Journal of Pharmaceutical & Biomedical Analysis
Vol. 8, No. 6, pp. 499–506, 1990
Printed in Great Britain

0731–7085/90 $3.00 + 0.00

French and/or European perspectives on biopharmaceutical characterization of drug dosage forms*

J.-M. AIACHE

Biopharmaceutics Department, Faculty of Pharmacy, 28 Place Henri-Dunant, P.O. Box 38, F-63001 Clermont-Ferrand Cédex, France

Abstract: In order to bring definitions of drug dosage forms up to date, it was necessary for the French Pharmacopoeia to propose assays allowing the quality control of the dosage forms to be based on the kinetics of drug release *in vitro*. Currently, five examples can be cited of dosage forms that can be characterized by release *in vitro*. (1) Oral solid dosage forms — for tablets, all the parameters of powders before compression (e.g. flowability, tableting properties) are being studied in addition to the dissolution tests. (2) Rectal dosage forms — the disintegration test of suppositories will be discarded and a new dissolution test using a special flow-through cell is now being studied. (3) Inhalations — since particle diameter is the most important factor for inhalation activity, a method has been developed to give the correct answer to this question. (4) Modified release drug dosage forms — these have been defined separately from the conventional forms. For the peroral route, they are: (i) accelerated release drug dosage forms, (ii) sustained release drug dosage forms and (iii) delayed release drug dosage forms. To emphasize the differences in the release kinetics, use of the paddle method, well known in the USP, and the flow-through cell has been suggested and described in the European Pharmacopoeia. Some associations and/or *in vitro–in vivo* correlations have increased the interest in the last method. (5) Transdermal delivery systems — these are defined separately from plaster and sticking-plaster. The use of a cell method was suggested to study the drug release and some comparisons between different techniques are presented.

Keywords: *Pharmacopoeias (European, French, German); tablets; capsules; dissolution testing; suppositories; flow-through cell;* in vitro–in vivo *correlation; modified release dosage forms; transdermal therapeutic systems; diffusion cell.*

Introduction

1 January 1993 will see the opening of the European Common Market and the free exchange and circulation of persons and goods. Among these goods there are, of course, the pharmaceuticals. Therefore, the 12 countries in the EEC have decided to normalize the drug dosage forms by definition. In this way the Health Authorities will find methods to control these dosage forms from the pharmaceutical point of view as distinct from the biopharmaceutical one.

Many explanations have been given for this normalization. Firstly, the language: there is as yet no plan for a single language, and the 12 countries will continue to use their own languages. Some dosage forms are designated by terms which do not have the same meaning in all countries. For example, if a French-speaking patient asks for a "tablette"† to treat a sore throat, he will receive from an English-speaking pharmacist a tablet and not a lozenge, which is the word for "tablette" in French. Secondly, the dossier: since 1986, all the drug registration dossiers have been normalized in EEC regulations, to be registered in all the European countries of the community according to a special procedure. This dossier is comprehensive and consists of several parts: a pharmaceutical part, a pharmacological and toxicological part, and a clinical part.

In the pharmaceutical portion (called "The Pharmaceutical Dossier"), one can find all of the elements related to: drug (active ingredients): synthesis, impurities and stability under different conditions; and drug dosage form: classification and name, precise definition, pharmaceutical and biopharmaceutical characteristics according to the official definition, development (history, justification and validation), quality control methodology to ensure the manufacturing reproducibility, manufacturing process with good manufactur-

*Presented at the Analysis and Pharmaceutical Quality (APQ) Section's Symposium of the Fourth Annual Meeting of the American Association of Pharmaceutical Scientists (AAPS), Atlanta, Georgia, October 1989.

†Small parallelepipeds weighing 1 g and containing about 60% sugar.

ing practices (GMP), and drug release rate and limits (correlated, if possible, to *in vivo* pharmacokinetic studies).

Thus it is necessary that all of the European countries of the community agree upon how the dosage forms in the European Pharmacopoeia are to be presented and defined with all their characteristics and the techniques to control them. Two examples of this are the classical dosage forms (tablets, capsules, etc.) and the newer forms (sustained release, transdermal therapeutic systems, etc.) with associated biopharmaceutical quality control data.

