CHAPTER I
INTRODUCTION AND OBJECTIVES OF THE INVESTIGATION

The most important property of a drug delivery system is its ability to deliver the active pharmaceutical ingredient (API) to the site of action in the body in an amount sufficient to produce the desired therapeutic response. This property of the drug delivery system is referred to as bioavailability. Bioavailability is more precisely defined as the rate and extent of absorption (availability) of drug to the systemic circulation. About 95% of all new potential therapeutics (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pHs and consequent low dissolution rate. These drugs are classified as class II drugs under BCS and pose challenging problems in their pharmaceutical product development process. The drug in solid dosage form (tablet) must undergo dissolution before it is available for absorption from gastrointestinal tract. Dissolution forms the rate limiting step in the absorption of drugs from solid dosage forms especially when the drug is poorly soluble.

Several modern organic drugs belong to class II category under BCS and exhibit low and variable dissolution rates. These drugs need enhancement in dissolution rate and bioavailability to derive their maximum therapeutic efficacy. Several conventional
methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, microemulsion and self-emulsifying systems are available to enhance the bioavailability of BCS Class II drugs.

Etoricoxib and aceclofenac, widely prescribed anti-inflammatory and analgesic drugs belong to class II under BCS and exhibit low and variable oral bioavailability due to their poor aqueous solubility. They are practically in soluble in water and aqueous fluids. As such their oral absorption is dissolution rate limited and they require enhancement in solubility and dissolution rate for increasing their oral bioavailability. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies. Surfactants also increase the solubility of lipophilic water-insoluble drugs by micellar
solubilization. In the present investigation two surfactants namely (i) Pluronic F127 (Poloxamer) and (ii) Kolliphor HS15 (Solutol) were tried to enhance the solubility and dissolution rate of the selected poorly soluble drugs. Pluronic F127 is a polyethylene oxide- polypropylene oxide- polyethylene oxide triblock co-polymeric surfactant of non-ionic nature and is used as a solubilizing agent\textsuperscript{6-8}. Pluronic F127 was also evaluated as carrier in solid dispersions for enhancing the dissolution rate of poorly soluble drugs\textsuperscript{9-11}. Kolliphor HS15 consists of polyglycol mono- and di-esters of 12-hydroxystearic acid (lipophilic part) with about 30% of free polyethylene glycol (hydrophilic part) and is used as non-ionic solubilizer and emulsifying agent\textsuperscript{12}. Kolliphor HS15 has been shown to be safe in various animal toxicity models with reduced histamine levels. Kolliphor HS15 has been approved in Canada and Argentina in marketed injectable-drug products\textsuperscript{13}.

Though cyclodextrin complexation and use of surfactants for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate. In the present investigation cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) were tried to enhance the solubility, dissolution rate and bioavailability of etoricoxib and aceclofenac. The major objective is to evaluate the individual main effects and combined (interaction) effects of cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15
and Pluronic F127) on the solubility, dissolution rate and bioavailability of etoricoxib and aceclofenac in a series of $2^2$ factorial experiments and to evaluate the feasibility of formulating etoricoxib and aceclofenac tablets with enhanced dissolution rate and dissolution efficiency employing drug-CD-surfactant complex systems.

The specific objectives of the investigation are as follows:

1. To evaluate the individual main effects and combined (interaction) effects of cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) on the solubility and dissolution rate of Etoricoxib and aceclofenac in a series of $2^2$ factorial experiments.

2. To evaluate the feasibility of formulating the Drug-CD-Kolliphor HS15 complex systems into compressed tablets with enhanced dissolution rate. The individual main and combined (interaction) effects of cyclodextrins (βCD and HPβCD) and Kolliphor HS15 on the dissolution rate of (i) Etoricoxib and (ii) aceclofenac from tablet formulations was investigated in a series of factorial experiments.

3. To evaluate the dissolution kinetics and characteristics of Drug-CD and Drug-CD-Surfactant inclusion complexes and tablets formulated employing them.

4. To evaluate the compatibility of the selected drugs with cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) by IR and DSC spectral studies.
5. To evaluate the physical state of drug in the drug-CD-
surfactant inclusion complexes by XRD.

6. Pharmacokinetic evaluation of (i) aceclofenac - βCD and (ii)
aceclofenac- βCD- Kolliphor HS15 complexes in comparison
to aceclofenac pure drug with a view to evaluate their in vivo
performance.

7. To evaluate the stability of selected tablets formulated
employing drug-CD- Kolliphor HS15 inclusion complexes.
Extensive experimentation, both in vitro and in vivo was
conducted to achieve the objectives and the results obtained
are presented and discussed in the subsequent chapters.

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Res. 2007; 23:2709-2728.


