CHAPTER 3

CYCLODEXTRINS IN PHARMACEUTICALS

3.0. INTRODUCTION

The number of papers and patents dedicated to the industrial application of cyclodextrins is steadily increasing, 35% of all patents and potential applications published before 1985 deal with pharmaceutical applications. The advantages of potential utilisations, the availability of cyclodextrins, and good economic reasons play a decisive role in the growing interest in cyclodextrins for the pharmaceutical industry. This is reflected in the increasing number of reviews on this topic [25,51,113,127,210,244,280,299,313,386,397,398,428).

Many new, and to a greater extent old, generic drugs need reformulation to a higher standard than was considered satisfactory some years ago. The search for new drugs, with exponentially rising expenses, continues. The search for new formulations, which is a less expensive exercise is resulting in more stable preparations, many with better bioavailability properties. This allows for the design of new, and more effective, drug delivery systems, and gives the main impetus for the research into cyclodextrin drug combinations.

As early as 1953, before its potential was even realised, the first patent by Freudenberg Cramer and Plieninger [47] for preparation of drug cyclodextrin complexes was taken out. In this one and a half page patent all of the advantageous effects of cyclodextrin complexation have been covered: unstable substances, such as azulene become storable. The rapid elimination of the readily soluble blood circulation regulator, pentamethylenetetrazole can be retarded. In the case of substances with an unpleasant taste, e.g. bromoisovaleryl-urea, complex formation results in the improvement of taste.

Systematic studies on the drug solubility enhancing effects of cyclodextrin were performed by Lach et al [30,159,161] in the 1960's. The solubility of all the studied drugs increased with increasing cyclodextrin concentration. Degree of improvement was strongly dependent on two fundamental properties of the drug: molecular size, and solubility in the absence of cyclodextrin.

First formulation experiments [49] as well as the first human bioavailability [52] results were published by Frümming at the beginning of the 1970's. The very limited availability, at realistic prices, and the lack of toxicity studies on β-cyclodextrin, impeded the continuation of his very promising work.

With the beginning of the cyclodextrin production in Japan many Japanese laboratories launched cyclodextrin research projects. Nagai's laboratory in Tokyo and Uekama's laboratory in Kumamoto produced results concerning the application in both the formulation and bioavailability enhancement of drugs. Simultaneously cyclodextrin production began in Hungary, and six months toxicity studies proved that β-cyclodextrin is not toxic.
The first legislated cyclodextrin containing products were the PGE2-β-cyclodextrin sublingual tablet in Japan, and in Hungary the flavour complexes for food flavouring.

In at least 10% of orally applied drugs the active ingredient seems to be complexable; for about half of these cases one or other physical or chemical properties can be modified to such an extent, that cyclodextrin is worth considering [270].

Taking into account all the factors, - according to very cautious estimations - in at least 2% of all currently produced tablets, the presence of cyclodextrin as a complexing agent or auxiliary substance is favourable. It means, that in the not too distant future, several thousand tons of the cyclodextrin market may be consumed by the pharmaceutical industry for production of oral preparations, and a smaller amount in other drug formulations.

3.1. ASPECTS OF DRUG FORMULATION WITH CYCLODEXTRINS

3.1.1. Purposes and advantageous effects

Cyclodextrins can be used in drugs either for complexation or as auxiliary additives such as carriers, diluents, solubilisers or tablet ingredients.

Inclusion complex formation of a drug results in the modification of its physical and chemical properties. These modifications are usually advantageous,

a. in the formulation of oral drugs:
   - liquid compounds can be transformed into a crystalline form which is suitable for tablet manufacturing;
   - bad smell and sometimes taste can be covered by complex formation;
   - incompatible compounds can be mixed when one or more reacting components are complexed;
   - the content uniformity of low dose tablets is improved by tabletting the microcrystalline complexes
   - cyclodextrins and their complexes are not generally hygroscopic.

b. improvement of physical and chemical stability:
   - volatile compounds can be stabilised against loss by evaporation;
   - cyclodextrin inclusion complexation protects oxidisable compounds against oxidation by air;
   - rate of decomposition, disproportionation, polymerisation, autocatalytic reactions etc., are considerably decreased;
   - sensitivity to light, gastric acid etc., is reduced;

c. bioavailability of poorly soluble drugs can be enhanced:
   - solubility in water as well as the rate of dissolution of poorly soluble substances can be increased;
   - after the oral administration of poorly water soluble drugs, higher blood levels can be achieved if they are complexed with cyclodextrin or a reduction of dose can be achieved.