Classical Dosage Forms

Much work has been carried out to define these classical dosage forms. It now seems necessary to add some new methods to improve their characterization and to give the manufacturers the means by which they may verify the biopharmaceutical quality of their dosage forms.

Oral solid dosage forms

In the European Pharmacopoeia, one can read the definitions of all the different kinds of tablets (coated, uncoated, enteric-coated, effervescent and modified-release tablets, and tablets for use in the mouth), gelatin capsules (hard and soft capsules, capsules with an enteric-coated shell and modified release micropellets) and granules (coated, uncoated, enteric-coated, effervescent and modified-release granules, and granules for the preparation of liquids for oral use). In these monographs, the main pharmaceutical test was that of disintegration, identical to the USP method. France and some other countries had introduced dissolution tests (rotating basket and paddle methods) into their own Pharmacopoeias, but the introduction of these dissolution methods in the European Pharmacopoeia occurred only recently in 1986. The introduction in the Pharmacopoeias of the complete formulae of tablets or capsules, etc. with limits for the dissolution tests is not planned. In addition to the dissolution test, some other biopharmaceutical controls have been developed for use on drug powder (pure or granulated before tabletting, for example) such as: flowability testing with a standardized glass funnel [1], tap density and packing volumes with a standardized graduated cylinder, and evaluation of particle size.

Rectal dosage forms

It is well known that the rectal route for drug administration is much more likely to be used in European countries than in the rest of the world. This route presents many advantages: it is easy to use for children, for example, and the drug bioavailability in an empty rectum is as good as the peroral route and sometimes better, because the first pass effect can be reduced or avoided if the drug is placed in the lower region of the rectum.

Two kinds of rectal drug forms have a European monograph: molded suppositories and soft gelatin rectal capsules [2]. The suppositories must be submitted to a disintegration test, but practically none of the manufacturers carry out this test because it tends to produce very inconsistent results.

A dissolution test which uses a special flow-through cell designed by Langenbucher (Fig. 1) [3] is now being studied. It consists of three transparent parts which fit into each other. The lower part is made up of two adjacent vertical chambers which join at the top. The suppository is placed in the first chamber and is subjected to an up-flow of liquid which fills this first chamber and then spills over into the second. The middle part has a convex cavity designed to collect softened lipid excipients which float on the aqueous dissolution medium. This part is also fitted with a metal grill which serves as a coarse filter. The upper part holds a paper or glass-fibre filter. A small metal "umbrella" can be placed in the second chamber to collect any large particles shed from the suppository and thus avoid obstructing the flow. The complete apparatus for testing rectal dosage forms is shown in Fig. 2. The dissolution medium contained in the flask (A) is stirred continuously with a magnetic stirrer (B). The liquid is aspirated with a peristaltic pump (C) and discharged into a spectrophotometer cell (D). The liquid then flows up into the flow-through cell (E) and out into a flask which is maintained in a water bath (F) heated to 37°C by means of a heating element (G).

Using this cell with indomethacin-containing suppositories, some particularly interesting *in vivo–in vitro* correlations are obtained. From the *in vitro* release rate data and the indomethacin pharmacokinetic parameters (rate of rectal absorption, rate of elimination, etc.), it was possible to reproduce the *in vivo* concentration–time profiles (Fig. 3) [4]. With this

