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PHARMACEUTICAL TECHNOLOGY

drug stability

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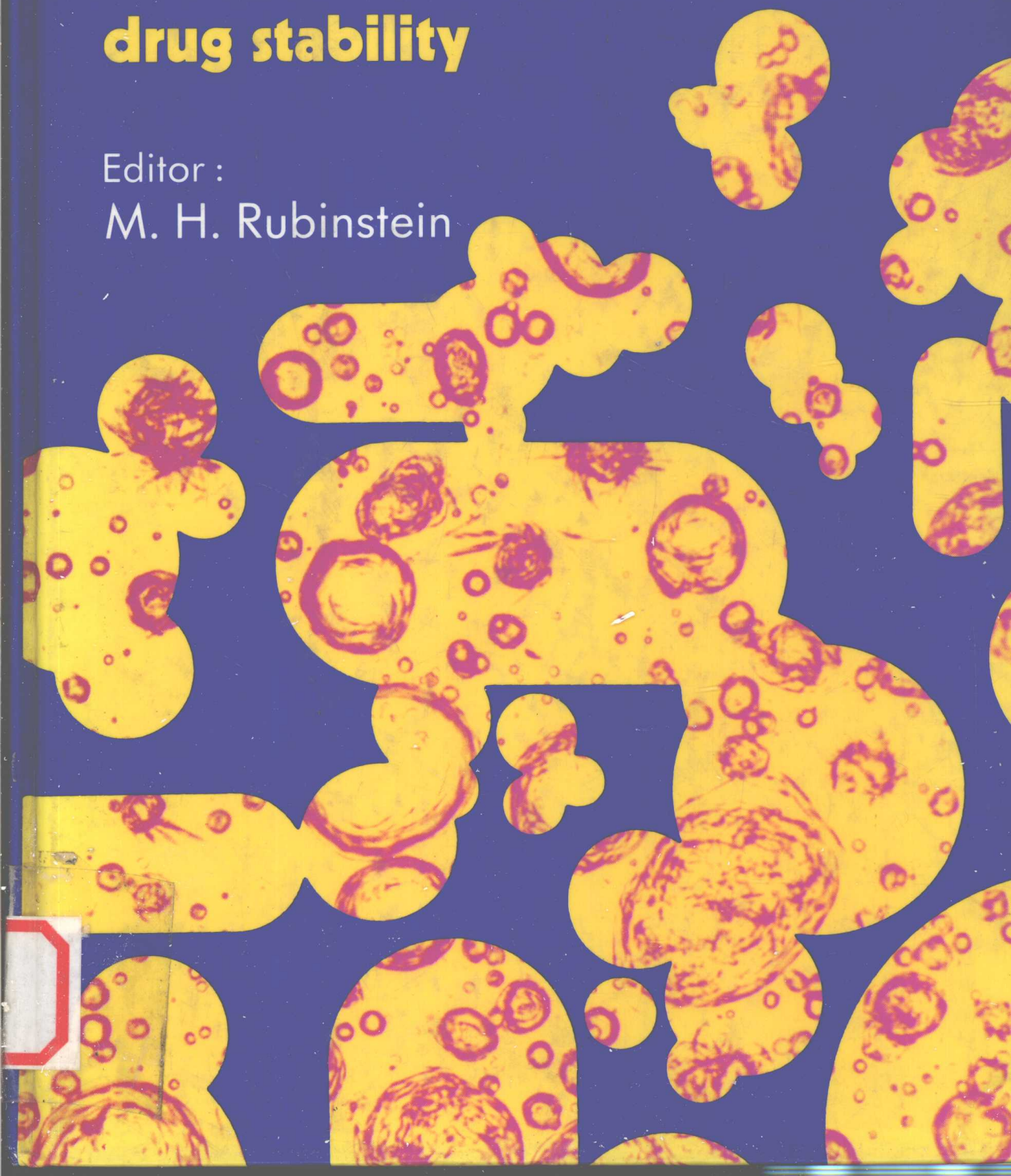

PHARMACEUTICAL TECHNOLOGY
Drug Stability

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PHARMACEUTICAL TECHNOLOGY
Drug Stability

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Preface

Pharmaceutical technology is the science of producing acceptable dosage forms which once administered, release the drug substance into the body at a predetermined time and rate. However, the dosage forms should also be stable and continue to release the drug at the same time and rate even after prolonged ageing. No measurable chemical or physical degradation must occur. The problems of producing dosage forms that are stable and remain so under differing climatic conditions is a science in itself and this third volume from a 'series within a series' is designed to reflect new advances and techniques for enhancing drug stability from formulated pharmaceuticals. It represents a range of highly topical areas from authors of international repute.

