CHAPTER II

REVIEW OF LITERATURE

Minocycline Hydrochloride

Minocycline hydrochloride is known chemically as 4, 7-bis (dimethylamino) 1, 4-4a, 5, 5a, 6, 11, 12a-octahydro-3, 10, 12, -12a-tetrahydroxy-1, 11-dioxo-2-naphthacenecarboxamide monohydrochloride and by the trivial name 7-dimethylamino-6-demethyl-6-deoxytetracycline hydrochloride as shown in Figure 1 (Florey, 1977).

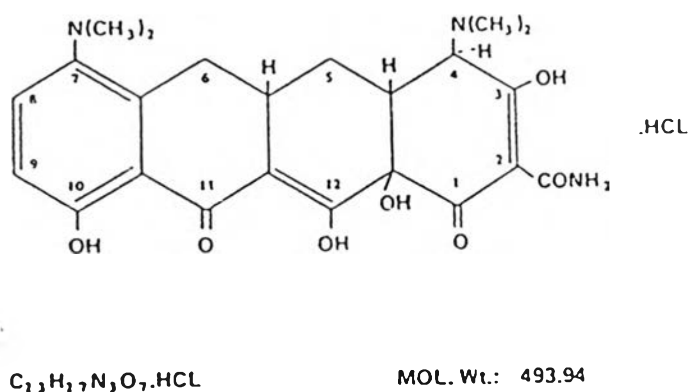

Figure 1 Structure of minocycline hydrochloride. (Florey, 1977)

Appearance, Color, Odor

Minocycline hydrochloride occurs as a yellow crystalline powder. It is essentially odorless and has a somewhat bitter taste (Florey, 1977).

Solubility

There are 16 possible ionic microstructures for minocycline. Thus, the observed solubility is generally not that of a single entity but represents the sum of the total of two

หอสมุดกลาง สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

or more species in a solution at a given pH value. Minocycline, unlike other antibiotics, contains two amino groups which are responsible for hundred-fold solubility of minocycline neutral in water over that of tetracycline. The solubilities of minocycline neutral, hydrochloride, dihydrochloride in water and minocycline hydrochloride dihydrate in various solvents are given in Table 1 and Table 2, respectively.

Table 1 Aqueous solubility of minocycline at 25°C (Florey, 1977)

Form of drug	pH of solution	Solubility at 25° C (mg/mL)
Neutral	6.7	52
Hydrochloride	3.9	15
Dihydrochloride	0.8	>500

Table 2 Solubility of minocycline hydrochloride $2H_2O$ in various solvents at 25°C(Florey, 1977)

Solvent	Solubility	
	mg/mL	% w/v
Hexane	0.004	0.0004
Benzene	0.02	0.002
Chloroform	0.13	0.013
Ethyl Acetate	0.3	0.03
Methyl Ethyl Ketone	0.4	0.04
1-Octanol	0.5	0.05
Acetone	0.6	0.06
Dioxane	0.7	0.07
1-Butanol	4.4	0.44
2-Propanol	7	0.7
Methanol	14	1.4
Water	16	1.6
Abs. Ethanol	42	4.2

Stability, Isomerization, Degradation

In the dry-powder state minocycline, like other tetracyclines, is stable at least 3-4 years when stored at room temperature (25°C). Minocycline, lacking hydroxyl group at both C_5 and C_6 does not form the anhydro, iso, or epi compounds, which are the common degradation compounds formed from other tatracycline antibiotics. However, it readily undergoes both 4-epimerization and oxidative degradation. Since the D ring of Minocycline is a substituted p-amino-phenol, it is more susceptible to oxidation than other tetracyclines.

Stability data for solutions of minocycline at various pH values minocycline solutions at pH 4.2 and 5.2 retained 90% of their initial potency for 1 week at room temperature. These solutions were more stable than any other tetracycline antibiotic solutions studied.

However, none of the tetracycline antibiotics is stable enough to permit the preparation of a preconstituted aqueous solution as a practical dosage form.