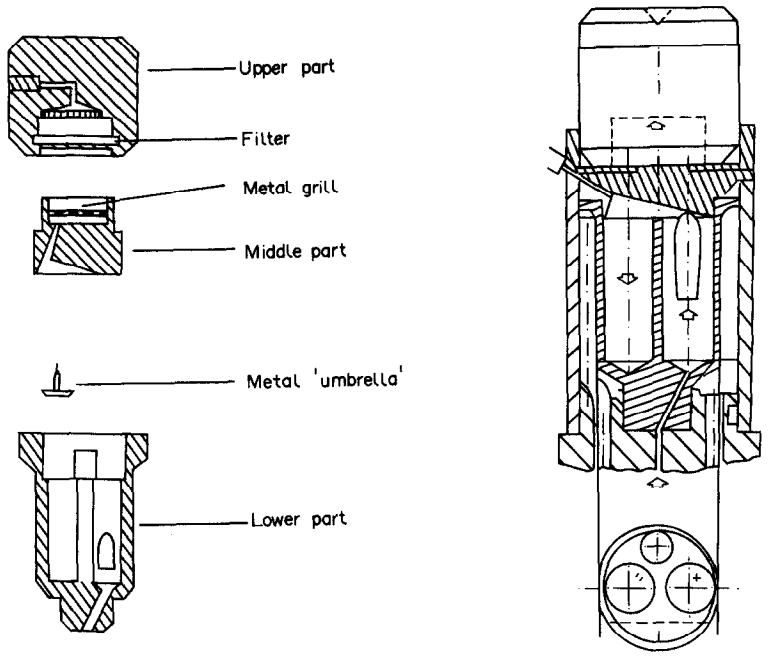

Figure 1
Suppository flow-through cell.

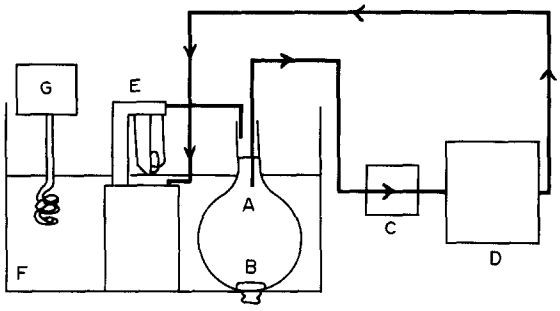

Figure 2
Complete test set-up.

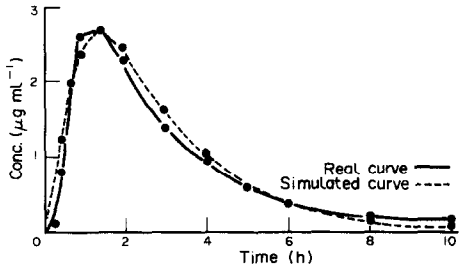

Figure 3
Experimental and simulated curves for a form containing indomethacin.

same cell, it is also possible to study rectal capsules and oily suspensions.

Another device, the Pharmatest, is also being studied. It consists of a horizontal dialysis cell, turning on its axis, in which the rectal form is introduced with a small volume of an artificial rectal fluid. This cell is introduced to another medium in which the active ingredient is evaluated. The release rates determined using this device are generally higher than those obtained using the flow-through cell.

Inhalations

The European Pharmacopoeia Commission has very recently adopted a monograph of preparations for inhalation. "Two categories of preparation for inhalation may be distinguished: liquid preparations for inhalation and solid preparations for inhalation, such as powders, tablets, capsules." "Preparations for inhalation that are converted into an aerosol are generally administered by one of the three following devices: nebulizers, pressurized metered-dose inhalers and dry-powder inhalers."

At the beginning of the monograph, it is said that the preparations for inhalation "are intended for administration to the lower respiratory tract for local or systemic effect". This sentence is followed by two statements of highest importance: "Preparations for inhalation should not adversely affect the functions of the mucosa of the respiratory tract and its cilia," and "The size of particles to be inhaled should be adjusted so as to localize their

deposition in the lower respiratory tract and verified by suitable methods of particle-size determination."

It would be assumed that techniques to address these two major issues would be added to the monograph, but they were not. Thus, it was necessary to develop methods to aid manufacturers in achieving these very important dosage characteristics. To evaluate the effects of aerosol particles as well as nasal solutions on the cilia and the mucosa, a tolerance test on the nasal mucosa of guinea-pigs has been developed and was recently published [5]. For the evaluation of particle size, it is convenient to use the method published recently in Pharmacopoeial Forum (1989) [6] as "stimuli for the revision process" for "Establishing more meaningful specifications and tests for metered-dose pressurized inhalers formulated as suspensions".

