

## PREFORMULATION STUDIES OF DRUG SUBSTANCES FOR SOLID DOSAGE FORMS

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### INTRODUCTION

The preformulation studies are the first steps in the pharmaceutical development of a drug substance into different dosage forms. The physical and chemical properties of a number of drug candidates are investigated and the aim of these studies is to identify critical properties in order to select the best candidate. For the selected candidate drug, the chemical and physical properties are investigated further, and in combination with excipients which constitutes basic information for the following formulation work.

When working with a new drug entity, it is often rational to divide the preformulation studies into three phases:

1. Selection of the physical form of the substance, i.e. acid, base, aprot or salt (1).
2. Selection of precipitation process, i.e. solvent system and technique.
3. Compatibility studies.

### PREFORMULATION STUDIES I

Time and amount of substance are often limited in the preformulation studies and this situation is frequently pronounced in the

very beginning. For the preformulation pharmacist, thus, it is of value to possess a program that enables time schedule and substance quantity to be estimated with reasonable precision for the first part of the preformulation studies (2). For a broad screening of a drug substance intended for a tablet formulation, as little as 10-12 g of substance may be needed in a 30-40 day program (3).

### Powder characterization

Scanning electron microscopy (SEM) is a simple method to obtain a general idea of particle size and morphology which requires only a few milligrams of substance. The SEM technique includes preparation and observation of the sample in vacuum which might bring about cracking and other changes in the particles due to evaporation of solvents and partial melting caused by the electron beam.

Particle size measurements can be performed with optical microscopy (4) using e.g. an automatic particle analysis. This technique requires less than 100 mg of sample, but care must be taken with the sampling of these small powder quantities in order not to obtain misleading results (4). Permeametry (Fisher Sub Sieve Sizer or Blaine) or sieve analysis requires gram quantities of the substance, but these techniques are nondestructive and the powder samples can be used e.g. in the stability studies.

The true particle density,  $D_t$ , defined as the weight divided by the volume of solid except interparticle voidage is measured conveniently with an air comparison pycnometer (3). Measurement of the X-ray density,  $D_x$ , can be considered important also in this early stage especially if the powder studied contains amorphous material (58).

The specific surface area can be calculated from the surface volume diameter obtained from the permeametry measurements and the true particle density. Measurement with gas adsorption (5, 6) and applying the B.E.T. equation can give valuable information, but the amount of substance required is about 1 g.

If the dose level of the new drug substance can be estimated in this early stage of development and the tendency is towards a high dose, knowledge about the bulk density properties is valuable. With limited substance quantities it is, however, difficult to measure and a modification of the DIN methods to determine the aerated and tapped bulk densities may have to be performed (7).

The appearance can be given in descriptive terms describing the most commonly encountered colors (8). Surface color can be measured successfully with tristimulus colorimetry (9). However, the coarseness of the powder can influence the results.

Odor and taste are characteristic for a drug substance. They are reviewed in order to detect e.g. the necessity for taste or odor masking (8).

#### X-ray powder diffraction

XRD-measurements in its simplest form provide information if the powder samples that have been precipitated are crystalline or not. The use of a Guinier-Hägg camera has proved to give more information about the bonding of solvents than measurements recorded with a refractometer and is to be preferred in the preformulation studies (10). Only 100-200 mg of substance is needed for these analyses.

#### Thermal analysis

Differential thermal analysis (DTA), differential scanning calorimetry (DSC), and thermogravimetry (TG) can be run on small quantities of substance (5-10 mg). They give valuable information about how water and organic solvents are bound to the material, when the substance melts or degrades, and if there is any indication for the presence of polymorphs. These standard methods are run on samples included in the hygroscopicity and stability tests as well as on powder samples from the compaction studies, preferably together with XRD-measurements.

