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Formulation and Evaluation of Cephalexin Extended-release Matrix Tablets Using Hydroxy Propyl Methyl Cellulose as Rate-controlling Polymer

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ABSTRACT

The present investigation reports the design and evaluation of six-hour extended release film-coated matrix tablets of cephalexin using different grades of hydrophilic polymer hydroxypropylmethylcellulose (HPMC) employing direct compression method. The preformulation studies performed included the physical compatibility studies, Differential Scanning Calorimetry analysis, drug characterization using Fourier Transform Infra Red spectroscopic analysis and particle size analysis using sieve method. The tablets were evaluated for weight variation, hardness, thickness and friability. Results of the studies indicate that the polymers used have significant release-retarding effect on the formulation. The dissolution profile comparison of the prepared batches P1 to P8 and market preparation (Sporidex AF 375) was done by using Food and Drug Administration-recommended similarity factor (f_2) determination. The formulation P8 (10% HPMC K4M, 15% HPMC 15cps) with a similarity factor (f_2) of 77.75 was selected as the optimized formulae for scale-up batches. The dissolution data of the best formulation P8 was fitted into zero order, first order, Higuchi and Korsemeyer-Peppas models to identify the pharmacokinetics and mechanism of drug release. The results of the accelerated stability study of best formulation P8 for three months revealed that storage conditions were not found to have made any significant changes in final formulation F3. The release of cephalexin was prolonged for 6 h by using polymer combinations of HPMC and a twice daily matrix tablet was formulated.

Key words: Cephalexin, differential scanning calorimetry, Fourier transform infra red spectroscopic, hydroxy propyl methyl cellulose**,** matrix tablets, release kinetics, similarity factor (f_2)

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. Extended-release oral drug formulations have been used since the 1960s to enhance performance and increase patient compliance.[1] By incorporating the dose for 24 h into one tablet from which the drug is slowly released, peaks of high plasma concentration and troughs of low plasma concentration can be prevented.[2] This helps to avoid the side-effects associated with high concentrations and the lack of activity associated with low concentrations giving better overall therapy. In biopharmaceutics, scientists generally

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are faced with an engineering problem; to develop drug delivery systems that hit a desired target. The target in pharmacokinetics is generally a plasma/blood drug concentration that lies between the minimum effect concentration (MEC) and minimum toxic concentration (MTC). Cephalexin is a semisynthetic antibiotic derived from cephalosporin C and is almost completely absorbed from the gastrointestinal tract with a bioavailability of 95%. Cephalexin has a half life of around 1.1 h.[3-5] To maintain the therapeutic range, the drug should be administered three to four times a day, which leads to saw tooth kinetics resulting in ineffective therapy.[6] Addressing this problem, we attempted to formulate extended-release tablets of cephalexin, which can provide a constant effective drug level for six hours, based on calculations considering pharmacokinetic parameters.

MATERIALS AND METHODS

Materials

The chemicals used in the experiment are: Cephalexin monohydrate (Aurobindo Pharma Ltd., India), microcrystalline cellulose PH102 (Weiming Industries, China), lactose anhydrous (DMV- Fonterra Excipients, Germany), HPMC 15cps, HPMC K4M, HPMC K15M, HPMC K100M (Feicheng Ruitai Fine chemicals, China), colloidal silicon dioxide (Degussa India Pvt. Ltd., India), magnesium stearate (Ferro Corporation, USA), Instacoat universal (Ideal Curves Pvt. Ltd., India), Sporidex AF 375 (Ranbaxy laboratories Pvt. Ltd., India). All the other reagents used were of analytical grade.

Methods

Preformulation studies

Preformulation investigations are done to characterize properties of raw materials including their physico-chemical, biopharmaceutical, and mechanical properties, as well as compatibility.

Physical drug excipient compatibility studies

The physical compatibility studies were coupled with the stability studies at higher temperature and humidity conditions. The drug excipient compatibility study protocol included the preparation of homogenous physical mixture in 1:1 ratio of drug and all possible excipients to be used in the formulation. The physical mixtures were sealed into 15-ml USP Type III flint glass vials and stored in a stability chamber (Servewell instruments Pvt. Ltd., Bengaluru, India) for 30 days at 40°C temperature and 75% relative humidity conditions. The initial state of the mixtures was noted and further evaluation for the possible occurrence of any interactions like physical or chemical changes, was performed after the 15th and 30th day.[7,8]

Differential scanning calorimetry

The DSC thermograms of pure drug, polymer and formulation were generated and investigated for presence of additional peaks or absence of peaks indicating possible polymer interactions or phase transformations. The thermal peaks give the melting points of the samples which can be used as a test for purity analysis and also for sample characterization by comparing with the standard melting points reported for corresponding samples.[7-9]

Drug characterization using FTIR spectroscopy

The authenticity of the drug cephalexin monohydrate was confirmed by comparing the absorption maxima with that of cephalexin monohydrate reference standard. The KBr pellet method was used to generate the IR spectrum (Shimadzu Corporation, Japan) of the raw material and the reference standard and spectrum was compared for identification and purity analysis of the sample. The overlaid spectrum confirms the authenticity of the raw material and is provided in Figure 1.[7,9]

Particle size analysis of drug

Active pharmaceutical ingredient (API) [cephalexin monohydrate] was analyzed for particle size distribution by means of sieving method using mechanical sieve shaker (Verder RETSCH Trading co. Ltd, China). A series of standard sieves namely 30#, 40#, 60#, 80# and 100# were stacked one above the other so that sieves with larger pore size (less sieve number) occupied top position followed by sieves of decreasing pore size (larger sieve number) towards the bottom. Weighed quantity of API was placed in sieve no. 40. Sieve shaker was set for 5 min at amplitude of 60. Remove

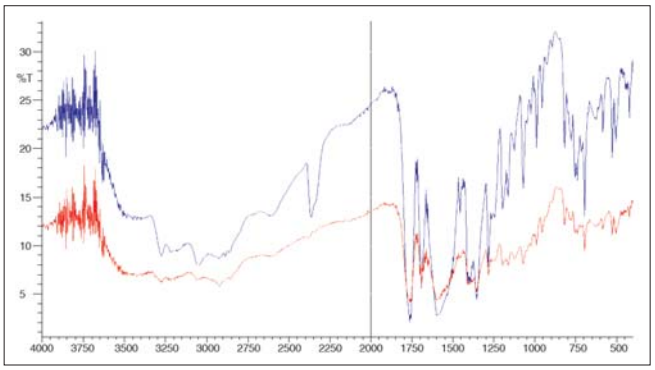

Figure 1: FTIR spectrum combined of cephalexin sample and cephalexin RS. The red spectrum and blue spectrum are of cephalexin RS and cephalexin sample respectively