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A Strategy of Improved Formulation Development in Pharmaceutical Industry

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I. Newly developed oral dosage forms of Cyclosporin A

Although Cyclosporin A (CsA) is a powerful immunosuppresant with little adverse effect on the bone marrow, CsA administered orally in the general formulation cannot obtain high bioavailability due to its poor aqueous solubility. To improve the solubility and enhance the bioavailability of poorly water-soluble CsA, many different approaches have been made in our laboratory.

(1) Solid dosage form

CsA was dissolved in oil and surfactant mixture and the dissolved mixture was adsorbed to water-insoluble porous carrier such as silica using organic solvent.
The silica containing dissolved CsA was dried and then encapsulated in hard gelatin capsules. It was found that these CsA capsules proved to be bioequivalent to Sandimmun soft capsules.

(2) Microemulsion preconcentrate

Microemulsions are thermodynamically stable, isotropically clear dispersions of two immiscible liquids such as oil and water, stabilized by an interfacial film of surfactant molecules. The advantages of microemulsions as drug delivery systems are the improvement of drug solubilzation and protection against enzymatic hydrolysis, as well as the potential for enhanced absorption due to surfactant-induced permeability changes.
For selecting a suitable microemulsion system for peptide drug delivery, it is important to know about the physicochemical properties of the microemulsion system such as the drug solubility, the area of the microemulsion region on the phase diagram and the resulting size of microemulsion.

For preparing microemulsion system for oral delivery of CsA in this study, Cremophor RH40 was used as major surfactant together with several minor surfactants. Propylene

carbonate was used as a cosurfactant which is relatively hydrophilic and able to solubilize CsA.

(3) Solid-state microemulsion preconcentrate

A solid dosage form of CsA was prepared through adsorption of CsA dissolved in surfactant to water-insoluble porous carrier. Microemulsion preconcentrate with various surfactant combination and surfactant/cosurfactant ratio were prepared using medium chain triglyceride(surfactant), propylene carbonate(cosurfactant). Solid state microemulsions were prepared using sodium alginate, Eudragit L100, hydroxypropyl methylcellulose phthalate (HPMCP) and cellulose acetate phthalate(CAP) as enteric carrier in various weight ratio.

As the result of in-vivo absorption studies, the newly formulated solid dosage form and microemulsion preconcentrate of CsA proved to be bioequivalent to the reference drugs, Sandimmun and Sandimmun Neoral respectively. Furthermore, the tested preparations showed the bioavailability with lower degree of inter-patient variability.
Solid-state microemulsion preconcentrate formed a microemulsion immediately after reconstitution and excellent microemulsion could be obtained with 1:1 weight ratio of Eudragit L100 to CsA microemulsion preconcentrate.

These results demonstrate that the newly formulated dosage forms are bioequivalent to the reference drugs respectively, and solid-state microemulsion preconcentrate could be applicable to formulate a delayed release dosage form of poorly water-soluble drug such as CsA.

II. Development of improved oral dosage form of Omeprazole

Omeprazole is the first proton pump inhibitor to be marketed and has become one of the best selling pharmaceuticals worldwide.

Omeprazole is very slightly soluble in water, but it is very soluble in alkaline solutions as the negatively charged ion. It degrades very rapidly in aqueous solutions at low pH-values. The moisture, solvents and acidic substances have a deleterious effect on the stability of omeprazole and should be avoided in pharmaceutical formulations.

Omeprazole is usually marketed as a gastro-resistant formulation because of its instability in an acidic environment. The world brand leader, Losec capsules, manufactured by the

originator, Astra-Zeneca, contains beads incorporating the active ingredients in a matrix which is protected against acid degradation by polymeric layers. The capsules are usually packed in bottles with a dessicant in a lid to provide further protection.

In order to develop an improved dosage form of Omeprazole, several different approaches have been made.

(1) Formulation

In order to prepare a formulation containing Omeprazole, a stabilizer contributing to alkaline environment is inevitably needed. At the designing stage of a formulation of omeprazole, L-arginine, basic amino acid, was choosed as a stabilizer because of its strong basicity and having no harmful effect to human body.

Although the original product, Losec™ capsules, formulated with capsule containing small enteric-coated pellets which were manufactured using double coating layers, a novel approach have been made in our laboratories on introducing a tablet dosage form with single coating layer.

(2) Stability

As the results of stability studies, the newly prepared Omeprazole formulation using L-arginine proved to be stable more than 3 years under the condition of room temperature. Furthermore, it was revealed that the newly prepared formulation is much more stable than Losec capsules when it was exposed to the environment of high temperature and humidity.

(3) Bioequivalence

The bioequivalence of test product (OMP™ tablets, CKD Pharmaceutical Corp.) and reference product (Losec™ capsules, Astra-Zeneca) was evaluated in 16 normal male volunteers following oral adminstration by randomized two period cross-over study.
In this study, it was concluded that OMP tablets are bioequivalent to Losec capsules.