### Dissolution rate, solubility

The rotating disc method to determine the intrinsic dissolution rate is rapid and convenient to use, consuming only around a gram of drug substance (11, 12, 91). In this early preformulation work, water is used as the dissolution medium if no special reasons speak for buffer solutions. In the second phase of the preformulation studies, the influence of pH on the intrinsic dissolution rate is monitored (13).

Due to the often limited amount of drug substance available, determination of the solubility by conventional equilibrium technique is difficult to perform, especially if the compound is easily soluble. The aqueous solubility can, however, be estimated by using a linear relationship between the intrinsic rate of dissolution and the corresponding solubility (11,14). This relationship has been found to be generally applicable for various compounds independent of chemical structure.

The general information about solubility and dissolution rate obtained from these measurements provides a good base for predicting eventual problems with the bioavailability (15-19) together with the measurements of ionization constant (20,21) and partition coefficient (22).

A correlation between the relative lipophilicity,  $\pi$ , (23) and the intrinsic dissolution rate has been shown for different disubstituted benzamide derivatives (3) and substituted benzoic acids (24). The dissolution rate decreases with increasing lipophilicity and this information can be of value when a series of candidate drugs is studied with different substituents in the same position of the molecule.

### Water adsorption

The water adsorption and desorption isotherms can be determined gravimetrically on 500 mg samples exposed to different relative humidities in hygrostats (3) using saturated salt solutions to maintain the humidities (25). In addition to the gravimetical

measurements, thermogravimetry and Karl Fischer analyses are performed since organic solvents present in the powder samples may be replaced by water.

Under the influence of water vapor, hydrates can be formed which might alter the crystal symmetry of the substance. These effects may occur instantaneously at exposure to water vapor above a critical partial pressure or slowly, sometimes stepwise, at long term storage (26, 27).

In the case of surface adsorption of water, the rate at which the water molecules are adsorbed (28-30) has been demonstrated to be related to the intrinsic dissolution rate in water (31). Within a homologous series of drug compounds, i.e. different derivatives of a mother molecule, a ranking can be obtained in order to select the best candidate with respect to both dissolution and water sorption properties.

### Stability

On the basis of the results from the hygroscopicity measurements, relative humidities are selected for the stability testing in the solid state of the drug candidates. The water sorption often follows a Type-II isotherm (32), and it can be reasonable to select a humidity below and above the threshold of the isotherm, e.g. 30 and 75 % RH at a moderately elevated temperature, 40 °C (3, 33). Higher temperatures can also be used e.g. 50 ° and 60 °C at specified humidities, but care must be taken when selecting the temperatures with respect to the melting and change in crystal form of the substance. Analysis is performed after e.g. 10 and 30 days, and if no substantial change has been observed, after 30 days at 40/75 and 60/30, the stability prognosis of the candidate is good (8). The amount of drug substance needed for this stability evaluation depends on the methods used for analysis. As a standard, one can calculate with 500 mg for each pull time which will give a total of 2.5 g for the study at 40 °C and two relative humidities.

Parallel to the stability testing in darkness, the light stability is studied. By using simulated sunlight (34), a test program with light exposure up to 48 h can be run at selected humidities. If the same humidities are used as in the darkness study, e.g. 30 and 75 % RH, with one temperature and two exposure times, a total amount of 2.5 g of substance is needed (3,34). In order to be able to measure the discoloration of the substance apart from the chemical degradation, compressed disks of the substance is used. The surface color can be measured before and after the light exposure with tristimulus colorimetry (9,34). More intensive light exposure may also be used successfully (34,35) where a FadeOmeter equipped with a carbon arc can be used (36). Light exposure can bring about chemical reactions that may continue in darkness. Thus, it is suggested that samples that have been exposed to light are stored in darkness in order to detect such changes (3).

### Compaction properties

The study of the compaction properties is conducted on either instrumented tablet machines (37,38) or in compaction simulators (39,40). The latter type of equipment seems to be the ideal testing device for use in preformulation studies, i.e. it operates with small amounts of drug substances and allows measurements to be performed under dynamic conditions similar to those under normal tableting. However, the instrumented excenter press also meets most of the requirements.