In addition to the classical quality control determinations such as metering performance, uniformity of spray content and content of active agents in discharged spray, which were described in a general monograph for pressurized dosage forms, the following will probably be added: (1) a specific requirement for pulmonary inhalation is that 80% of the particles will have an aerodynamic diameter <8 μm (the aerodynamic particle size diameter controls the particle behaviour in the respiratory tract); (2) a deposition of the emitted dose test. The device which is being studied is described in the British Pharmacopoeia (1988) as Apparatus A in Appendix XVII C: the twin impinger sampling apparatus. It is a simplified cascade impactor with three stages: throat, upper impinger and lower impinger (Fig. 4). The metered-dose inhaler or nebulilzer is placed at the mouthpiece of the device as the vacuum pump is started. The aerosol particles can deposit according to their aerodynamic diameter either in the throat by impaction, in the upper impinger if the particles have a diameter >6.4 μm, or in the lower impinger if their diameter is below that. The liquids can catch the drug in which it can be evaluated. At present, the validation of this device is carried

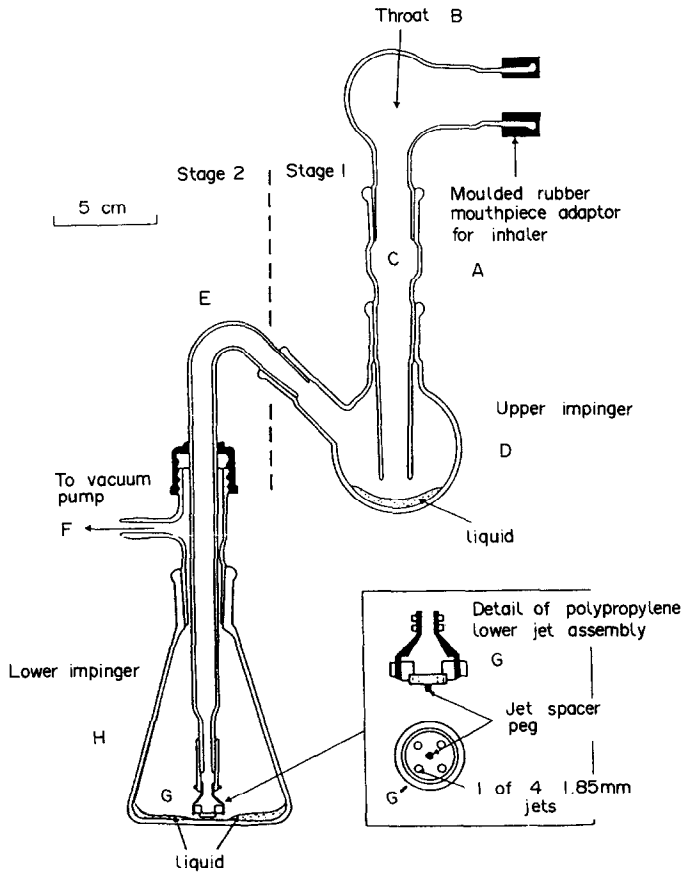

Figure 4
Twin impinger sampling apparatus.

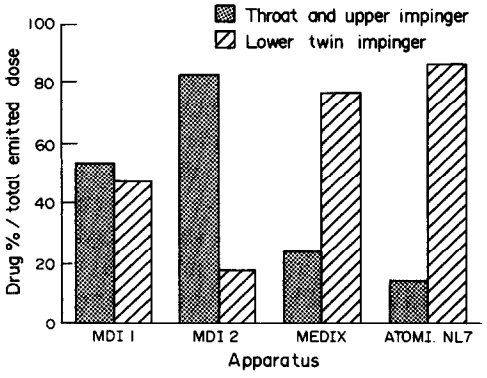

Figure 5
Comparison of the results obtained using a twin impinger (metered dose inhalers: MDI, nebulizers; MEDIX, Atomosor NL7).

out in two ways: the first procedure evaluates the performance of the device (accuracy, reproducibility) and the second procedure establishes a correlation between this *in vitro* deposition of the emitted dose and the *in vivo* deposition according to the aerodynamic particle diameter using scintigraphic methods. It is also possible to compare the performances of metered-dose inhalers with those of classical nebulizers (Fig. 5). For metered-dose inhalers, the amount of emitted dose deposited in the lower impinger is 18–42%, whereas for nebulizers it is 78–85%. However, by scintigraphy *in vivo*, it is possible to see that for metered–dose inhalers only about 10% of the emitted particles can reach the lower respiratory tract, while with a true nebulizer the deposition in the full respiratory tract is very rapid and close to 90% after a few minutes of inhalation.

