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SHORT COMMUNICATION

Dissolution Enhancement of Cefprozil by Solid Dispersion Technique

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ABSTRACT

Oral route is the most preferred route of drug delivery for most of the drugs but it presents a considerable challenge for water insoluble drugs. In the present work solid dispersions of cefprozil were prepared in order to improve the water solubility and thereby its bioavailabilty. The solid dispersions were prepared using mannitol and PEG-6000 as the solubility enhancing agent. The solid dispersion was formulated as tablet and the disintegration and dissolution study were performed. The result revealed increased dissolution of cefprozil and improved bioavailability.

Keywords: Cefprozil, solid dispersion, PEG-6000, solubility enhancement, mannitol

Introduction

The phenomenon of solubility is very important for understanding the drug dissolution absorption and the bioavailability of a particular drug molecules and its distribution phenomenon. Such knowledge is important for the pharmacist, for it permits him to choose the best solvent system for a drug or combination of drugs. Solubility is of fundamental importance in a large number of scientific disciplines and practical applications.

Bioavailability refers to the extent to and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action[1].

Bioavailability of a drug is largely determined by the properties of the dosage form (which depend partly on its design and manufacture), rather than by the drug's physicochemical properties, which determine absorption potential. Differences in bioavailability among formulations of a given drug can have clinical significance; thus, knowing whether drug formulations are equivalent is essential.

Orally administered drugs must pass through the intestinal wall and then through the portal circulation to the liver; both are common sites of first-pass metabolism. Thus, many drugs may be metabolized before adequate plasma concentrations are reached. Low bioavailability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs. Various approaches are applied for the improvement of bioavailability of drug molecules. One such approach is formulation of solid dispersions of the drug in various carriers[2].

Materials and methods

Cefprozil was obtained as a generous gift sample from Lupin laboratories Ltd., mannitol and PEG 4000 were purchased from S.D.Fine chemicals, Mumbai. Cross Povidone was obtained as gift sample from Medibios Laboratories Pvt. Ltd., Tarapur. All other chemicals and reagents used were of analytical grade.

Preparation of solid dispersion[3-6]

Solid dispersions containing Cefprozil and carrier in the proportion of 1:1, 1:2, 1:4, 1:8 and 1:10, were prepared by melt-solvent method using mannitol, and solvent evaporation method using PEG-4000.

Solid Dispersion with Mannitol

Cefprozil was dissolved in acetone, and the solution was incorporated into the melt of mannitol at 165ºC, by pouring into it. It was kept in an ice bath for sudden cooling. The mass was kept in the desiccator for complete drying. The solidified mass was scrapped, crushed and passed through 80 mesh sieve to obtain the solid dispersion.

Solid Dispersion with PEG-4000

Accurately weighed quantities of PEG-4000 in the above stated proportions were carefully transferred into boiling tubes, and dissolved in

acetone. To these solutions, accurately weighed quantities of cefprozil was added, and allowed to dissolve. The solution was transferred to a petridish, the solvent was allowed to evaporate at room temperature, and the dispersions were dried at room temperature for 1h, and then dried at 65° for 6 h in a hot air oven. The mass obtained in each case was crushed, and sifted through 80 mesh sieve.

Drug Content Analysis of Solid Dispersions

An accurately weighed quantity of the solid dispersions equivalent to 250 mg of Cefprozil was taken into a 100mL flask and 100mL of acetonitrile: water (1:1) was added to it. The drug was dissolved and analyzed at 325nm using UV-Visible spectrophotometer. The drug content was analyzed from calibration curve.

***In vitro* dissolution study**

The quantity of solid dispersions equivalent to 250mg of Cefprozil, was filled in colorless hard gelatin capsule by the hand filling method. Dissolution study of capsules was conducted using USP dissolution apparatus type 1, in 900 ml of 0.1 N HCL, maintained at 37±0.5° at a speed of 50 rpm. Five milliliters of samples were withdrawn at time intervals of 0, 10, 20, 30, 45 and 60 min. The volume of dissolution fluid was adjusted to 900 ml, by replacing each 5 ml aliquot withdrawn with 5 ml of fresh 0.1 N HCL. The concentration of Cefprozil in each sample was determined by using standard curve equation.