The additional amino group in minocycline, beside contributing to increased solubility of minocycline neutral in water, is also responsible for differences in physico-chemical and physiological properties. The isoelectric point of minocycline is a full pH unit higher (pH 6.4) than that of most other tetracycline antibiotics (pH ca. 5.5) and consequently has a potential therapeutic significance. This property accounts for its greater partitioning character into lipoid material at essentially neutral pH, including thyroid, brain and fat tissue (Florey, 1977).

Antimicrobial Activity

The spectrum of antibacterial activity of minocycline *in vitro* is similar to that of the other tetracyclines, but the level of activity of minocycline is generally slightly greater than that of tetracycline and its analogues. Against tetracycline-sensitive and -resistant *Staphylococcus aureus*, including methicillin-susceptible and –resistant strains, minocycline is more active *in vitro* and *in vivo* (vide infra) than other tetracyclines. This activity has been confirmed in clinical studies in patients with pulmonary or skin and soft tissue infections caused by tetracycline-resistant *Staphylococcus aureus*, and is apparently due to the ability of minocycline to penetrate the cell wall of staphylococci

which have become impermeable to tetracycline as a mechanism of acquired resistance (Brogden, Speight, and Avery, 1975).

Pharmacokinetic Properties

Minocycline is almost completely absorbed after oral administration. After a single 200 mg dose, peak serum levels of about 2 to 3 μg/mL are attained in 2 hours in healthy subjects and absorption is not appreciable influenced by the presence of food or milk. The absorption of minocycline may be adversely affected by the simultaneous administration of iron-containing haematinics and by antacids containing aluminium hydroxide, calcium and magnesium ions, all of which interfere with the absorption of tetracyclines and consequently, lower their *in vivo* antimicrobial activity. In patients or subjects given an initial dose of 200mg followed by 100mg every 12 hours, peak serum levels on the third or fourth day are somewhat higher than after a single 200mg dose, and remain about 1 to 1.5 μg/mL just prior to the next dose (Brogden, Speight, and Avery, 1975).

Side-effects

Side effects with minocycline are generally those common to other tetracyclines. Those reported most frequently include gastro-intestinal upset and dizziness, and inter-quently: skin rashes, black hairy tongue, glossitis and oral and vaginal moniliasis. A high hearing loss has been reported in some studies. The symptoms were reversible on discontinuing treatment. Minocycline has no proven phototoxic potential (Brogden, Speight, and Avery, 1975).

Dosage

The usual dose for adults is 200 mg intially followed by 100 mg every 12 hours, taken with food or milk. Therapy should be continued for 1 to 3 days after the characteristic symptoms and fever have subsided. In uncomplicated gonorrhoea in males, a single 300 mg dose has given the most satisfactory results with minimal side-effects (Brogden, Speight, and Avery, 1975).

Microencapsulation

Microencapsulation is a process of applying relatively thin coating to small particles of solid, liquid, or gas and the resulting product is known as microcapsules (Bakan, 1986; Madan, 1978). Microcapsules developed for use in medicine consist of a solid or liquid core material containing one or more drugs enclosed in coating as shown in Figure 2. The core may also be referred to as the nucleus or filler and the coating as the wall or shell. Microcapsules usually have a particle size range between 1 to 5000 μm (Bakan, 1986; Deasy, 1984).

Microencapsulation may be used for a number of reasons (Bakan, 1986, 1994; Li et al., 1988; Madan, 1978). These include:

1. stabilization of drug sensitive to oxygen, light, moisture, etc.
2. providing controlled and/or sustained release of materials following application.
3. prevention of vaporization of volatile drugs.
4. taste masking of bitter drugs.
5. masking of unpleasant odors.
6. preparation of free-flowing powder.
7. modification of physical properties of drugs.
8. elimination of incompatibilities.
9. reducing toxicity.
10. reducing gastric irritation.

