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Preformulation Studies on Celecoxib with a View to Improve Bioavailability

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Accepted 25 June 2003

Revised 26 March 2003

Received 28 March 2002

The present study has three primary objectives. Firstly, in view of the low aqueous solubility of celecoxib, solid dispersions of the drug were prepared and evaluated. Different carriers were chosen and a constant drug to carrier ratio was maintained. The solid dispersions obtained were subjected to solubility and dissolution studies including dissolution rate and efficiency. The best carrier was polyvinylpyrrolidone-vinyl acetate co-polymer, as it increased the solubility by a factor of ten. It also exhibited marked increase in the dissolution rate and efficiency. Secondly, the effect of the surfactant sodium lauryl sulphate on the dissolution rate of celecoxib was investigated. The solubility of a poorly soluble drug is one of the most important factor influencing its dissolution rate and bioavailability. Presence of a surfactant in the dissolution medium permits an experimental situation similar to *in vivo* conditions and hence results in meaningful *in-vitro* observations. Dissolution study was conducted using various concentrations of sodium lauryl sulphate employing USP dissolution rate testing apparatus 1. Ultimately, a dissolution medium, which gave reproducible results *in vitro* was designed. Finally, possible drug excipient interactions between celecoxib and the commonly used excipients including those used in the preparation of its solid dispersions were investigated by storing their respective mixtures at various temperatures and humidity conditions followed by evaluating them with reference to physical and chemical stability and the results were confirmed by IR and DSC spectral studies. Polyvinylpyrrolidone was found to be the most satisfactory excipient. Degradation was evident with all other excipients studied although only at elevated temperatures.

Celecoxib is a NSAID, which exhibits potent antiinflammatory and analgesic action by inhibiting prostaglandin synthesis by specifically inhibiting COX-2 enzyme¹. It is practically insoluble in water and aqueous fluids and because of this; its oral bioavailability is dissolution rate limited. In addition,

very low values for the dissolution of the drug were obtained in *in vitro* dissolution studies using buffer pH 1.2 as dissolution media. To overcome the above problems and to improve its aqueous solubility, solid dispersions of the drug were prepared and evaluated. To obtain an experimental condition similar to *in vivo* (i.e., taking into consideration the bile acids present in the stomach) sodium lauryl sulphate was included in the dissolution media and the effect

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of its concentration on the dissolution rate of the drug was studied². Additionally, the stability of celecoxib in presence of commonly used excipients was also investigated.

Celecoxib was obtained as a gift sample from Cadila Health Care Ltd., Bangalore. Polyvinylpyrrolidone-vinyl acetate copolymer (PVPVA), Plasdane and Polymethylvinylether-maleic anhydride copolymer (PMVEMA) were obtained as gift samples from ISP specialities, Hyderabad. Sodium lauryl sulphate (SLS), lactose, microcrystalline cellulose (MCC), Polyvinyl pyrrolidone (PVP), starch, polyethylene glycol (PEG) 4000 and PEG 1450 were of AR grade and were purchased from commercial sources.

Carriers such as plasdane, PVPVA, PMVEMA, PEG 4000 and PEG 1450, lactose and starch were used to prepare solid dispersions. Fusion method³ was employed and drug:carrier in the ratio of 1:2 was selected in view of the dose (100 mg) of the drug. Starch and lactose did not fuse with the drug and hence solid dispersions were not made using these carriers.

Solubility studies on both pure drug and its solid dispersions were conducted in a thermostatic shaker water bath by shaking the concerned saturated solutions for 24 h at 37±2°. Finally, the solutions were filtered and after suitable dilution, the drug concentration was determined spectrophotometrically at 253.5 nm.

A quantity of solid dispersion equivalent to 100 mg celecoxib and 100 mg of pure drug^{4, 5} were weighed and filled into hard gelatin capsules. The size of the capsules was 1, which was selected based on the fill material and the capsules used were transparent. The dissolution rate of celecoxib capsules was studied using USP⁶ dissolution rate testing apparatus 1. A dissolution medium of 900 ml of buffer pH 1.2, a speed of 75 rpm and a temperature of 37±2° were employed in the test. Five millilitres aliquot of dissolution medium was withdrawn at intervals of 10, 20, 30 and 45 min, suitably diluted and assayed spectrophotometrically at 253.5 nm.