Novel Drug Dosage Forms

To prevent incorrect descriptions or names or abusive trademarks, it was also necessary to introduce the current definitions of these sophisticated novel dosage forms into the pharmacopoeias as quickly as possible. Two examples will be presented, modified release dosage forms and transdermal therapeutic systems.

Modified release dosage forms

In the latest edition of the French Pharmacopoeia, the following definitions were introduced: "Modified release dosage forms are preparations, the drug release of which is different from that of conventional release dosage forms administered by the same route. This deliberate modification is made using an appropriate and reproducible method. Conventional release dosage forms are preparations, the drug release of which has not been deliberately modified. The kinetics of the drug release of such forms corresponds to their theoretical norms. For instance, for capsules, after the opening of the gelatin shell; for non-coated tablets, after their disintegration and disaggregation. The drug dissolution or diffusion rate from a dosage form in determined experimental conditions is a proof of the release. For modified release dosage forms, it is closely related to the formulation, whereas for conventional release dosage forms it depends essentially on the physical properties of the drug."

Three kinds of modified release dosage forms are defined.

Accelerated release dosage forms. These are preparations, the drug release of which is more rapid than the drug release of conventional release dosage forms administered by the same route. The drug dissolution or diffusion rate from accelerated release dosage forms in determined experimental conditions must be higher than the drug release of convention release dosage forms. They are represented in France by either effervescent tablets or freeze-dried powders presented in tablet form.

Sustained release dosage forms. These are preparations, the drug release of which is slower than that of conventional release dosage forms administered using the same route. The drug dissolution or diffusion rate from such forms under determined experimental conditions must be lower than the drug release rate from conventional dosage forms.

For oral dosage forms they are generally presented as tablets or hard capsules. They are obtained either by: division of the whole unit dose into fractions which release the drug at different times (laminated coating tablets, multiple-layer tablets or coated micropellets; these are called repeat-release dosage forms); retention of the whole unit dose in a delivery system that controls the rate rather than the time of release (e.g. matrix tablet or oral osmotic systems; these are called sustained or extended release dosage forms); or the combination of both processes.

Delayed release dosage forms. These are preparations, the drug release of which is delayed in the system due to an appropriate manufacturing process. Under pre-determined experimental conditions (e.g. pH), a delayed release dosage form releases a conventional release dosage form.

According to these definitions, the determination of the drug dissolution rate is of primary importance as a proof of the release rate. Thus, the German and French Pharmacopoeias, followed shortly by the European, have introduced the flow-through cell (Fig. 6) in addition to the rotating basket and the paddle methods. It deals with transparent and inert material mounted vertically with a filter system preventing escape of undissolved particles. Standard cell diameters are 12 and 22.6 mm; the bottom cone is usually filled with small glass beads about 1 mm dia, with one bead of about 5 mm dia to protect the fluid entry tube. A wire tablet carrier is available for positioning of special dosage forms. The major interest of this cell is that the volume of dissolution medium is not limited. One can use, for example, 5 l in an open circuit or 100 ml in a closed circuit. Furthermore, it is very easy to test the dosage form under increasing pH, from gastric (1.5) to intestinal (7.2). By using this device *in vitro* and the deconvolution of *in vivo* data, good *in vitro–in vivo* correlations, such as those presented by Niklasson *et al.* [7], are easily established; input kinetics *in vivo* can be superimposed on the *in vitro*–dissolution curve. A special cell has been built on the same principle to study the intrinsic dissolution rate of pure powders. A new automatic device, the Bio-Dis, which was designed by Becket *et al.* essentially for micropellets, has been introduced in the pharmaceutical market and was recently described in the Pharmacopoeial Forum [8].

