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Original Article

A statistical study on the development of micro particulate sustained drug delivery system for Losartan potassium by 3^2 factorial design approach

Gokul Khairnar, Jitendra Naik *, Vinod Mokale

Department of Pharmaceutical Technology, University Institute of Chemical Technology, North Maharashtra University, Jalgaon 425 001, Maharashtra, India

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ABSTRACT

The purpose of this study was to investigate the effect of polymer and surfactant concentration on drug loading and *in vitro* drug release of micro particulate drug delivery system of Losartan potassium (LST). Microparticles were prepared by O/O solvent emulsification method. A 3^2 full factorial design was used to derive statistical equation and construct contour plots to predict responses. The independent variables selected were polymer concentration (A), surfactant concentration (B). Dependent variables were percentage drug loading (Y1) and percentage drug release at 12 h (Y2). The *in vitro* drug release profile of prepared microparticles was compared with marketed tablet formulation. The release profile of microparticles was found to be sustained as compared to the marketed formulation. The drug loading was found to be in the range of 15.32% (F6) to 22.27% (F5). FT-IR analysis revealed no drug excipient interference. The morphology of evaluated microparticles at −1 level was found to be spherical and smooth in nature while at higher level +1 it was found to be rough, irregular, with erosion, cracks and wrinkles on the surface. In XRD analysis crystalline pattern of pure LST was changed to amorphous pattern when converted to microparticles.

1. Introduction

Hypertension remains a major clinical challenge worldwide, because of both the direct consequences of high blood pressure (cerebral hemorrhage, hypertensive heart failure, progressive renal failure) and the secondary consequence of accelerated atherosclerosis and its complications in the aorta, coronary and cerebral arteries [1,2]. Hypertension is responsible for the death of 7.6 million peoples per annum worldwide [3]. The WHO has identified high BP i.e. hypertension as one of the major causes of premature morbidity and mortality in both developed and developing countries. In developed countries, heart disease and stroke respectively are the first and third ranked causes of morbidity and mortality [4]. A new analysis shows that in 2000 more than a quarter of the world's population was hypertensive a number totaling nearly one billion and suggests that by 2025, that number will climb to 29%, or about 1.56 billion people worldwide. The magnitude of the burden needs not only an increase in awareness, treatment, and control of this condition, but also concerted efforts that target primary prevention [5]. Treatment of high BP most commonly involves the use of alpha-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers or diuretics [6].

Losartan potassium (LST) is a nonpeptide angiotensin II receptor antagonist used for the treatment of hypertension [7,8]. LST is freely soluble, white to off-white free-flowing crystalline powder. The terminal half-life of LST is about 2 h. Following oral administration, LST is well absorbed and undergoes substantial first-pass metabolism; the systemic bioavailability of LST is approximately 33%. LST is available in the market under brand name of Losakind containing 25 mg, 50 mg or 100 mg. About 14% of an orally-administered dose of the LST is converted to the active metabolite. Losakind can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg [9,10]. LST is an effective antihypertensive drug but is extensively bound to plasma proteins and also causes GI disorders, neutropenia, acute hepatotoxicity, migraine and pancreatitis [11–14]. So in order to reduce the dosing frequency and side effects of the LST sustained drug delivery is required to prolong the drug release.

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* Corresponding author at: Department of Pharmaceutical Technology, University Institute of Chemical Technology, North Maharashtra University, Umavi Nagar, Post Box No. 80, Jalgaon 425 001, Maharashtra, India. Fax: +91 257 2258403.
E-mail addresses: jitunaik@gmail.com, jbnaik@nmu.ac.in (J. Naik).

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Polymeric microspheres or microparticles are spherical in nature and their dimensions range between 1 and 1000 μm. These polymeric microspheres are manufactured from natural, synthetic, semi synthetic, waxy or other protective materials. They have wide applications in medical, food, cosmetics, ink, pigments, chemical reagents and pharmaceutical field to protect, stabilize, deliver or control the release of the encapsulated compound [15–17]. Particulate drug delivery systems like microspheres or nanoparticles have been developed to improve the bioavailability and to enhance the pharmacokinetic properties, which can lead to improve the patient compliance [18,19]. Microspheres have been widely accepted as a means to achieve oral and parenteral controlled release drug delivery system [20]. Usually microspheres are produced by solvent evaporation, and emulsification techniques.