The surface tension of gastrointestinal fluids is a bit lower compared to that of water solutions due to presence of bile salts. The presence of surfactants in the medium for solubility and/or dissolution testing permits an experimental condition similar to *in vivo* conditions. In view of the low aqueous solubility of celecoxib, it is difficult to get meaningful *in vitro* results using the USP stated dissolution media. Crison *et al.*⁷ investigated the influence of various surfactants on

griseofulvin solubility. The best results were obtained with SLS hence the surfactant chosen for the purpose of this study was also SLS. Various concentrations of SLS that include 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0% w/v in water were prepared and 900 ml of the same was filled into dissolution apparatus and pure celecoxib equivalent to 100 mg was put into each basket. Dissolution medium without surfactant was also included in the study for the purpose of comparison⁸. A speed of 75 rpm and a temperature of 37±2° were employed for the study. A five millilitre aliquots of dissolution media was withdrawn at time intervals of 10, 20, 30 and 45 min, suitably diluted and assayed spectrophotometrically at 253.5 nm.

Drug excipient compatibility testing was carried out with lactose, starch, microcrystalline cellulose, polyvinylpyrrolidone, PVPVA and PMVEMA. Physical mixtures of the drug and the respective excipient were stored at different conditions of temperature (RT, 37°, 45° and 60°) and relative humidities (75% and 90% at RT) and were analysed for changes in appearance and assay values every month for a period of 6 mo.

The inherent solubility of the drug in distilled water and 0.1 N hydrochloric acid was 2.4 and 3.5 µg/ml, respectively. Solubility studies carried out on solid dispersions indicated that all the carriers used increased the solubility of the drug. Among the carriers studied PVPVA brought about the highest improvement in solubility which is nearly 10 times the solubility of the pure drug in water as indicated in Table 1. Rank order improvement in solubility brought about by the

TABLE 1: SOLUBILITY OF SOLID DISPERSIONS OF CELECOXIB IN WATER.

Carrier/drug	Drug carrier ratio	Solubility in water (µg/ml)
Plasdane	1:2	10.1
PVPVA	1:2	19.0
PMVEMA	1:2	18.7
PEG 4000	1:2	7.2
PEG 1450	1:2	8.0
Lactose	1:2	Did not fuse
Starch	1:2	Did not fuse
Pure drug	-	2.4

Solid dispersions were prepared by fusion method. Solubility was determined in water in a thermostatically controlled water bath for a period of 24 h.

carriers used based on 't' test at 5% level of significance is as follows: PVPVA>PMVEMA>PLASDONE>PEG 1450>PEG 4000>Pure Drug.

Capsules prepared with solid dispersions of the drug gave rapid and fast dissolution of celecoxib when compared to the capsule containing only the pure drug. Among the carriers investigated PVPVA copolymer gave the highest dissolution (93%) of the drug followed very closely by PMVEMA (89%) as indicated in fig. 1. The mechanisms responsible for increased solubility and dissolution rate of these could be due to the following reasons that include easy and rapid dispersibility of the carriers, possible reduction in particle size and deposition of the drug in the amorphous form in the solid dispersion, since the amorphous form of a compound is the highest energy form of a compound, which produces faster dissolution.

Studies on the effect of the surfactant viz., SLS on the dissolution rate of pure celecoxib indicated that incorporation of surfactant in the dissolution medium increased the dissolution rate of the drug. The increase in the dissolution rate increased with the increase in concentration of the surfactant. SLS increased the dissolution rate of celecoxib through significant incorporation of the drug into surfactant micelles. It could finally be concluded that the results obtained confirm the justification of surfactants' inclusion in

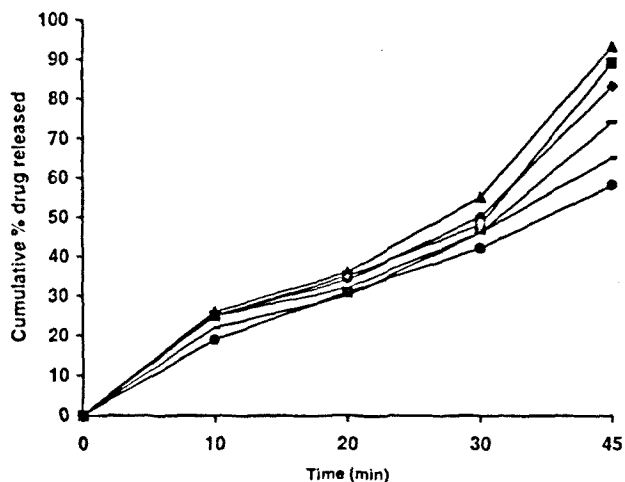


Fig. 1: Dissolution characteristics of solid dispersions and pure drug.

Drug release from pure drug celecoxib and its solid dispersions was assessed in simulated gastric fluid using a buffer solution of pH-1.2. (▲) PVPVA, (■) PMVEMA, (◆) Plasdone, (-) PEG 1450, (▣) PEG 4000 & (●) PURE DRUG.

the dissolution medium because of its similar mechanical characteristics with the bile acids present in the GIT as indicated in fig. 2.

