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Fabrication of liquid and solid self-double emulsifying drug delivery system of atenolol by response surface methodology

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ABSTRACT

Self Double Emulsifying Drug Delivery System (SDEDDS), a concoction of hydrophilic surfactants and water-in-oil (w/o) emulsions, can spontaneously emulsify to water-in-oil-in-water (w/o/w) double emulsions in gastrointestinal aqueous environment, with hydrophilic drugs present in internal water phase. In this study, we developed SDEDDS of atenolol by response surface methodology. A 3^2 full factorial design was applied for optimization procedure. Independent variables were oil phase and span 80, whereas, response variables were zeta potential (Y1), % drug release at 300 min (Y2), $T_{85\%}$ (Y3), mean dissolution time (Y4) and % dissolution efficiency (Y5). Drug loading capacity (500mg/g-water) was increased by using tartaric acid. Microscopic studies confirmed the formation of double emulsions, besides, SEM, TEM and AFM. Responses Y1, Y2, Y3, Y4 and Y5 as exhibited by optimized formulations OF1 were −42 mv, 96%, 180 min, 86 min and 68%, and OF2 were −45 mv, 98%, 184 min, 79 min and 69% respectively. Formed globules were of size-range 182 ± 6 to 308 ± 3 nm. Optimized formulations were solidified by adsorption technique. *Ex vivo* intestinal permeability studies revealed that atenolol SDEDDS exhibited better drug permeation compared to atenolol or atenolol-tartaric acid solution. Histopathology studies confirmed SDEDDS exerted no serious local damages.

1. Introduction

Multiple emulsions are complex systems, termed as “emulsions of emulsions” [1]. A double emulsion being the simplest of multiple emulsions in which a primary emulsion is re-emulsified into a dispersion medium. These formulations specifically water-in-oil-in-water type have proved to be good oral bioavailability enhancers of protein, peptidomimetic or high solubility low permeability (BCS class III) drugs, since they may directly get absorbed as oil droplets from intestine [2]. These emulsions are also safer to administer and easier to prepare than others since no organic solvents are required in their preparation [3]. In double emulsions the drug is present in the inner hydrophilic core which serves as a protection and storage chamber. Limited application of these formulations is due to their instability during shelf-life. Double emulsions contain more interfaces and are even more thermodynamically unstable than single emulsions. This problem can be overcome by use of SDEDDS in place of double emulsions. In SDEDDS the external water phase is not added. SDEDDS can spontaneously emulsify in the aqueous gastrointestinal (GI) environment forming water-in-oil-in-water (w/o/w) double emulsions with drugs encapsulated in the internal water phase. SDEDDS are stable formulation systems, as compared to conventional thermodynamically unstable double emulsions. SDEDDS can be filled directly into soft or hard gelatin capsule which are easy to administration and storage [4]. SDEDDS has a number of advantages which include prevention of inactivation and enzymatic deterioration of peptide and protein drugs in GI tract; better absorption of drugs as compared to other formulations, SDEDDS can get spontaneously emulsified by the peristaltic movement *in vivo* instead of artificial emulsification *in vitro*; SDEDDS appreciably helps the patients by lessening the dose volume [5]. It is also reported that SDEDDS can improve absorption

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Abbreviations

w/o/w	Water-in-Oil-in-Water
SDEDDS	Self-Double Emulsifying Drug Delivery System
SEM	Scanning Electron Microscopy
TEM	Transmission Electron Microscopy
AFM	Atomic Force Microscopy
XRD	X-Ray Diffraction
FTIR	Fourier Transform Infrared Spectroscopy
RSM	Response Surface Methodology

greatly without causing serious toxic effect on tissues [6].