One can find a number of methods for interpreting compaction data from instrumented tablet machines (41), e.g. compaction energy versus tablet porosity (Heckel plots, 42,47) and radial versus axial pressure cycles (43) along with several others (44,45). The choice of methods and the interpretation of the results have been discussed (43,45), and the use of force-displacement measurements in preformulation and early formulation work has been evaluated (46).

Determination of the maximum upper ( $UPP_{max}$ ) and lower ( $LPP_{max}$ ) punch pressures, the total work ( $W_{tot}$ ) performed by the upper

punch, the work of expansion ( $W_{\text{exp}}$ ) and the net work performed by the upper punch ( $W_{\text{net}} = W_{\text{tot}} - W_{\text{exp}}$ ) has been suggested to be used in a preformulation program (3). When performing the measurements on five or six tablets compressed to a relative density of 0.7-0.9, a total amount of 4-5g substance is consumed.

## PREFORMULATION STUDIES II

When the candidate drug and the physical form of it has been selected in the first part of the preformulation study, it is the proper time to select the precipitation technique and solvent system to be used in the final purification of the synthesis. Different solvents and mixtures of solvents can produce a variety of solid products of the same drug substance. Formation of polymorphs is a well-known phenomenon where the drug molecules can exist in different space lattice arrangements (48-52). Furthermore, at crystallization, solvent molecules can be entrapped in the crystal lattice stoichiometrically giving a solvate or a pseudopolymorph.

When selecting the solvent/mixture and precipitation technique, several demands must be fulfilled. The yield must be as high as possible and the purity must be satisfactory without too many recrystallizations which will affect the yield. The same crystalline product must be obtained from batch to batch, i.e. the process must be reproducible. This is of great importance in the scaling up of the synthesis process but is often difficult to foresee at this early stage. A good prerequisite is a cooperation between the preformulation pharmacist and a process chemist in this part of the preformulation work where both the economical and process related questions of the substance production can be considered together with the pharmaceutical formulation and production.

The combination of test methods employed in this second phase of the preformulation studies is in principle the same as those described in Phase I. The amount of substance available is hopefully larger, perhaps in the range of 10-30g. The main purpose is

to focus on the critical properties of the drug substance, i.e. solubility if the substance has a low solubility (53-55) and compaction properties if the candidate selected was best from other points of view but has poor binding properties. It can be of interest to study the critical properties of the substance after compaction and milling (56,57) which can have an impact on several physical and chemical properties (58).

The formation of polymorphs in the precipitation process is of particular interest. Suitable techniques are DSC and TG with which also the first derivative of the signals can be recorded (10). X-ray powder diffraction (XRD) which may be completed with single crystal X-ray diffraction for determination of crystal symmetry class and unit cell dimensions is also valuable. This is of interest for determination of the crystallographical density,  $D_x$ , which compared to the true density determined in the air comparison pycnometer can give valuable information about the presence of amorphous material in the product (59).

When studying the existence of polymorphs and their properties, a combination of techniques is required. An example is the preformulation work on a substituted benzamide derivative (26,27,60). The substance could be obtained as either anhydrous with monoclinic symmetry, anhydrous with orthorhombic symmetry or as a monohydrate with orthorhombic symmetry, all depending on the water content in the precipitation medium. The anhydrate with orthorhombic symmetry was found to be physically unstable at storage. Thus, after a short time, a 0.5 hydrate was formed which in turn, after long term storage (up to 6 months), formed the monohydrate. By combining TG, DTG with XRD and extending the storage time for the samples run in the stability studies up to 6 months, this could be detected. A precipitation medium with low water content was then selected which yielded the stable monoclinic anhydrate.

Zimeldine dihydrochloride is another example where a combination of test methods was used to study the efflorescence of the substance during storage giving rise to an increased surface area reflected by an increased water adsorption (10). By performing



DSC, TG, DTG, and XRD combined with determination of the specific surface area by gas adsorption on powder samples in the stability studies, it was found that the four water molecules in each unit cell moved slightly which caused the crystals to crack slowly.