Among the polymeric materials ethyl cellulose is widely used in pharmaceutical development of products. Ethyl cellulose (EC) is a non –toxic, stable, compressible, inert, hydrophobic polymer that has been widely used to prepare pharmaceutical dosage forms [21]. EC has been extensively used as a sustained release polymer in various dosage forms e.g. tablets, suspensions, microparticles, nanoparticles [22]. EC is non –toxic, stable, compressible, inert, low cost, hydrophobic polymer with FDA approval for internal use that has been widely used to prepare pharmaceutical dosage forms [23]. High viscosity grades of EC are used in drug encapsulation. Microparticles designed for oral treatment target the gastrointestinal (GI) tract, and encapsulation can enhance GI treatments. Toxic drugs which cause side effects when administered in large quantities, or insoluble drugs which require large doses to promote absorption, can be administered with a lower frequency and smaller quantity [24–29]. Sustained release formulations in microparticles by a single dose would be a clinically important means of extending the duration of action of LST. Sustained release formulation with reduced dose could be an interesting and suitable way to minimizing the complications and improving the patient compliance [30–33].

The aim of this work was to investigate the effect of surfactant and polymer on dug loading and drug release profile of LST sustained micro particulate drug delivery system prepared by O/O solvent emulsification method. LST loaded EC microparticles would deliver LST at a sustained rate for a prolonged period of time as compared to the marketed formulation. Development of sustained drug delivery system for oral formulation of drugs will definitely bring a reduction in daily dose and be cost effective. It can reduce the chance for both under and overdosing as well as number of repeated administrations, provide more localized to better use of active agents and increase patient compliance.

2. Material and methods

2.1. Materials

Losartan potassium (LST) was a kind gift sample from the Wockhardt Research lab (Aurangabad, India). Ethyl cellulose 20cp viscosity grade (EC), Methanol, Span 80, n-hexane were obtained from Merck Specialties Private Limited (Mumbai, India). Light liquid paraffin was purchased from RFCL Limited (New Delhi, India). All other chemicals used were of analytical grade.

2.2. Preparation of LST loaded microparticles

The O/O emulsion solvent evaporation method was applied with slight modification, to the fabrication of LST loaded EC microparticles [29,34]. Briefly, LST (200 mg) and EC were dissolved in a 20 ml of methanol (Organic Phase) and sonicated for 10 min to get a clear, transparent solution. The resulted organic phase was transferred into a 10 ml syringe and added drop by drop into 100 ml light liquid paraffin containing varying concentrations of span 80 (emulsifier) as external aqueous phase maintaining 1000 RPM of overhead stirrer (Remi electrotechnik Limited, Thane, India) to produce O/O emulsion. The stirring was continued until complete evaporation of methanol. 20 ml of n-hexane was added to the emulsion for the hardening of the microparticles. Stirring was further continued up to complete evaporation of n-hexane. Emulsion containing solid microparticles were separated by vacuum filtration, washed with n-hexane, air dried and used for further evaluation. Table 1 represents the different levels of excipients used.

2.3. Experimental design for optimization

During development of LST microparticles, drug loading was the highlighted issue due to its high water solubility. Multiple initial trials were conducted including W/O, W/O/W, W/O/O solvent emulsification method to improve the drug loading of the LST [29]. But none of the method was found to be efficient for the improvement of the drug loading. During these batches we found that polymer concentration, surfactant concentration had a great influence on the DL and DR, hence decided to select as independent variable. A full factorial 3^2 design was employed to reduce the number of trials to attain the maximum number of information on the product properties and for the optimization of LST loaded EC sustained release microparticles. This design is suitable for investigating the quadratic response surfaces and for constructing a second-order polynomial model, thus enabling optimization of the formulation parameters. Mathematical modeling, evaluation of the ability to fit to the model and response surface modeling were performed by employing Design-Expert software. The concentration of polymer (A) and the concentration of surfactant (B) were defined as the selected independent formulation variables or factors. DL and DR at 12 h were used as the dependent variables or responses. In this experimental design, trails were performed at 13 possible combinations.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2 \quad (1)$$

where Y is the response; b_0 is the intercept, and b_1, b_2, b_3, b_4, b_5 are regression coefficients. X_1 and X2 are individual effects; X_1^2 and X_2^2 are polynomial terms of individual effects; X_1X_2 is the interaction effect.

3. Evaluation of microparticles

3.1. Yield of microparticles

LST loaded microparticles from each batch were weighed accurately and yield of microparticles was calculated by using a formula [35].

$$\%\,\text{Yield} = \text{Weight of dried microsphere}/(\text{Weight of drug} + \text{Weight of polymer}) \times 100 \quad (2)$$

Table 1
Variable and three levels.

Independent variable	Low level (−1)	Medium level (0)	High level (+1)
A = Polymer conc.	1000 (1:5)	1400 (1:7)	1800 (1:9)
B = Surfactant conc.	0.6%	0.8%	1.0%
Dependent variables			
Y1 = %DL			
Y2 = %DR			

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