Formulation of tablets of the solid dispersions

Tablet formulation was developed from the solid dispersions of Cefprozil with Mannitol, using Cross Povidone as the disintegrating agent. Talc (2%), sodium lauryl sulfate (1%), and magnesium stearate (1%), were used as glidant-lubricant. The average weight of the tablets was adjusted to 500mg, using lactose and microcrystalline cellulose, in equal proportions. All the ingredients were mixed properly and compressed into tablets. The tablets were stored in polyethylene bags and evaluated for characteristics in triplicate.

Evaluation of the tablets of solid dispersions

Compressed tablets were then evaluated for hardness, disintegration, friability, and drug content. Hardness was measured by Monsanto type hardness tester. For disintegration test, one tablet was placed in each tube of disintegration apparatus, and the test was carried out using distilled water as a disintegrating media at 24±2°C. Friability was determined in Roche friabilator. For drug content analysis, twenty tablets were accurately weighed and finely powdered. The quantity of powder, equivalent to 250 mg of Cefprozil was taken into a 100 ml volumetric flask and 100mL of acetonitrile: water (1:1) was added to it. The drug was dissolved and analyzed at 325nm using UV-Visible spectrophotometer. The drug content was analyzed from calibration curve.

***In vitro* dissolution study of tablets**

In vitro dissolution study of the tablets was conducted using USP dissolution apparatus type I at 50 rpm, using PBS pH 7.2 as a dissolution media maintained at 37±0.5°C. Samples were withdrawn at various time intervals, filtered through a 0.45micron membrane filter, diluted, 100mL of acetonitrile: water (1:1) was added to it. The drug was dissolved and analyzed at 325nm using UV-Visible spectrophotometer. The drug content was analyzed from calibration curve.

Results and Discussions

The solid dispersions were prepared using melt dispersion and solvent evaporation technique and were easily obtained. The tablets of the solid dispersions were made on a single punch manually operated tablet punching machine.

The results obtained for the evaluation of solid dispersions and the tablet formulation of the solid dispersions are depicted in tables below.

Table 1: Cumulative percentage yield of Cefprozil released from Mannitol solid dispersions

Time (min)	Pure Cefprozil	Solid dispersion of Cefprozil-Mannitol				
		1:1	1:2	1:4	1:8	1:10
15	2.42	5.29	7.91	9.40	15.16	15.15
30	4.95	6.83	9.95	12.21	19.67	19.14
45	10.17	10.66	16.40	18.16	24.77	23.91
60	15.11	16.73	19.21	22.11	27.45	27.39

Table 2: Cumulative percentage yield of Cefprozil released from PEG 4000 solid dispersions

Time (min)	Pure Cefprozil	Solid dispersion of Cefprozil-PEG 4000				
		1:1	1:2	1:4	1:8	1:10
15	2.42	3.22	5.90	8.42	13.18	13.01
30	4.95	5.14	7.91	10.56	16.13	15.44
45	10.17	10.66	13.43	16.15	21.01	20.90
60	15.11	15.71	17.13	21.08	24.28	27.83

The mean hardness of formulation was found to be 3.7 kg/cm^2. The results of the disintegration test revealed that the formulation has faster disintegration, and it disintegrates within three min (152 s). The friability and assay of formulation was found to 0.42% and 100.31% respectively.

The formulation of solid dispersion tablets exhibited around 76% drug release in 30 minutes. The results obtained indicate that the solid dispersion of Cefprozil with Mannitol was better in releasing drug as compared to that of PEG 4000. At around 1:8 ratio the solid dispersions exhibited maximum drug release, may be due to improved wettability by the carrier. At further increase in concentration of the carrier the dissolution of Cefprozil decreases which may be as a result of accumulation of the carrier leading to decrease in solubility of the drug.

The formulation developed from the solid dispersion of Cefprozil with Mannitol was found to be disintegrating rapidly and was having a very good dissolution profile. This indicates that the formulation would be helpful in improving the release of Cefprozil in tablet dosage form.

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