It can, thus, be of value to extend the stability studies in this phase up to 6 months, but often the time schedule is very tight and decisions must be made before such a long time has passed. It must, however, be considered important to plan the storage tests with the possibility to perform analyses up to at least 6 months which can give valuable information in the third phase of the preformulation studies and in the early formulation studies.

### PREFORMULATION STUDIES III

The third phase of the preformulation studies is mainly concerned with the compatibility of the drug substance with different excipients. These studies may be considered as a base for the first formulation studies. Compatibility studying does not contain only the survey of the chemical stability of the drug substance in mixtures with the excipients, but comprises also the compaction properties and other physical properties that may be of interest, e.g. flowability.

The planning of the compatibility studies is preferably performed with the use of factorial design (61). Excipients included should be fillers (lactose, mannitol), disintegrants (starch, microcrystalline cellulose), binders (polyvinylpyrrolidone, gelatine), lubricants (magnesium stearate, stearic acid), and granulating liquids (water, alcohol), (62-64). With 5 factors, this will mean 32 experiments in a complete factorial study which often may be considered too much. Two possibilities are given to elude this problem, either to run a series of  $2^3$  or  $2^4$  studies where the results from the previous study will guide the planning of the following (65). This technique will take longer time and this is a drawback with respect to the often tight time schedule of the preformulation studies. Another technique, the reduced factorial

design, is available building on the assumption that interactions between three or more variables are of minor interest and can be ignored compared to the main effects and the two-variable interactions (66,67). This technique enables 3 variables to be investigated in 4 experiments, up to 7 variables in 8 experiments, and up to 15 variables in 16 experiments.

The chemical stability in the compatibility studies is, in most cases, followed by chemical analysis upon storage at moderately accelerated conditions, e.g. 40 °C, 30 and 75 % RH for 1, 3, and up to 6 months. Changes in appearance of the powder mixtures is not uncommon and is conveniently followed by tristimulus colorimetry (34,35,65). In order to facilitate these measurements, compressed disks of the powder mixtures are prepared and stored in the stability study. These disks can be compressed in an instrumented tablet machine for studying the compaction behavior as part of the compatibility studies.

In case a light sensitive drug substance is studied, light exposure can be performed in artificial sunlight (34). A useful technique to predict the light stability in sunlight or in daylight from light exposure in artificial sunlight can be employed in these studies (60). It is based on numerical convolution by weighing discoloration data for the drug/excipient mixture in artificial sunlight with the discoloration data for the pure drug in sunlight or daylight.

Differential Thermal Analysis (DTA) and Differential Scanning Calorimetry (DSC) have been used as alternatives to the quantitative assay after isothermal stress tests in drug-excipient interaction studies (69-78). Many problems have, however, been associated with the interpretation of the curves, and the use of DTA and DSC in the compatibility studies must, in most cases, be considered as a complement to the quantitative assay of the active ingredient after isothermal stress tests (79).

When the drug substance has very poor stability and no improvement can be achieved by precipitation of another crystal form, the compatibility studies may be focused on stabilizing the substance

by spray drying, freeze drying, or coprecipitation with hydrophobic substances such as triglycerides, paraffins, or long chain alcohols. Similarly if the drug substance has a poor solubility, the rate of dissolution may have to be increased by increasing the specific surface area or by hydrophilization (80-90). Measurement of the intrinsic dissolution rate is of significance in these studies (11-13,91).

### CONCLUSIONS

The first part of the preformulation studies of a new drug entity, i.e. selection of the candidate drug and physical form of it, can be run on a total quantity of 10-12g within a time period of 30-40 days.

Selection of precipitation process in the second phase of the preformulation studies can be performed with the same program as in Phase I. In this second phase, it is, however, common to focus on the critical properties of the substance. Stability studies are performed at both accelerated and shelf life conditions with samples reserved for analysis up to as much as 6 months of storage.