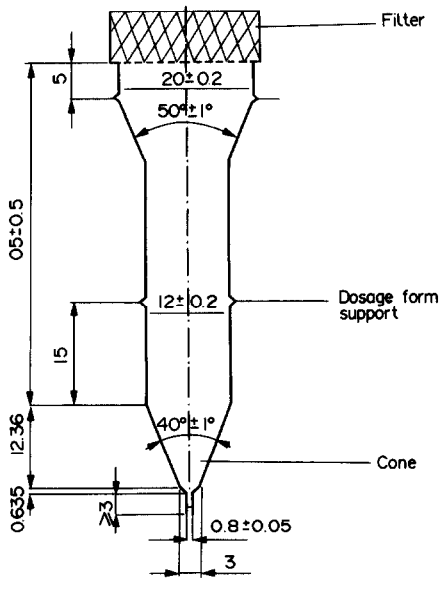

Figure 6
The flow-through cell method. The dimensions are in millimetres.

Transdermal therapeutic systems

These systems are defined within the same monograph as all cutaneous adhesive dosage forms, therapeutically active or not. These last dosage forms are designed to adhere to the skin with simple pressure. They are as follows: (a) non-therapeutically active adhesive dosage forms designed to fix the dressing material (adhesive plasters) or to isolate or protect the skin (non-therapeutic sticking plaster dressings); (b) therapeutically active adhesive dosage forms designed to exert a local action (plasters, therapeutic sticking plaster dressings, cutaneous testing devices) or to exert a systemic action, i.e. transdermal therapeutic systems (TTS).

Definition of transdermal therapeutic systems (TTS)

Transdermal therapeutic systems are devices designed to be applied on the skin in a particular area. They hold or are the vector for one or more drugs designed to exert a systemic action after release and penetration through the skin. They can be composed of:

(1) Either a semi-solid or solid preparation in which the drug(s) is (are) dispersed or dissolved at a defined concentration, usually high. This preparation, designed to release its drug according to a precise rate pattern, is placed directly on the skin, to which it is designed to adhere spontaneously as a result of its composition. The preparation is usually placed at the centre of an adhesive support which keeps it in close contact with the site of delivery (e.g. a waterproof sticking plaster);

(2) A reservoir, one side of which is a membrane which, when placed on the skin, has permeability properties through the skin with defined rate and pattern. This reservoir contains the active drug(s) at a defined concentration, usually high, dispersed or dissolved in the preparation, the composition of which does not affect the processes of release and diffusion

of the drug through the membrane. As the release rate must be indicated on the label, it is compulsory to introduce a drug release test designed to evaluate the capacity of TTS for releasing their drug(s) in a determined medium. The method consists in using a special cell, designed some years ago by Bottari *et al.* [9], which is made up of a reservoir and a lid. The reservoir contains a central chamber designed to receive the transdermal therapeutic system. The diameter of this chamber ≤36 mm. The lid, which fits onto the reservoir, has a central aperture with a diameter of ≤32 mm. This is designed to fix the system in the centre of the cell and restrict the area of diffusion. The lid is held in place by nuts on threaded studs around the cell. The cell is used with or without a diffusion membrane if the dosage form has one (Fig. 7). The transdermal therapeutic system is placed in the cell with its membrane outward, that is, placed in direct contact with the dissolution medium. After closing, the cell is placed at the bottom of a standard dissolution reactor where it remains in a horizontal position due to its weight. The paddle is placed 2.5 cm above the cell and turns at about 100 rpm to ensure homogeneity of the medium (Fig. 8).

The Food and Drug Administration has presented another device that is very close to that of the French Pharmacopoeia, whereas the United States Pharmacopeia has essentially presented the devices used by the different manufacturers of TTS in the USA. Aiache *et al.* have recently carried out a comparative study between the French cell and the rotating cylinder described in the USP and have found good correlation between the two devices [10].

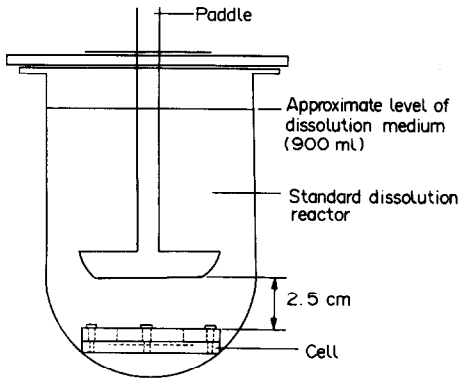

Figure 7
Diagram of the cell in the reactor.