Cyclodextrins have been used for many years to form inclusion compounds with a variety of drug molecules. The first chapter presents a comprehensive review of the current areas that cyclodextrins have in modern pharmaceutical formulation. They can enhance the thermal and oxidative stability of drug molecules and in some instances hydrolysis can be reduced. Inclusion compounds may also improve drug dissolution rate and increase drug absorption through biological membranes. So cyclodextrins are exciting and important compounds which will obviously play a very important role in pharmaceutical formulation in the 1990s.

Liposomes have attracted a lot of interest in recent years as unique drug carrier systems. In the second chapter liposomes have been used to stabilize local anaesthetics and the degradation kinetics evaluated, whilst in Chapter 3 the processing factors influencing the stability of freeze-dried sodium ethacrynate have been investigated. Later chapters look at the use of colloidal and porous silica as carriers and stabilizing systems in solid, semi-solid and liquid dosage forms. New analytical techniques have not been ignored and in Chapter 9 the advantage in terms of selectivity, time saving and economy of using short and ultra-short HPLC columns for drug analysis in dissolution testing, is presented. Finally in Chapter 12 a control system is

described for monitoring changes in particle growth by crystallization in pharmaceutical suspensions.

As with the predecessor volumes (*Tableting Technology,* Volume 1, and *Controlled drug release,* Volume 1, published by Ellis Horwood Ltd in 1987), the book is based on contributions made to the prestigious series of annual conferences held to review progress in pharmaceutical technology on a worldwide basis. This volume includes all the latest developments, incorporating international discussion from Harrogate (1986), Canterbury (1987) and London (1988).

August 1988

Michael H. Rubinstein

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Cyclodextrins, their value in pharmaceutical technology

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SUMMARY

Cyclodextrins are cyclic oligosaccharides consisting of a variable number of glucose units (usually 6 to 8). The ring formed by cyclodextrins is externally very hydrophilic and relatively apolar internally. In liquid or solid medium, these molecules are capable of forming inclusion compounds with many other molecules. The inclusion compounds thus formed display interesting properties and may increase the stability of the guest molecules. Greater stability may be shown towards heat, resulting in lower volatility or higher thermal resistance. In addition, greater stability towards oxidation may result. It may also be important for products in solution, since in certain cases, hydrolysis is inhibited to varying degrees.

For relatively insoluble active ingredients, inclusion may improve the solubility or drug dissolution rate. Depending on the stability constant of the inclusion compound formed, a better passage of the active ingredient through membranes may be observed. *In vivo,* this may be reflected by an increase in bioavailability, with a simultaneous increase in therapeutic effectiveness.

INTRODUCTION

Cyclodextrins have been known for nearly a century and have been isolated by Villiers [1] in 1981 from the degradation products of starch. The description of their preparation, isolation and main characteristics was made by Schardinger in the years 1903 to 1911 [2–4].

Cyclodextrins and inclusion compounds

Cyclodextrins are cyclic oligosaccharides produced by the enzymatic degradation of starch. The enzyme, cyclodextrin glycosyl transferase, is produced by different bacilli, especially *Bacillus macerans*. Depending on the reaction conditions, cyclodextrins contain six, seven or eight glucose units, connected by α-(1,4) bonds, known as α-, β- and γ-cyclodextrins. The particular form of the molecule requires a special arrangement of the different functional groups. Generally the interior of the cyclodextrin cavity is apolar in relation to water, and the exterior is hydrophilic.

Table 1 — Properties of the main cyclodextrins

Cyclodextrin	No. of glucoses	Molecular weight	Solubility in water ($g/100\,cm^3$)	Cavity dimensions (Å)		
				Depth	i.d.	o.d.
α-cyclohexaamylose	6	972	14.50	7.9–8.0	4.7–5.2	14.6±0.4
β-cyclohexaamylose	7	1135	1.85	7.9–8.0	6.0–6.4	15.4±0.4
γ-cyclohexaamylose	8	1297	23.20	7.9–8.0	7.5–8.3	17.5±0.4

Some of the properties of cyclodextrins are given in Table 1. Cyclodextrins are water-soluble; β-cyclodextrin being the least soluble. Solubility increases sharply with temperature, allowing easy recrystallization on cooling.