Preformulation Studies III form the base for the first formulation studies and they are preferably planned by using factorial design. Depending on the critical properties of the substance, the compatibility studies with different excipients may be run within 40-50 days using 30-100 g of the substance. The stability studies are performed at moderately accelerated shelf life conditions and run up to 6 months.

### REFERENCES

1. S. M. Berge, L. D. Bighley and D. C. Monkhouse, J. Pharm. Sci., 66, 1 (1977).
2. M. J. Akers, Can. J. Pharm. Sci., 11, 1 (1976).
3. C. Graffner, M.-E. Johansson, M. Nicklasson and H. Nyqvist, J. Pharm. Sci., 74, 16 (1985).
4. T. Allen, "Particle Size Measurement," Chapman and Hall, London, 1975.

5. S. Brunauer, P. H. Emmett and E. Teller,  
J. Am. Chem. Soc., 60, 309 (1938).
6. S. J. Gregg and K. S. W. Sing, "Adsorption, Surface Area and Porosity," Academic Press, New York 1967.
7. DIN 53192 and 53194.
8. D. A. Wadke and H. Jacobsson, in "Pharmaceutical Dosage Forms: Tablet, Vol. 1," H. A. Liebermann and L. Lachman, eds., Dekker, New York, 1980, p. 1.
9. R. S. Hunter, "The Measurement of Appearance," John Wiley, New York, 1975.
10. H. Nyqvist and T. Wadsten, Acta Pharm. Suec., 21, 253 (1984).
11. M. Nicklasson, A. Brodin and C. Stenlander,  
Acta Pharm. Suec., 19, 25 (1982).
12. M. Nicklasson, A. Brodin and L.-O. Sundelof, Acta Pharm. Suec., 19, 109 (1982).
13. M. Nicklasson, A. Brodin and H. Nyqvist, Acta Pharm. Suec., 18, 119 (1981).
14. W. E. Hamlin, J. J. Northam and J. G. Wagner, J. Pharm. Sci., 54, 1651 (1965).
15. P. A. Shore, B. B. Brodie and C. A. M. Hogben,  
J. Pharm. Exp. Ther., 119, 361 (1957).
16. L. S. Schanker, P. A. Shore, B. B. Brodie and C. A. M. Hogben,  
J. Pharm. Exp. Ther., 120, 528 (1957).
17. L. S. Schanker, D. J. Tocco, B. B. Brodie and C. A. M. Hogben,  
J. Pharm. Exp. Ther., 123, 81 (1958).
18. C. A. M. Hogben, L. S. Schanker, D. J. Tocco and B. B. Brodie,  
J. Pharm. Exp. Ther., 120, 540 (1957).
19. C. A. M. Hogben, D. J. Tocco, B. B. Brodie and L. S. Schanker,  
J. Pharm. Exp. Ther., 125, 275 (1959).
20. A. Albert and E. P. Serjeant, "The Determination of Ionization Constants," Chapman and Hall, London, 1971.
21. J. M. Kolthoff, S. Bruckenstein and R. G. Bates, "Acids and Bases in Analytical Chemistry," Interscience, New York, 1966.
22. P. Buri, Labo Pharma, 307, 181 (1981).

