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Development, characterization and solubility enhancement of comparative dissolution study of second generation of solid dispersions and microspheres for poorly water soluble drug

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ABSTRACT

The poor dissolution characteristics of water-insoluble drugs are a major challenge for pharmaceutical scientists. Reduction of the particle size/increase in the surface area of the drug is a widely used and relatively simple method for increasing dissolution rates. The objective of this study was to improve solubility, release and comparability of dissolution of a poorly soluble drug using two different types of formulations (solid dispersions and microspheres). Hydrochlorothiazide was used as a model drug. The solid dispersions and microspheres were prepared by solvent evaporation method using ethyl cellulose, hydroxypropyl methylcellulose in different drug-to-carrier ratios (1:1, 1:2 w:w). The prepared formulations were evaluated for interaction study by Fourier transform infrared spectroscopy, differential scanning calorimetry, percentage of practical yield, drug loading, surface morphology by scanning electron microscopy, optical microscopy and *in-vitro* release studies. The results showed no interaction between the drug and polymer, amorphous state of solid dispersions and microspheres, percentage yield of 42.53% to 78.10%, drug content of 99.60 % to 99.64%, good spherical appearance in formulation VI and significant increase in the dissolution rate.

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1. Introduction

Among all newly discovered chemical entities about 40% of drugs are lipophilic and fail to reach the market due to their poor aqueous solubility [1]. For orally administered drugs solubility is one of the rate limiting parameters to achieve their desired concentration in the systemic circulation in pharmacological response [2]. According to the equation of Noyes and Whitney, this may be achieved by reduction of the particle size/increase in the surface area of the drug which is accessible for the dissolution medium and an enhancement of its solubility in addition to a relatively simple method for increasing dissolution rates [3]. However, altering the drug particle itself carries obvious limitations which are inadequate for enhancement of bioavailability. Therefore, additional physical changes, including control of drug release from their formulations should be taken into consideration [4]. Moreover, there are two key strategies to alter the release and subsequent absorption of drugs: one is based on a modification of the drug, and the other is based on a modification of the dosage form as a new drug delivery system [5].

The new drug delivery systems are having an edge over conventional ones in terms of many biopharmaceutical parameters; among such drug delivery systems are controlled/prolonged release solid dispersion [6,7] and micro particles/microsphere [8,9]. These systems can achieve therapeutically effective concentration of the drug in the systemic circulation over an extended period of time with better patient compliance [10,11]. Water insoluble carriers are generally used to produce a controlled release formulation. The properties of the carriers have major influences on the release profile of the dispersed drug, specifically the second generation carriers. These carriers include ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, cellulose acetate phthalate, ethyl acetate, Chitosan, and methacrylic acid copolymers [12].

In order to investigate the effect of second generation polymers on the dissolution release mechanism of poorly soluble drugs from solid dispersions (SD) and microspheres (MS), hydrochlorothiazide [(6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7 sulfonamide) (HCT), a poorly water soluble drug (0.7 mg/ml)] was used as a model drug for these purposes. The HCT is a potent diuretic which inhibits the kidney's ability to retain water. It is widely used in the management of hypertension in combination with cardiovascular drugs. It is a white or nearly white, almost odorless, crystalline powder and has a slightly bitter taste. Hydrochlorothiazide is considered as a class IV drug according to the BCS. It has low and variable oral bioavailability which is attributed to poor solubility, slow dissolution and poor membrane permeability [13]. Hydrochlorothiazide is absorbed from the GI tract and apparently not metabolized and excreted unchanged in urine. At least 61% of the drug is reportedly eliminated from the body when excretion is essentially completed within 24 h post administration. The oral bioavailability of the drug was reported to be 60–80% of the administered dose [14]. In this study, two different types of formulations such as solid dispersions and microspheres were prepared by solvent evaporation method using ethyl cellulose (EC) and hydroxylpropyl methylcellulose (HPMC) in different drug-to-carrier ratios (1:1, 1:2 w:w). These preparations may release the maximum amount of the drug for controlling/prolonged period of time and it may also increase the residence time; this in turn may increase the bioavailability when compared to conventional drug multiple dosing regimen.

2. Materials and methods

2.1. Materials

Hydrochlorothiazide was obtained from IPCA Laboratories Ltd. (Mumbai, India). Hyroxypropyl methylcellulose was purchased from Colorcon, Mumbai. Ethylcellulose and Poly vinyl alcohol (PVA) were procured from Sigma-Aldrich, Germany. All other chemicals were of analytical reagent grade.

2.2. Preparations of solid dispersions by solvent evaporation method

The physical mixture of the drug and water soluble carrier were dissolved in 20 ml of common solvent (5% acetic acid for FI, FII and Acetone for FIII, FIV) and the resulting clear solution is rapidly heated for evaporating the solvent and to get a glassy solid mass. The obtained solid mass was transferred onto aluminum plates and the solvent was left to evaporate in open air for 2 days. After complete removal of the solvent the solid dispersions were granulated and stored at 25 °C in desiccators [11,15].

2.3. Preparations of microspheres by emulsion solvent evaporation method

In this technique the drug is dissolved in a polymer which was previously dissolved in 50 ml of solvent and the resulting solution is added to aqueous phase containing 5 ml of 1% PVA as stabilizing agent. The above mixture was agitated at 500 rpm, then the drug and polymer (EC & HPMC) were transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with de-mineralized water and desiccated at room temperature for 24 h [16].

Different concentrations and ratios of polymers used in the formulation of solid dispersion and microspheres are mentioned in Table 1.

2.4. Analytical method for drug concentration measurements (UV method)

The ultraviolet spectrophotometric method was selected in the present study for the estimation of hydrochlorothiazide. The drug solution [20 µl/ml in 0.1M HCl] was scanned in between the wavelength of 400–200 nm. The wavelength of 273 nm was selected and utilized for further quantitative analysis.