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Original research

Formulation and optimization of Embelin nanosuspensions using central composite design for dissolution enhancement

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ABSTRACT

The purpose of the present investigation was to improve solubility and dissolution properties of poorly water soluble drug, Embelin, a herbal active ingredient by preparing nanosuspensions. The wet media milling technique was employed for the preparation of nanosuspensions. Further, nanosuspensions were freeze dried to generate nanocrystals. Rotatable central composite design was adopted to study the effects of independent variables viz. amount of stabilizer (Pluronic F68) and amount of milling agents (Zirconium beads) on dependent variables, particle size and % drug release at 30 min. Relationship between dependent and independent variables were further investigated by multiple linear regression analysis. A significant increase was found in the solubility and dissolution rate of the formulations. Differential scanning calorimetry and Powder X-ray diffraction studies confirmed decrease in drug crystallinity. Surface electron microscopy and Transmission electron microscopy revealed plate like morphology. Results suggested remarkable improvement in the dissolution properties of Embelin by preparing nanocrystals.

1. Introduction

The poor aqueous solubility of drugs resulting in poor oral bioavailability has always been a challenging problem in pharmaceutical research. Solubility and gastrointestinal permeability are the major rate limiting steps for bioavailability and absorption [1]. Akin to many discovered chemical entities, isolated herbal active ingredients show poor aqueous solubility [2]. Till date, many formulation approaches such as salt formation, use of surfactants, use of prodrugs etc were utilized to solve the problem of solubility. Over last ten years, nanoparticle engineering has emerged for pharmaceutical applications [3]. Nanosuspensions have been widely used to deal with the problems associated with poor dissolution properties and erratic bioavailability. Nanoparticles with size ranging from 200 to 500 nm increase the saturation solubility, dissolution rate and probably the mucoadhesion of drug which might further improve the oral bioavailability [4]. In addition, nanocrystals present merits such as high drug loading, enhanced stability and less toxicity in comparison to other nanoparticles [5]. Nanosuspension formulation of some of the drugs are already in market instanced by Tricor® (fenofibrate), Cesamet® (nailone) [6].

Embelin (ELN) (Fig. 1) is a benzoquinone found in the fruits of Vidanga. ELN shows wide range of medicinal properties such as antibacterial, antifertility and antioxidant [7–9]. ELN is also studied for its antihyperglycemic effect in alloxan induced diabetes and its cytotoxic effect [10,11]. ELN have been studied for its hepatic antioxidant activity, free radical scavenging activity and lipid peroxidation in albino rats [12]. Despite of such medicinal activities of ELN, it suffers from dissolution rate limited bioavailability [13]. With this objective the present study was to formulate ELN nanocrystals with the aim to improve its solubility and dissolution properties which might further improve its oral bioavailability.

Quality by Design (QbD) is a systematic approach to design, development and delivery of any pharmaceutical product or process with predefined product specifications [14]. QbD comprehends the application tools such as: design of experiments (DoE), risk assessment and process analytical technology for pharmaceutical development [15]. Central composite design (CCD) is one of the efficient designs to study the effect of different independent variables on dependent variables of formulation. Regression analysis using ANOVA is performed to enlighten the interactions between different variables to determine the optimum formulation.

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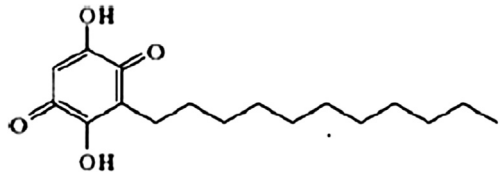

Fig. 1. Chemical structure of Embelin.

2. Materials and methods

2.1. Materials

ELN was a gift sample from BR Nahta Pharmacy College, Mandsaur, India. Pluronic F68 was gift sample from Torrent Pharmaceuticals ltd, Ahmedabad, India. Mannitol was purchased from SD Fine Chem, Mumbai, India. Zirconium beads were obtained from Unigenetics Pvt Ltd, Delhi, India. Double distilled water was used throughout the study.