23. F. E. Norrington, R. M. Hyde, S. G. Williams and R. Wooston, *J. Med. Chem.* 18, 604 (1975).
24. J. H. Collett and L. Koo, *Pharm. Acta Helv.*, 51, 27 (1976).
25. H. Nyqvist, *Int. J. Pharm. Tech. Prod. Mfr.*, 4, 47 (1983).
26. H. Nyqvist and T. Wadsten, *Thermochim. Acta*, 93, 125 (1985).
27. H. Nyqvist and T. Wadsten, *Thermochim. Acta*, 95, 425 (1985).
28. L. van Campen, G. L. Amidon and G. Zografi, *J. Pharm. Sci.*, 72, 1382 (1983).
29. L. van Campen, G. L. Amidon and G. Zografi, *J. Pharm. Sci.*, 72, 1388 (1983).
30. L. van Campen, G. L. Amidon and G. Zografi, *J. Pharm. Sci.*, 72, 1394 (1983).
31. M. Nicklasson and H. Nyqvist, *Acta Pharm. Suec.*, 20, 321 (1983).
32. A. N. Martin, J. Swarbrick and A. Cammarata, in "Physical Pharmacy", Lea and Febiger, Philadelphia, 1973, p. 434.
33. P. Brisard and S. R. Gunning, *Labo Pharma*, 307, 173 (1981).
34. H. Nyqvist, *Acta Pharm. Suec.*, 21, 245 (1984).
35. H. Nyqvist, P. Lundgren and I. Jansson, *Acta Pharm. Suec.*, 17, 148 (1980).
36. H. Nyqvist, M. Nicklasson, P. Lundgren, A.-S. Fyhr and U. Stjernfelt, *Acta Pharm. Suec.*, 19, 91 (1982).
37. J. B. Schwartz, *Pharm. Tech.*, 5, 102 (1981).
38. K. Marshall, *Pharm. Tech.*, 7, 68 (1983).
39. B. Hunter, in "Enlargement and Compaction of Particulate Solids," N. G. Stanley-Wood, ed., Butterworths, London, 1983, p. 148.
40. J. E. Rees, J. A. Hersey and E. T. Cole, *J. Pharm. Sci.*, 61, 1313 (1972).
41. T. M. Jones, *Int. J. Pharm. Tech. Prod. Mfr.*, 2, 17 (1981).
42. R. W. Heckel, *Trans. Metall. Soc. AIME.*, 221, 671 (1961).
43. J. Krycer, D. G. Pope and J. A. Hersey, *Drug Dev. Ind. Pharm.*, 8, 307 (1982).
44. T. M. Jones, *Acta Pharm. Tech. Suppl.* 6, 141 (1978).
45. J. Krycer, D. G. Pope and J. A. Hersey, *Int. J. Pharm.*, 12, 113 (1982).

46. G. Ragnarsson, "Evaluation of Tabletting Properties in Preformulation and Formulation Work," Dissertation at the Faculty of Pharmacy, University of Uppsala, 1985.
47. P. Humbert-Droz, D. Mordier and E. Doelker, *Pharm. Acta Helv.*, 57, 136 (1982).
48. J. Haleblan and W. McCrone, *J. Pharm. Sci.*, 58, 911 (1969).
49. S. Rosenstein and P. Lamy, *Am. J. Hosp. Pharm.* 26, 598 (1969).
50. G. S. Mewada, D. R. Parikh and S. Somsekhar, *Sci. Cult.*, 39, 378 (1973).
51. J. Haleblan, *J. Pharm. Sci.*, 64, 1269 (1975).
52. S. Byrn, "Solid State Chemistry of Drugs," Academic Press, New York, 1977.
53. A. J. Aguiar, J. Krc, A. W. Kinkel and J. C. Symyn, *J. Pharm. Sci.*, 56, 847 (1967).
54. A. J. Aguiar and J. E. Zelmer, *J. Pharm. Sci.*, 58, 983 (1969).
55. S. Miyazaki, T. Arit, R. Hori and K. Ito, *Chem. Pharm. Bull.*, 22, 638 (1974).
56. A. G. Mitchell and G. R. B. Down, *Int. J. Pharm.*, 22, 337 (1984).
57. H. K. Chan and E. Doelker, *Drug Dev. Ind. Pharm.*, 11, 315 (1985).
58. Y. Takahashi, K. Nakashima, H. Nakagawa and J. Sugimoto, *Chem. Pharm. Bull.*, 32, 4963 (1984).
59. H. Nyqvist and T. Wadsten, *Acta Pharm. Suec.*, 22, 215 (1985).
60. H. Nyqvist and C. Graffner, *J. Pharm. Sci.*, Submitted for publication, 1985.
61. H. Sucker, *Informationsdienst APV*, 17 (1/2), 52 (1971).
62. H. Leuenberger and W. Becker, *Pharm. Acta Helv.*, 50, 88 (1975).
63. H. Leuenberger, in "Pharmaceutische Technologie," H. Sucker, P. Fuchs and P. Speiser, eds., Georg Thieme Verlag, Stuttgart, 1978, p. 64.
64. H. M. El-Banna, A. A. Ismail and H. A. F. Gadalla, *Pharmazie*, 39, 163 (1984).
65. K. Ellstrom and H. Nyqvist, in "Proceedings from the Swedish Pharmaceutical Society Congress," Stockholm, 1985, p. 132.
66. R. Carlson, A. Nilsson and T. Lundstedt, *Kemisk Tidskrift*, 96, 43 (1984).