One of the most interesting properties of cyclodextrins is their ability to form inclusion compounds with a wide variety of molecules, which apparently only have to satisfy a single condition: namely to be adaptable entirely, or at least partially, to the cavity of the cyclodextrins [5]. Inclusion compounds are usually prepared in a liquid medium.

In the case of water-soluble materials, a drug is added to an aqueous solution of cyclodextrin, usually in stoichiometric quantities. The mixture is heated with agitation for several hours, or even several days. The inclusion formed precipitates spontaneously or by cooling. The water solubility of the drug can very often be increased by incorporating a suitable additive [6,7]. The mixture can also be freeze-dried or spray-dried [6,8–10]. The final product in this case is amorphous.

If the substance to be included is insoluble in water, it is dissolved in an organic solvent and added, with agitation, to a hot aqueous solution of cyclodextrin. Crystallization takes place within hours or days.

In some cases, the formation of the complex in the solid phase is thermodynamically spontaneous, although its stability is greater in aqueous solution than in the solid phase [11]. Inclusion is normally achieved by microgrinding [11,12].

The inclusion of a drug molecule in a cyclodextrin molecule consititutes a true molecular micro-encapsulation that is likely to alter the physico-

chemical and even the biological properties of the drug molecule considerably. This has encouraged research into application in the area of formulation. In Japan, these investigations culminated in the marketing of a prostaglandin E_2/β-cyclodextrin complex, Prostarmon, marketed by Ono [13].

At the pharmacological technological level, the applications of inclusions are essentially in the improvement of molecule stability [14] and, above all, the improvement of their solubility and bioavailability [15].

Improved stability

The improvement of stability may have three essential objectives: heat stability, oxidation resistance and hydrolysis resistance (or stability in aqueous solution).

Heat stability

Substances included in cyclodextrins to improve their stability may be liquid or solid.

Reduction of volatility

The reduction of volatility can be demonstrated by a rise in the boiling point or evaporation conditions of the liquids, or of sublimation for solids. Szejtli [16–20] prepared inclusion compounds with many volatile substances, including spices, plant flavours and essences, camphor, menthol and thymol. The inclusion compounds obtained facilitated the handling of the products, particularly as they transform a liquid into solid. The volatility of the substances produced is sharply reduced, and this has been closely investigated with anethole [16].

The value of these inclusions is to permit improvements in the quality of the pharmaceutical dosage forms in which they are incorporated, especially suppositories [18,19] and inhalations [17,20]. In suppositories, their melting point and hardness are often lowered by adding volatile substances, and the incorporation of these substances as inclusions often overcomes these drawbacks [19]. In the case of inhalations containing high proportions of volatile essences, the preparation is liquid, difficult to handle, and is sometimes volatilized too rapidly if mixed with boiling water. By solidifying the product, inclusion facilitates handling and slows down its vaporization while at this same time prolonging its effect [20].

The reduction of volatility can be examined by differential thermal analysis or by thermogravimetry. These techniques were used by Uekama for inclusions of clofibrate in β-cyclodextrin [21], cinnamic acid in β-cyclodextrin [22], and benzaldehyde in α-, β- and γ-cyclodextrins [23]. Nakai *et al.* [24] used thermogravimetry to analyse inclusions of parahydroxybenzoic acid in α- and β-cyclodextrins. The sublimation of parahydroxybenzoic acid at 180°C and 210°C is considerably reduced, particularly with α-cyclodextrin, and this is probably due to a closer adjustment of the molecule in the α-cyclodextrin cavity than in that of β-cyclodextrin.

An interesting stabilization effect achieved by inclusion in β-cyclodextrin, is that of the 5-mononitrate of isosorbid [25]. This is a volatile

substance, and, during the storage of tablets, needles are formed at the surface, especially at certain temperatures and humidities. An inclusion eliminates this process and also reduces the degradation of the product with time.