It is mentioned that solid self emulsifying drug delivery systems can be prepared, to incorporate liquid or semisolid ingredients into powders utilizing diverse solidification techniques such as adsorption, spray drying, melt granulation, extrusion–-spheronization and eutectic mixing. It has potential advantages such as dosing precision offered by solid filling, ease of transfer, portability and storage, better patient compliance as well as diversity in solid dosage form options [7]. Solid SDEDDS preparation by two step emulsification is reported by Hu et al., 2015 [8]. The main aims of this study were to develop and characterize SDEDDS formulations. Atenolol, a BCS class III drug, was chosen as a model drug. Drug loading capacity in inner aqueous phase was increased by use of tartaric acid as solubility modulator [9]. Considering optimization of formulations, searching for the suitable concoction of variables to produce the optimum formulation is quiet difficult [10]. Response surface methodology (RSM) is a collection of statistical techniques helpful in designing and evaluating the relationship between a response and a set of variables of interest. The data so obtained from an experiment can be used to deduce inferences about the optimization procedure [11]. RSM requires minimum experimentation and time, thus showing to be far more fruitful and economical than the conventional formulation development methods [12]. Based on the design of experiments, RSM encircles the generation of polynomial equations and of response over the experimental domain to determine the optimum formulation(s) [13]. Factorial design is an efficient tool for estimating the influence of individual variables and studying their interactions using minimum experiments [14]. If minimization of the number of levels for more than 1 factor becomes necessary, then it may mean selecting a design with all factors taking 3 levels. The possible designs are all sub-sets of experiments from the 3^k factorial designs, where k denotes the independent variables, and the domain is again cubic. The 3^2 full factorial design being simplest and consists of 9 experiments. Its use in development and optimization has been described quite frequently in the pharmaceutical literature [15].

A 3^2 full factorial design was used to find the optimized formulation with highest desirability (closer to one) considering all the response variables. Different levels of independent variables, oil phase and span 80 were selected whereas, the response variables were zeta potential (Y1), % drug release at 300 min (Y2), $T_{85\%}$ (Y3), (MDT) mean dissolution time (Y4) and % (DE) dissolution efficiency (Y5). The developed formulations were characterized by assessing microscopy, optical clarity, particle size analysis, zeta potential and *in vitro* dissolution studies. Optimized formulations were subjected to morphological studies. At last, the *ex vivo* permeability of atenolol was evaluated in rat intestine for the atenolol-SDEDDS and atenolol aqueous solution and atenolol-tartaric acid aqueous solution.

2. Material and methods

2.1. Materials

Atenolol was a kind gift from Zydus Cadila Healthcare Ltd., Ahmedabad, India. Captex 355 EP was obtained from Abitec Corporation. Oleic acid was purchased from Loba Chemie. Tween 80 was purchased from Ozone International, Mumbai, India. Span 80 was obtained from Merck Schuchardt OGH, Hohenbrunn, Germany, Sodium Bicarbonate from Ranbaxy Fine Chemicals Limited, Chandigarh, India, L(+) Tartaric acid was obtained from Rankem, RFCL Limited, New Delhi, India. Aerosil 200 Pharma was obtained from Evonik Industries, Germany. Sodium hydroxide, potassium dihydrogen phosphate, hydrochloric acid and methanol were purchased from Central Drug House (Mumbai, India).

2.2. Drug excipients compatibility studies

To check the retention of chemical identity of drug in physical mixture of drug and various excipients, pure drug and different physical mixtures of drug with excipients were subjected to XRD and FTIR studies.

2.2.1. X-ray diffraction (XRD)

The following samples were subjected for X-Ray Diffraction studies at 2θ angle by X-Ray Powder Diffractometer (Bruker AXS D8 Advance).

1. Pure atenolol,
2. Physical mixture of pure atenolol, tween 80, span 80, oleic acid and captex 355 (in ratio 1:0.25:0.25:0.25:0.25),
3. Physical mixture of pure atenolol, span 80 and oleic acid (in ratio 1:0.5:0.5) and
4. Physical mixture of pure atenolol, tween 80 and captex 355 EP (in ratio 1:0.5:0.5).

2.2.2. Fourier transform infrared spectroscopy (FTIR)

The FTIR absorption spectra of the pure drug, various pure excipients and physical mixtures of drug with different excipients in 1:1 ratio were taken and scanned in the range of 4000–600 cm^{-1} using KBr disc method (Schimadzu FTIR 8400S). The spectra were observed for characteristic peaks of drug.

2.3. Solubility studies

Solubility of atenolol in various surfactants (Span 80, Span 20 and Tween 80) was studied by the shake flask method. An excess amount of atenolol (approximately 1 g) was added to each capped vial containing measured amount of the surfactant. After sealing, the mixture was vortexed for 10 min and then kept for 24 h at 50 °C in a shaking water bath (RSB-12, Remi, India) to facilitate the solubilization. The samples were centrifuged (C845/8Remi, India) at 3000×*g* for 15 min followed by filtration of supernatant to remove the undissolved atenolol. The filtrate was taken and diluted with methanol for quantification of atenolol by UV spectrophotometry (Shimadzu UV-1800) at 227 nm with proper adjustment of blank solutions.