2.2. Methods

2.2.1. Preparation of nanocrystals

Nanosuspensions of ELN were prepared by media milling method using water as media. Zirconium beads were used as a milling agent and Pluronic F68 was used as stabilizer. Nanosuspensions were prepared using different concentrations of stabilizer in distilled water and stirred on a magnetic stirrer (Remi, Mumbai, India) at 1000 rpm for 16 h at room temperature. The prepared suspension was then centrifuged at 5000 rpm for 10 min, supernatant was removed and the solid sediment was freeze dried using 3% w/v Mannitol as cryoprotectant (Hetro Dry Winner, Denmark).

2.2.2. Formulation and optimization of nanosuspensions using central composite design

A rotatable central composite design (CCD) was selected to investigate the effects on critical quality attributes of nanosuspension. Amount of stabilizer and amount of zirconium beads were identified as critical formulation parameters and the factor levels were suitably coded. Particle sizes in nm and % drug release in 30 min (CDR30) were taken as the response variables. Independent factors and their levels used in this study are shown in Table 1. The design consists of total 9 experimental runs which included 4 factorial points, 4 star points and 1 centre point and analysed by the statistical software package Design Expert® 8.0.7.1 (Stat-Ease Inc., USA). The batch size (5 ml), drug concentration (2% w/v), Pluronic F68 as stabilizer, milling agent (zirconium beads) and solvent system (water) were kept constant in the experimental trials.

2.3. Characterization of ELN nanocrystals

2.3.1. Particle size determination

Particle size, polydispersity index and zeta potential were determined by photon correlation spectroscopy using Malvern Zetasizer (Malvern Instruments, UK). All data presented are the average values of three samples. Samples were suitably diluted with de-ionized water before analysis.

2.3.2. In vitro dissolution studies

In vitro drug release studies of ELN nanocrystals and pure drug were carried out in USP type II dissolution apparatus (Model Disso 2000, Lab India) using 900 mL of phosphate buffer (pH 7.4) as dissolution media with conditions of 50 rpm and temperature 37 ± 0.5 °C. Aliquots of 5 ml was withdrawn at suitable time interval (5, 10, 15, 20, 30 45, 60 and 90 min), filtered using Whatman filter paper (0.22 μ), appropriately diluted and then analysed spectrophotometrically at λmax 291 nm by UV/Visible spectrophotometer (UV-1800 Shimadzu, Japan).

2.4. Characterization of optimized ELN nanocrystals

2.4.1. Saturation solubility studies

Solubility studies were carried out in phosphate buffer pH 7.4. Excess of ELN and ELN nanocrystals were added to 5 ml of solvent and the mixtures were shaken for 48 h at 37 °C. Suspensions were centrifuged at 5000 rpm for 10 min, supernatant was removed and thereby analysed spectrophotmetrically at λmax 291 nm after appropriate dilutions for drug concentration.

2.4.2. Differential scanning calorimetry (DSC)

DSC analysis was carried out using differential scanning calorimeter (Shimadzu, DSC 60 TSW 60, Japan). Samples (ELN and optimized formulation) were accurately weighed and placed in aluminium pan and closed with a lid. Study was carried out

Table 1
Factors investigated using central composite design.

Independent variables	Levels				
	-α	−1	0	+1	+α
X1 = Amount of Stabilizer (Pluronic F68) (%w/v)	0.08	0.10	0.15	0.20	0.22
X2 = Amount of milling agent (Zirconium beads) (gm)	1.2	2	4	6	6.8

Table 2
Effect of independent variables on particle size and drug release at 30 min.

Run	*X1* (amount of stabilizer, %w/v)	*X2* (amount of milling agent, gm)	*Y1* (particle size, nm)	*Y2* (% cumulative drug release at 30 min)
EN1	−1	−1	304.64 ± 3.17	65.55 ± 0.88
EN2	+1	−1	307.11 ± 5.66	68.10 ± 1.49
EN3	−1	+1	265.27 ± 3.54	82.24 ± 1.93
EN4	+1	+1	267.19 ± 6.47	84.67 ± 2.78
EN5	−1.41	0	297.99 ± 7.46	61.92 ± 3.01
EN6	+1.41	0	274.93 ± 5.40	80.76 ± 2.35
EN7	0	−1.41	332.06 ± 11.10	63.82 ± 1.93
EN8	0	+1.41	237.15 ± 3.41	92.37 ± 0.86
EN9	0	0	252.28 ± 4.16	88.68 ± 1.29