Higher heat resistance

In the same way that inclusion raises the boiling point and evaporation and sublimation temperatures, it can also raise the melting point. This has been observed for metronidazole included in β-cyclodextrin [26] and for prostaglandin F_{2_α} [27]. Another demonstration of higher heat resistance is the elevation of the decomposition temperature. Szejtli investigated a series of aromatic oils [16]. In the case of essence of marjoram, for example, the volatile compounds are liberated and can be identified by thin film chromatography above 100°C in the case of the pure product, or in the form of a physical mixture with β-cyclodextrin, with their decomposition occurring at 240°C. If inclusion is carried out, the volatile substances only appear above 160°C, and decomposition only takes place above 300°C.

Oxidation resistance

Oxygen

The protective action of complex formation with cyclodextrins can be investigated by placing the products to be tested in a Warburg apparatus, under oxygen, at 37°C. The absorption of oxygen is measured at regular time intervals.

Using this method, Szejtli [28,29] showed an improvement in the stability of vitamin D_3, when it is complexed with β-cyclodextrin. From these results, it would appear that pure vitamin D_3 can fix 140 μl/mg of oxygen, and that the physical mixture is worse than this. However, the inclusion complex fixed only 11.2% of this amount over the same experimental time period (500 h).

Szejtli [16] used the same method to study the oxidation resistance of vegetable essences complexed with β-cyclodextrin.

Oxidation accelerators

Heat, light and metal salts (copper sulphate) all increase the degradation of vitamin D_3 by oxidation. This can be inhibited, and considerably reduced, by inclusion of the vitamin in β-cyclodextrin [28,29]. The product so treated can be presented in tablet form, having better stability against heat than tablets of the pure vitamin [28,29]. The complex vitamin D_3/β-cyclodextrin preserves 94% of its therapeutic activity, even after being stored for seven days at 60°C [30]. Similarly, the inclusion of vitamin A in α-cyclodextrin increases its stability against heat [31]. The sensitivity to light of clofibrate [21] and guaiazulene [32] is reduced by inclusion in β- and γ-cylodextrins.

Resistance to hydrolysis and to degradation in solution

The foregoing results tend to imply that the inclusion of a drug molecule in cyclodextrin generally imparts good stability to the molecule. In actual fact, this is not always the case, especially for stability in aqueous medium. Many

molecules have been investigated, and the results vary considerably depending on the drug molecule, the type of cyclodextrin employed, and the pH of the medium. A number of results are reviewed below, to show this diversity.

The stability of vitamin K_3 inclusions in solution, investigated by Szejtli [33] is poor irrespective of the pH, and β-cyclodextrin actually accelerates decomposition. Møllgaard Andersen and Bundgaard showed that the degradation of hydrocortisone in β-cyclodextrin is accelerated in alkaline medium, whereas it is virtually unchanged in a neutral or acidic media [34]. This can be explained by the degradation mode of hydrocortisone, which is different in alkaline and acid media. These authors [35] further investigated the stability of betamethasone 17-valerate in aqueous alkaline solution, in which this drug undergoes a rearrangement into the less active 21-valerate. While α-cyclodextrin has no effect on this rearrangement, β-cyclodextrin was found to accelerate it, and γ-cyclodextrin slowed it down substantially. These results are explained by the differences of conformation of the inclusion compounds (1/1) formed. With nitrazepam, Møllgaard Andersen and Bundgaard [36] also showed that the presence of β-cyclodextrin has no effect on hydrolysis in 0.1 M hydrochloric acid medium. This could have been due to the ionization of the nitrazepam at this pH, since the ionized products do not easily form inclusions with cyclodextrins.

Various investigations have been conducted with aspirin. Nakai and Terada [12,37], examining its stability in the solid state, associated with α-, β- and γ-cyclodextrins, in the form of inclusions, physical mixtures, or ground mixtures, showed that, if the acetoxyl groups are free, the molecule is relatively stable, and if they are connected by hydrogen bonds to the hydroxyl groups of the cyclodextrins, the aspirin molecule becomes unstable.

Nakai [23] investigated the hydrolysis of aspirin at pH 1.0 in the presence of α-, β- and γ-cyclodextrins. The degradation constant does not vary in the presence of α-cyclodextrin, but is reduced with β- and γ-cyclodextrins; the effect of β-cyclodextrin being more pronounced. This is owing to the impossibility of including aspirin in α-cyclodextrin, of its good inclusion in β-cyclodextrin, and its excessively loose inclusion in γ-cyclodextrin, leaving a void into which a proton or molecule of water can penetrate.