67. S. Akhnazarova and V. Kafarov, "Experiment Optimization in Chemistry and Chemical Engineering," MIR Publishers, Moscow, 1965.
68. H. Nyqvist and M. Nicklasson, *Acta Pharm. Suec.*, 21, 367 (1984).
69. H. Jacobsen and G. Reier, *J. Pharm. Sci.*, 58, 631 (1969).
70. J. K. Guillory, S. C. Hwang and J. L. Lack, *J. Pharm. Sci.*, 58, 301 (1969).
71. G. Hentze and H. Voegelé, *Pharm. Ind.*, 33, 519 (1971).
72. H. Jacobsen and J. Gibbs, *J. Pharm. Sci.*, 62, 1543 (1973).
73. K. C. Lee and J. A. Hersey, *J. Pharm. Pharmacol.*, 29, 515 (1977).
74. A. S. Geneidi and L. El-Sayed, *Pharm. Ind.*, 40, 1074 (1978).
75. A. S. Geneidi and H. Hamacher, *Pharm. Ind.*, 42, 315 (1980).
76. G. S. Geneidi, H. H. El-Shattawy and A. S. Geneidi, *Sci. Pharm.*, 49, 172 (1981).
77. H. H. El-Shattawy, *Drug Dev. Ind. Pharm.*, 8, 819 (1982).
78. A. A. van Dooren, *Drug Dev. Ind. Pharm.*, 9, 43 (1983).
79. A. Li Wan Po and P. V. Mroso, *Int. J. Pharm.*, 18, 287 (1984).
80. W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, 58, 1505 (1969).
81. A. Hoelgaard and N. Møller, *Arch. Pharm. Chem. Sci. Ed.*, 3, 34 (1969).
82. O. J. Corrigan and R. F. Timoney, *J. Pharm. Pharmacol.*, 27, 759 (1975).
83. D. Duchêne, S. Henry, B. Legendre, S. Souleau and F. Puisieux, *Pharm. Acta Helv.*, 18, 103 (1981).
84. D. J. Allen and K. C. Kwan, *J. Pharm. Sci.*, 58, 1190 (1969).
85. A. Hoelgaard and N. Møller, *Arch. Pharm. Chem. Sci. Ed.* 3, 65 (1969).
86. J. L. Ford and M. H. Rubinstein, *Pharm. Acta Helv.*, 53, 327 (1978).
87. J. L. Ford and M. H. Rubinstein, *Pharm. Acta Helv.*, 54, 353 (1979).
88. J. L. Ford and M. H. Rubinstein, *Pharm. Acta Helv.*, 55, 1 (1980).
89. J. L. Ford and M. H. Rubinstein, *Pharm. Acta Helv.*, 58, 101 (1983).

90. J. L. Ford and P. N. C. Elliott, *Drug Dev. Ind. Pharm.*, 11, 537 (1985).
91. M. Nicklasson and A. B. Magnusson, *Pharm. Res.*, 6, 262 (1985).