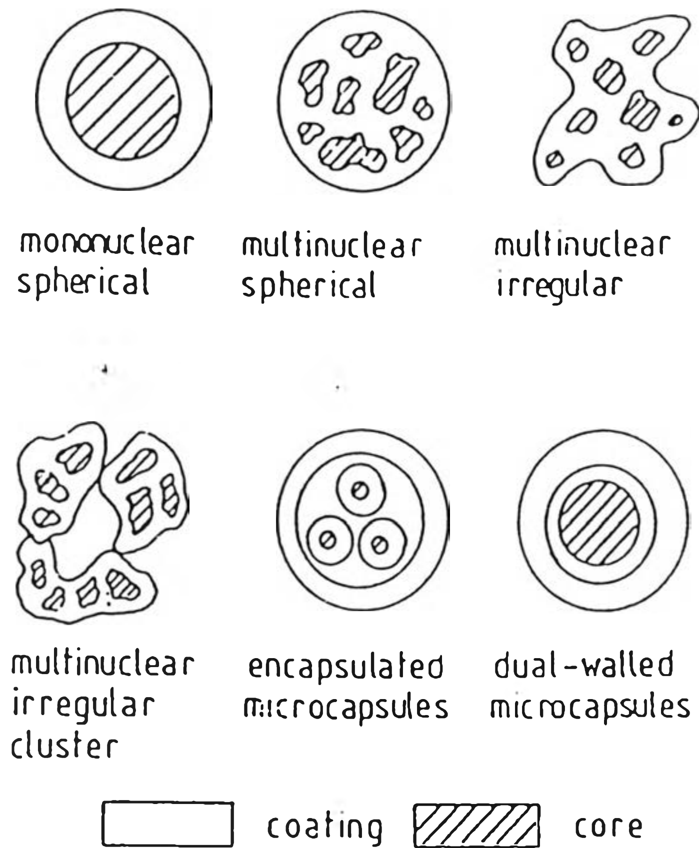

Figure 2 Some typical structures of microcapsules. (Deasy, 1984)

History of Microencapsulation Technique

The first research leading to the development of microencapsulation procedures for pharmaceuticals was published by Bungenburg de Jong and Kaas in 1931 and dealt with the preparation of gelatin spheres and the use of a gelatin coacervation process for coating. In the late 1930s and 1940s, Green and co-workers of The National Cash Register Co., Dayton, Ohio, developed the gelatin coacervation process, which eventually lead to several patents for carbonless carbon paper. This product used a gelatin microencapsulated oil phase usually containing a colorless dye precursor. The microcapsules were afixed to the under-surface of the top page and released the dye precursor upon rupture by pressure from the tip of the writing instrument. The liberated dye precursor then reacted with an acid clay coating on the top surface of the underlying page to form the copy image (Deasy, 1984).

Microencapsulation Procedures

Many microencapsulation procedures have been developed for the coating of pharmaceuticals. There are difficulties to classify simply under any one heading; however, they can be classified roughly into 3 major categories which are physicochemical, chemical, and physical methods (Kondo, 1978). These major microencapsulation procedures were summarized briefly in Table 3 (Bakan, 1986, 1994; Deasy, 1984; Kondo, 1978; Madan, 1978; Watts, Devies, and Melia, 1990). The emulsification/solvent evaporation procedure used in this research will be presented in more details in the next topic.

Table 3 Summary of major microencapsulation procedures

Process	Principle	Type of core	Type of coating
1. Physicochemical Methods			
1.1 Coacervation/ Phase - Separation	Reduction in the solvation of polymeric solute(s) in a medium to form coacervate droplets to deposit and coat the dispersed plase.	Vehicle-insoluble drug (s)	Vehicle-soluble - polymer (s)
1.2 Solvent Evaporation	The emulsification of a polymer solution containing drug into an immiscible liquid phase containing an emulsifier and the solvent is removed from the dispersed droplets to leave a suspension of drug containing polymer microcapsules.	Solvent-soluble and solvent-insoluble - drug(s), but insoluble in manufacturing vehicle.	Solvent-soluble-polymer(s), but insoluble in manufac-turing vehicle.
2. Chemical Methods			
Interfacial Polymerization	Reaction of various monomers at the interface of two immiscible liquid phases to form a film of polymer that encapsulates the dispersed phase	High-molecular-weight materials such as enzymes and hemolysates.	Water soluble and water-insoluble monomers

Table 3 (continued)

Process	Principle	Type of core	Type of coating
3. Physical Methods			
3.1 Air Suspension	Polymer solution is spray-applied to the suspending and moving particles in the coating zone portion of the coating chamber of air suspension apparatus.	Non-volatile and solid drug(s).	Water-soluble or organic solvent-soluble polymer(s).
3.2 Pan Coating	Polymer solution is spray-applied to the desired solid core material, which is deposited onto spherical substrates, e.g. nonpariel seeds in the coating pan while rotating.	Non-volatile and solid drug(s).	Water-soluble or organic solvent-soluble polymer(s).
3.3 Spray Drying	Dispersing the core material into a coating solution and then the mixture is atomized into a hot air stream to remove the solvent from the coating material.	Solvent-insoluble drug(s).	Solvent-soluble polymer(s).