The results of work on indomethacin are contradictory. Szejtli [38], reported that inclusion in β-cyclodextrin does not protect indomethacin from degradation at pH 8.0. However in a patent, the Sumimoto Chemical company reports a stabilizing effect of the inclusion [39], and Hamada [40] confirmed this result, suggesting also that the addition of α-cyclodextrin has no effect.

For barbiturates, Nagai [41] reported that the degradation of hexobarbital in alkaline solution at pH 12 is increased by β-cyclodextrin and slightly decreased by α- and γ-cyclodextrins. Min [42] and Kyoko [43] reported an improvement in the stability of aqueous solutions of phenobarbital and various barbiturates by the addition of β-cyclodextrin. Fujioka [44] investigated the degradation of bencyclane in acidic medium and showed that its inclusion caused a reduction in degradation, dependent on the cyclodextrin used; the rising rank order being α, γ and β.

Proscillaridin is unstable in gastric medium. Uekama [45] showed that inclusions in α-, β- and γ-cyclodextrins reduce the instability at pH 1.46 at 37°C. However, this result is only really significant with β- and γ-cyclodextrins, since the α cavity is too small and cannot protect the proscillaridin.

According to Møllgaard Andersen and Bundgaard [26], the hydrolysis of metronidazole benzoate is reduced by inclusion in β-cyclodextrin, and the inclusion also appears to slow down the growth of crystals in suspension.

Many patents, particularly Japanese, report the inclusion of prostaglandins in α- and β-cyclodextrins, as well as their methylated derivatives [46–52]. Although their interpretation is often difficult, an improvement in stability generally appears to be the case in aqueous solutions, as well as in the storage of freeze-dried products. Uekama [53] showed that the inclusion of prostaglandin E_1 in γ-cyclodextrin increased its heat stability and slowed down its conversion to prostaglandin A_1.

Many other substances have also been investigated, including ampicillin and methicillin, whose hydrolysis rates were significantly decreased by inclusion in β-cyclodextrin [54]. Similarly, the presence of β-cyclodextrin slows down the degradation of cinnarizine in acidic solution [55].

Improved dissolution and bioavailability

In vitro *investigations, higher water solubility*

Demonstration of the effect of cyclodextrins

Hamada *et al.* [40] studied the influence of α- and β-cyclodextrins on the solubility of a series of non-steroidal anti-inflammatory substances, by comparing it with that of glucose. For these products, glucose appears to have no effect, α-cyclodextrin is either ineffective or only slightly effective, and β-cyclodextrin causes an increase in solubility. These results are explained by the formation of inclusion compounds, in accordance with the size of the drug molecules in comparison with the dimensions of the cyclodextrin cavity.

It is unnecessary for the inclusion to be preformed for higher solubility to occur. This was shown by Corrigan and Stanley, working on phenobarbitone [56], and on benzothiazide derivatives [57]. In both cases, simple physical mixtures of the active ingredients with β-cyclodextrin displayed better solubility than the active ingredients themselves. The products obtained after freeze-drying of a solution of these mixtures yielded increased solubility. This can be explained either by the hydrophilic nature of the freeze-dried products and their amorphous character, or by the existence in the freeze-dried mixture of a varying proportion of preformed inclusion compound.

Solubility diagram and stability constant

Higuchi's [58] solubility analysis method was applied by different authors to various active ingredients in the presence of cyclodextrins. Uekama, for example, studied digitoxin [59], digoxin [60], eighteen steroid hormones

[61], proscillaridin [45], spironolactone [62], clofibrate [21], flurbiprofen [63], propylparaben [64], prostaglandins E_1 [53] and F_{2_α} [27]. This method was also applied by Møllgaard Andersen and Bundgaard to hydrocortisone [34] and to spironolactone [68].

If the solubility increases linearly with cyclodextrin concentration, the curve is said to be of Higuchi's type A_L, and corresponds to the formation of an inclusion compound with the stoichiometry of 1/1. The curves are of Higuchi's type B_S if, after a linear rise, a plateau is observed, followed by a decrease corresponding to the precipitation of a microcrystalline inclusion compound with a different stoichiometry.

The plotting of these diagrams serves to calculate an apparent stability constant from the straight part of the curves. This constant reflects the correct adjustment of the guest molecule inside the cavity of the host molecule. Hence, for example, the stability constants calculated by Seo *et al.* [62] for the inclusion compound of spironolactone with α-, β- and γ-cyclodextrins are 960, 27 500 and 7600 M^{-1} respectively. As a rule, steroids display better interaction with β- or γ-cyclodextrins, as α-cyclodextrin is much too small to allow inclusion [61].