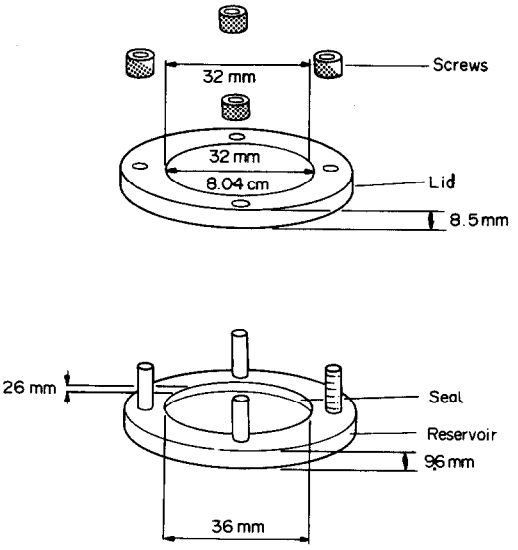

Figure 8
Diagram of the cell.

Conclusions

The European Pharmacopoeia, with the help of the Pharmacopoeia Commissions of each of the European countries, is trying to normalize as well as possible not only the drugs as raw or starting materials but also the dosage forms in order to obtain a standardized presentation of the registration dossiers and to increase their quality. Therefore, it must be indicated that these dossiers are supervised by experts who take on the responsibility for the content of the dossier taking their stand on all the propositions of the manufacturers. When writing a report according to the EEC rules, an expert must: (1) work on dossiers corresponding to his main research field(s) and describe objectively all the results obtained by the manufacturer; (2) discuss the limits and the protocols used to test the product (analytical, pharmacological, toxicological or clinical protocols) in order to draw conclusions. For instance, from the analytical point of view, he comments on the drug and gives his opinion on the analytical techniques used by the manufacturer, their validity and the manufacturing processes compared with GMP for the active ingredients as well as for the finished product; (3) control all these techniques by himself and sometimes propose a modification of the official technique if he can validate it; produce a synopsis of all the data and explain them in his report; and (4) give a justification of the proposals of every manufacturer, for the active ingredients as well as for the finished product.

Thus, being an expert involves responsibility. He must have complete knowledge of the drug development or even participate in it. His report must bear witness to the quality of the product in order to convince the Health Authorities. An expert is, therefore an "eye" and a "brain", and above all he must act impartially without ever the appearance of a conflict of interest.

The combination of the European Pharmacopoeia monographs and the expert is intended to ensure the best quality of the drug dosage forms marketed in Europe.

References

[1] Notes techniques pro pharmacopoeia, France, No. 569, Bull. Ordre 320 (1989).
[2] Pharmacopée francaise, 10th edn, July (1987).
[3] F. Langenbucher, in *Rectal Therapy*, Proceedings of the Symposium on the Advantages and Problems Encountered in Rectal Therapy (B. Glas and C.J. de Blaye, Eds), pp. 103–104.
[4] J.-M. Aiache, M. Islasse, E. Beyssac, S. Aiache, R. Renoux and J.P. Kantelip, *Int. J. Pharm.* **39**, 235–242 (1987).
[5] J. Lévrier, S. Molon-Noblot, D. Duval and K.G. Lloyd, *Fund. Clin. Pharmacol.* **3**, 471–482 (1989).
[6] P.A. Haywood, M. Martin-Smith, J.M. Padfield *et al.*, Pharmacopeial Forum: Stimuli to the Revision Process, 5193–5202, May–June (1989).
[7] M. Niklasson, C. Graffner and M.I. Nilsson, *Int. J. Pharm.* **40**, 165–171 (1987).
[8] USP Drug Research and Testing Laboratory and USP Subcommittee on Biopharmaceutics, Pharmacopeial Forum: Stimuli to the Revision Process, 4984–4992, March–April (1989).
[9] F. Bottari, G. Dicolo, E. Nannipieri, M.F. Saettone and M.F. Serafini, *J. Pharm. Sci.* **63**, 1779–1783 (1974).
[10] J.M. Aiache, J.M. Cardot and S. Aiache, *Int. J. Pharm.* **55**, 147–155 (1989).

[*Received for review 1 November 1989; revised version received 14 May 1990*]