Various microencapsulation procedures will give the different particle size ranges of microcapsules as shown in Table 4 (Bakan, 1986, 1994).

Table 4 Microcapsule size ranges produced by various microencapsulation processes (Bakan, 1986, 1994)

Microencapsulation process	Size range (μm)
Coacervation / Phase separation	2 – 5000
Solvent evaporation	5 – 5000
Interfacial polymerization	2 – 2000
Air suspension	35 – 5000
Pan coating	600 – 5000
Spray drying	5 – 600

Solvent Evaporation Procedures

Microencapsulation by emulsification/solvent evaporation is conceptually a simple procedure. It involves, first, the emulsification of a polymer solution-containing drug (either dissolved or in suspension) into a second, immiscible liquid phase containing an emulsifier to form a dispersion of drug-polymer-solvent droplets. In the second step, the solvent is removed from the dispersed droplets by application of heat, vacuum, or by allowing evaporation at room temperature to leave a suspension of drug-containing polymer microspheres that can then be separated by filtration or centrifugation, washed, and dried (Figure 3). This technique can be tailored to produce microspheres over a wide size range, from less than 200 nm to several hundred microns, and by choice of suitable solvent systems drugs have high or low aqueous solubilities can be encapsulated into a wide range of polymers (Watts, Devies, and Melia, 1990).