Finally, pre-formulation studies were conducted to investigate possible drug-excipient interactions between celecoxib and the commonly used excipients like lactose, starch, MCC and PVP and also those used for making the most satisfactory solid dispersions of the drug. Drug/excipient mixtures were evaluated to allow a proper choice of the additive and to achieve an optimum drug concentration. The appearance of the drug excipient mixture remained the same during the course of the study. During the drug content estimation, interference by excipients was taken into consideration by measuring the absorbance of drug against blank, which contained the concerned excipients. There was no change in the drug content at the end of 6 mo. IR and DSC studies were also carried out to establish identity of the drug in the mixture, which indicated that the drug did not undergo any interactions under the conditions of investigation for the period of the study at room temperature (IR and DSC data not shown). Hence, the excipients studied could

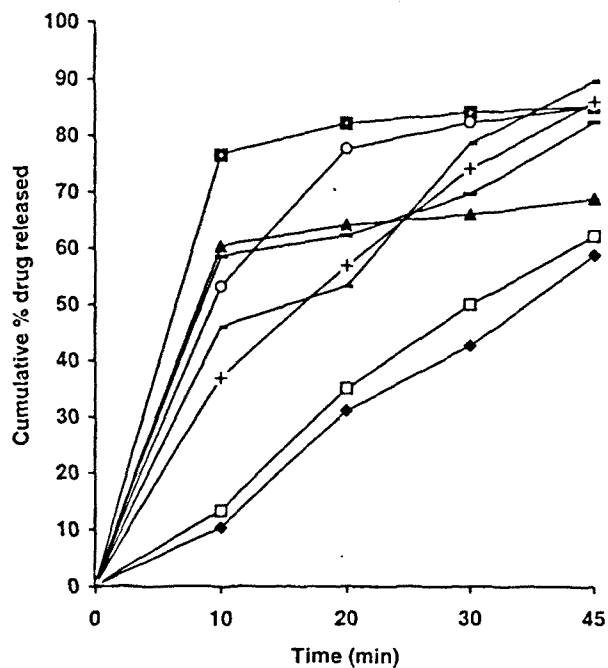


Fig. 2: Effect of SLS concentration on the dissolution rate of celecoxib.

Drug release pattern of pure celecoxib in the presence of varying concentrations of SLS. (◆) PURE DRUG, (□) 0.1%, (△) 0.5%, (-) 1.0%, (+) 1.5%, (-) 2.0%, (○) 2.5% & (■) 3.0%.

be safely used for the preparation of solid dispersions of celecoxib and improve its dissolution and bioavailability on oral administration.

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Antimicrobial Activity and Structure-Activity Relationship of Acyclic Nucleosides

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Accepted 25 June 2003

Revised 31 March 2003

Received 16 August 2002

Various acyclonucleoside analogs were synthesized and evaluated for antibacterial and antifungal activity. All the acyclic nucleosides exhibited good antifungal activity compared to the standard drug clotrimazole. However, none of the compounds possess broad-spectrum antibacterial activity. The structure-activity relationships of acyclic nucleosides were studied in order to develop the most potential antifungal agent for preclinical evaluation.

Acyclic substituted pyrimidines (acyclic nucleosides or acyclonucleosides)¹ are the sugar modified nucleoside analogs possessing biological and pharmacological activities. This group of compounds has gained increasing importance through their biological activities, particularly in the field of antiviral chemotherapy². A number of acyclonucleoside analogs are used clinically for the treatment of herpes simplex virus type-1 (HSV-1), type-2 (HSV-2), varicella zoster (VZV) and HIV-infections^{3,4}. It has been found that acyclonucleosides are monophosphorylated by viral thymidine kinase to the monophosphates and subsequently converted into diphosphates and then to the corresponding triphosphates by cellular enzymes. The triphosphate forms are then recognized by viral reverse transcriptase as substrate and the corresponding nucleoside triphosphates are incor-

porated into growing DNA chains, which lead to DNA chain termination⁵. Besides antiviral activity, acyclonucleosides are also used as antitumor agents⁶⁻⁸. In addition, various acyclonucleosides are potent inhibitor of certain enzymes, such as uridine phosphorylase, thymidine phosphorylase, which are involved in the catabolism of clinically useful nucleosides. Chu and coworkers⁹ synthesized 5-benzylacyclouridine and 5-benzyloxybenzylacyclouridine (Fig. 1, I and II) and were found to be good inhibitors of uridine phosphorylase. Goudgaon *et al.*¹⁰ synthesized phenylselenenyl- and phenylthio-substituted pyrimidines (Fig. 1, III and IV) as potent inhibitors of dihydrouracil dehydrogenase and uridine phosphorylase. Some of the pyrimidine compounds like 5-fluorouracil is used clinically for the treatment of various types of cancer. Hitchings *et al.* showed substituted pyrimidines possessed marked antimalarial¹¹ and antileukemic¹² properties. Hence the synthesis and biologi-

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