic drugs (using CNZ as a model drug). A 2^4 full factorial design was utilized for the optimization of the effects of the lipid:drug ratio, % Pluronic F-127, % Sterotex, and ratio between Gelucire 43/01:Gelucire 50/13 on drug loading and release extent from the prepared beads. The pharmacokinetic parameters obtained from the optimized CNZ lipid beads and Stugeron® as the marketed reference product were compared in healthy human volunteers.

2. Materials and methods

2.1. Materials

Cinnarizine HCl (CNZ) was supplied as a gift sample by Minapharm Pharmaceuticals Ltd. (Cairo, Egypt), Gelucire 43/01 (hard fat, melting point 43 °C, HLB = 01) and Gelucire 50/13 (Stearoyl macrogol-32 glycerides, melting point 50 °C, HLB = 13) were kindly obtained as gift samples from Gattefosse (St Priest, Cedex, France), Sterotex NF (hydrogenated cotton seed oil, white solid powder, melting point 63 °C) was kindly supplied by Abitec Corp. (Janesville, WI), Pluronic F-127 (Ethylene Oxide/Propylene Oxide Block Copolymer, melting point 56 °C, HLB = 22) was provided by BASF (Ludwigshafen, Germany), and Hydrochloric acid (HCl) is of analytical reagent grade.

2.2. Preparation of Cinnarizine floating lipid beads

Floating lipid CNZ beads were prepared according to the method of Siepmann [10]. Briefly, the lipids were molten at 65 °C, mixed well and then CNZ was dispersed. The molten dispersion containing the drug was then added to 100 ml pre-chilled water (4 °C) at a rate of 5 ml/min via 23 gauge syringe and stirred at 100 rpm on a magnetic stirrer (model SP 72220-26, Barnstead/Thermolyne, USA). Finally, the formed beads were filtered through Whatmann 41, collected, and stored in glass vials.

2.3. Formulation of Cinnarizine floating lipid beads using 2^4 full-factorial designs

A full factorial design (2^4) was employed in the formulation of CNZ floating lipid beads for the screening of the influence, and optimization of the four studied factors namely: Lipid (Gelucire 43/01, Gelucire 50/13 and Sterotex):drug ratio (A), percent of Pluronic F-127 (calculated using the total weight of beads including the drug) (B), percent of Sterotex (calculated from the lipid content) (C), and Gelucire 43/01:Gelucire 50/13 ratio (ratio in the remaining lipid content after calculating the amount of Sterotex) (D), each at two levels, as shown in Table 1. The observed responses were the percent of drug released after 1, 5, and 8 h (Y_1, Y_2, and Y_3, respectively) in addition to the percent of drug loaded in the beads (Y_4) using Minitab® software (version 16.1.1). Sixteen formulae were suggested and randomly arranged by the software and duplicate experimentation was carried out. The results of the observed responses were presented as mean ± standard deviation.

2.4. Evaluation of CNZ lipid beads

2.4.1. Floating behavior

The prepared beads (about 20 beads) were placed in 100 ml of 0.1 N HCl containing 0.02% Tween 20 at room temperature. Tween was added to mimic the wetting effect of the surfactants, naturally present in the gastrointestinal tract [11,12]. The mixture was stirred at 100 rpm on a magnetic stirrer. The time required to start floating, as well as time duration of floating was determined by visual observation.

2.4.2. In-vitro release study

The release of CNZ from the prepared floating beads was determined using USP paddle type (II) dissolution apparatus (Hanson Research, USA). A weighed amount of beads equivalent to 25 mg drug was placed in the dissolution vessel. Nine hundred milliliters of 0.1 N HCl containing 0.02% w/v Tween 20 was used as the dissolution medium [9]. The dissolution fluid was maintained at 37 ± 0.5 °C at a rotation speed of 100 rpm. Five milliliter samples were withdrawn at the specified time intervals, filtered through a 0.2 μm Millipore filter, and the initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. Samples were analyzed using a UV–visible spectrophotometer (Shimadzu, Japan) at 253 nm. The experiment was performed in duplicate.

2.4.3. Loading efficiency determination

CNZ content in lipid beads was determined by grinding accurately weighed 50 mg beads in 10 ml of 0.1 N HCl, followed by sonication at 70 °C for 15 min and then, allowed to cool at room temperature. The lipid was solidified and the drug solution was filtered through Millipore filter 0.2 μm [13]. The samples were analyzed for drug content by a validated UV spectrophotometer method at 253 nm using UV–visible spectrophotometer (Shimadzu, Japan) after suitable dilutions. The experiment was performed in duplicate. The loading efficiency was calculated using the following equation:

$$\text{Loading efficiency } (\%) = (\text{Calculated drug content} / \text{Theoretical drug content}) \times 100.$$

Table 1
2^4 full factorial design layout: factors and responses.

Factors (independent variables)	Level used	
	−1	+1
A: Lipid:drug ratio	2:1	6:1
B: % Pluronic	6%	12%
C: % Sterotex	0%	2%
D: Gelucire 43/01:Gelucire 50/13 ratio	5:1	8:1
Responses (dependent variables)	**Constraints**	
Y_1: Release (%) after 1 h	$7\% \leqslant Y_1 \leqslant 27\%$, target = 17%	
Y_2: Release (%) after 5 h	$32\% \leqslant Y_2 \leqslant 52\%$, target = 42%	
Y_3: Release (%) after 8 h	$57\% \leqslant Y_3 \leqslant 77\%$, target = 67%	
Y_4: Loading efficiency (%)	$80\% \leqslant Y_4 \leqslant 100\%$, maximize	