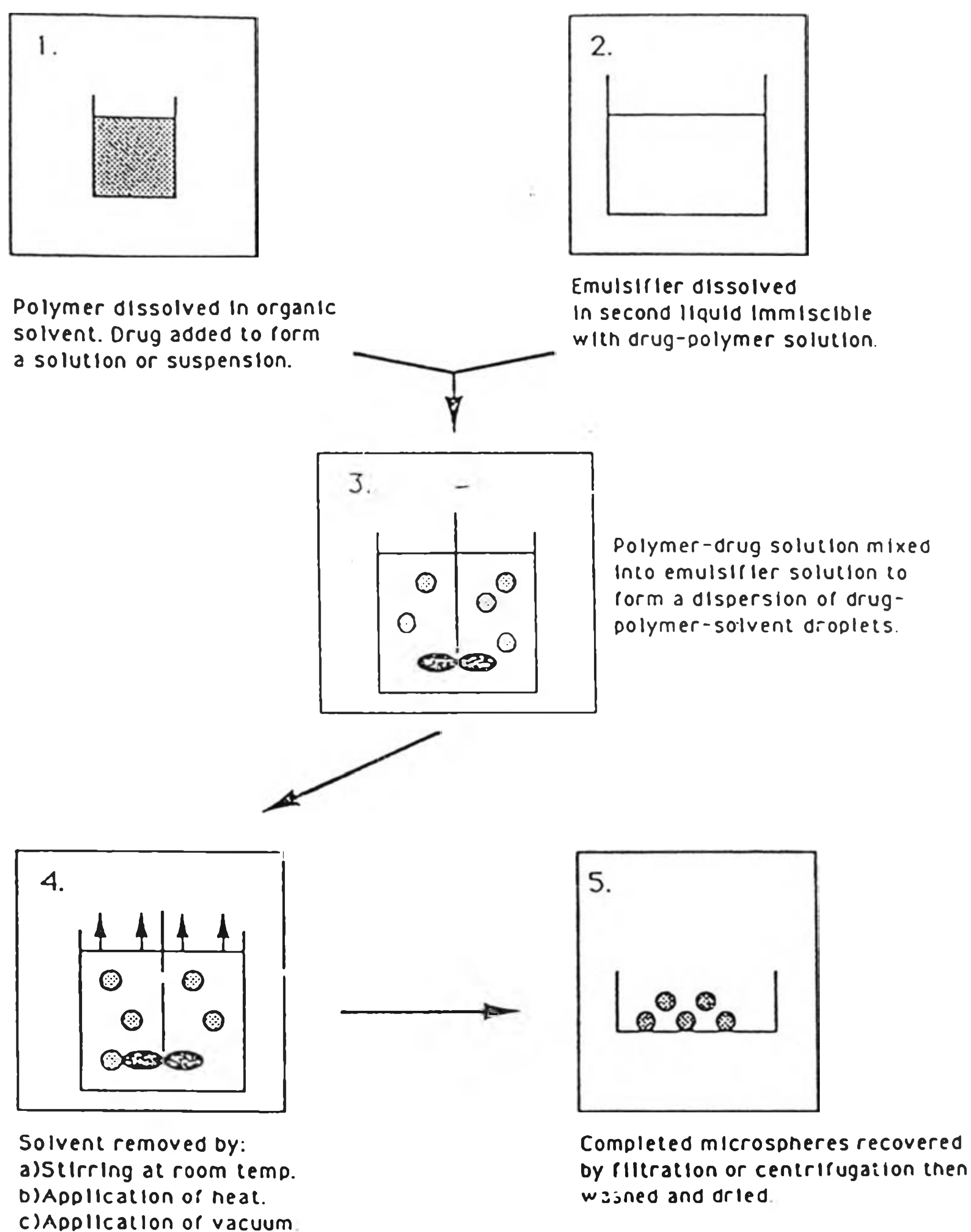

Figure 3 Schematic diagram of microsphere formation by solvent evaporation procedure. (Watts, Devies, and Melia, 1990)

There were two types of solvent evaporation, each having the concept of emulsion and are as follows : (Watts, Devies, and Melia, 1990; Hincal and Calis, 2000)

1. Single-emulsion solvent evaporation
2. Multiple-emulsion technique

1. Single-Emulsion Solvent Evaporation

For single-emulsion solvent evaporation, there are two systems to choose: oil-in-water (o/w) or water-in-oil (w/o)

1.1 Oil in Water Emulsion Solvent Evaporation Technique

Oil in water emulsion is more widely used than w/o emulsions due to the simplicity of the process and easy clean-up requirement for the final product. In this process, both the drug and the polymer should be insoluble in water, while a water-immiscible solvent is required for polymer (Hincal and Calis, 2000). The diagram representation of o/w emulsification-solvent evaporation technique is shown in Figure 4.

Problems to the efficient incorporation of water-soluble active substances into biodegradable polymer microspheres using o/w emulsification with solvent evaporation are originating to a great extent from the separation and/or removal of water-soluble material into the aqueous continuous phase.

In general, this method is particularly suitable for microencapsulaton of lipophilic drugs that can be either dispersed or dissolved in the dispersed phase of a solvent. Clonazepam, testosterone, cisplatin and diclofenac sodium are some examples of drugs that have been encapsulated by this technique (Hincal and Calis, 2000).