Dissolution of inclusion compounds

Solubility diagrams remain too theoretical for practical application, because they are plotted when equilibrium is reached, in other words after four to ten days of agitation. Thus, the analysis of the dissolution kinetics of solid inclusion compounds is often preferable, because this can be used to reveal not only an improvement in solubility, but also the rate of passage into solution. These studies also help to point out the value of using a solid inclusion from the formulation standpoint, rather than the simple physical mixture [38,69], or a freeze-dried or spray-dried product [9,10].

A comparison of the inclusion compounds obtained with different cyclodextrins is interesting. Inclusion compounds with flurbiprofen in β- and γ-cyclodextrins [63] display stability constants of 5100 and 460 M^{-1} respectively, and the crystallinity of the inclusion in γ-cyclodextrin is less pronounced than that of the inclusion in β-cyclodextrin. The results of the dissolution of these substances reveal not only faster dissolution for the γ-cyclodextrin inclusion compound, but also a progressive dissociation of this compound in aqueous medium, rapidly causing precipitation of free flurbiprofen.

For the more convenient study of these dissociation mechanisms, rather than using the dissolution method which consists of dispersing a quantity of test product in the dissolution medium, it is often more interesting to use the rotary disc method. This method offers the advantage of linearizing the dissolution curves when dissolution is uniform, but, on the other hand, if the inclusion compound decomposes in aqueous medium, the released active ingredient reprecipitates, and the curve obtained by the rotary disc method displays a negative curve versus time. Because it offers a particularly clear representation, this method has often been used [45,60-62,68,70,71].

Diffusion through semi-permeable membranes

The foregoing studies help to establish a hypothesis according to which water-soluble inclusion compounds, by dissociation, increase the bioavailability of the active ingredients they contain, a hypothesis which needs to be substantiated. This is why both Szejtli [72] and Uekama [21,62,71,73,74] investigated the possibilities of diffusion of active ingredients or their inclusion compounds through semi-permeable membranes. To do this, they employed systems comprising a cellophane membrane between a donor compartment and an acceptor compartment, each equipped with an agitation system. With the donor and acceptor compartments filled with water, and the test products (active ingredient alone and inclusion compound) added in the solid state to the donor compartment, then the diffusion of the inclusion compound is often not as significant as expected. In some cases, such as fendiline in β-cyclodextrin [72], it is lower than that of the active ingredient alone, and, in other cases, such as that of flurbiprofen in β- and γ-cyclodextrins [71], although it is better than that of the active ingredient alone, it does not agree with the comparative effect of these cyclodextrins on dissolution.

To explain these results Otagiri *et al.* [71] compared them with that obtained by placing the solutions of active ingredient and inclusion compound directly in the donor compartment. In this case, the active ingredient (flurbiprofen) diffused better than the inclusion compound. Diffusion is closely dependent on molecular size, and the inclusion compounds diffuse with greater difficulty than the drug molecules. In addition, diffusion must be related to the stability constant: the higher the constant the less the diffusion (for inclusion compounds, 1/1, of flurbiprofen, $K\beta = 5100\ M^{-1}$ and $K\gamma = 460\ M^{-1}$).

These studies show that this investigative method is perhaps not a good indication of possible absorption *in vivo*.

Interface transfer

Hoping to develop an experimental model imitating the *in vivo* absorption of inclusion compounds, Uekama *et al.* [64] used an *in vitro* dissolution model $S/L_w/L_o$ (solid phase/aqueous liquid phase/organic liquid phase) [76,77]. The model consists of a rotary disc in an organic phase. With pure substances, a good correlation was observed between the theoretical concentration of product passing from the solid phase to the organic liquid phase and the experimental values. With inclusion compounds, the mechanism was much more complex, and the theoretical calculation of diffusion became problematic. However, the measurement of the concentration in the organic phase always remained a good indication of *in vivo* absorption for active ingredients resorbed by passive diffusion.

In situ *resorption*

In addition to the *in vitro* experimental model, Uekama developed and used an *in situ* experimental model, $S/L_w/$*in situ* (solid phase/aqueous liquid phase/*in situ*). This model consists of perfusing *in situ* a predetermined