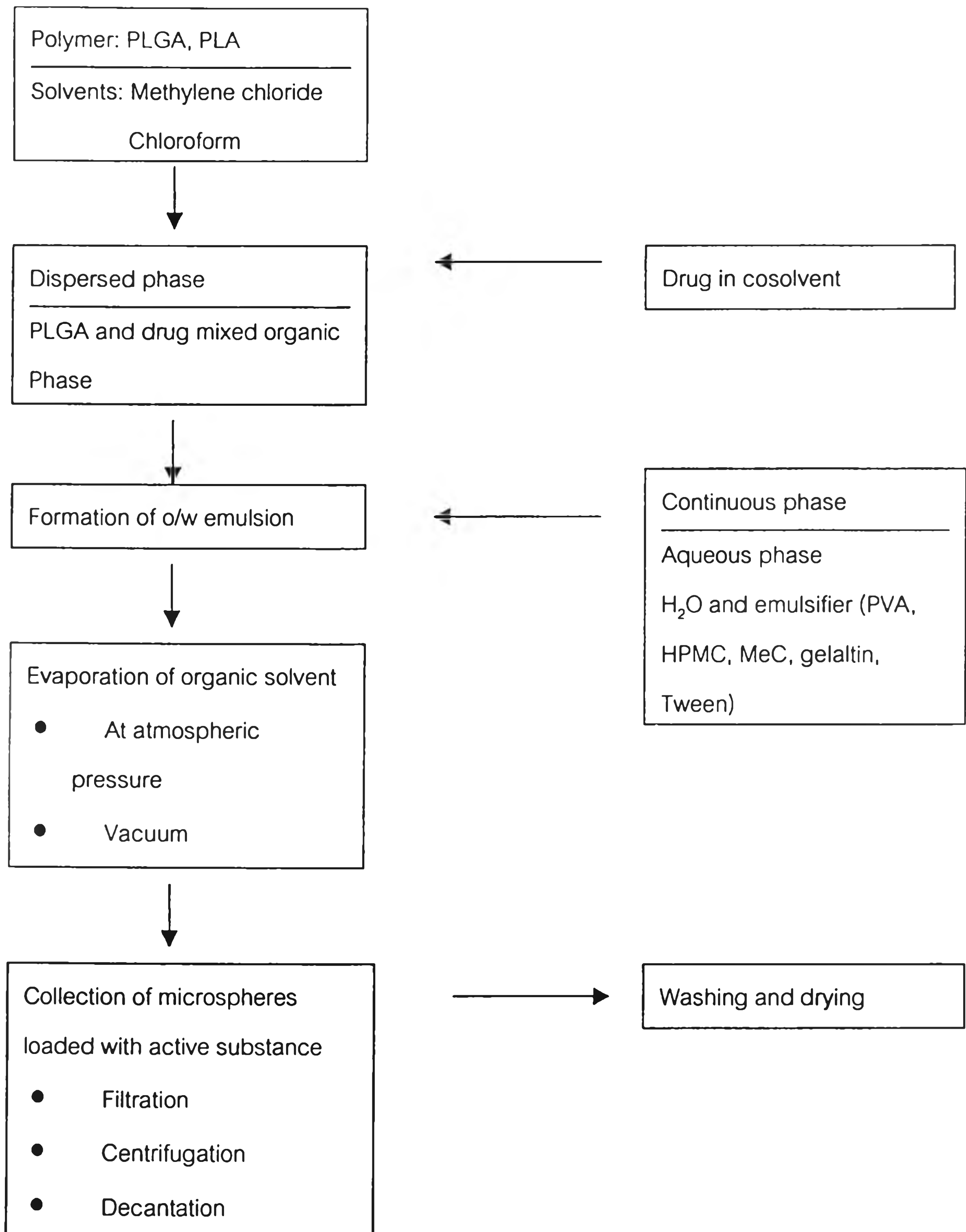

Figure 4 The diagram of o/w emulsification-solvent evaporation technique .
(Hincal and Calis, 2000)

1.2 Oil in Oil Emulsification-Solvent Evaporation Technique

Oil in oil, sometimes referred as water in oil emulsification process, was developed for the encapsulation of highly water soluble drugs. Water soluble drugs such as theophylline, caffeine and salicylic acid could not be loaded efficiently using o/w emulsion method, whereas drugs with low water solubility such as diazepam, hydrocortisone, and progesterone were successfully entrapped in microspheres.

In this technique, polymer and drugs, contained in polar solvent such as acetonitrile, are emulsified into an immiscible lipophilic phase, such as light mineral oil commonly being used, and surfactant such as Span. However, an important drawback of using an oil external phase is cleaning up the final product. The oil has to be removed using organic solvent such as n-hexane, which themselves may present problems in terms of completeness of removal (Watts, Devies, and Melia, 1990). Diphenhydramine hydrochloride, mitomycin C, cephradine and phenobarbitone are some examples of drugs that have been encapsulated by this technique (Hincal and Calis, 2000).

2. Multiple-Emulsion Technique

Multiple-emulsion or double emulsion technique is used for the efficient incorporation of water-soluble peptide, protein, and other macromolecules. In this technique, the polymers are dissolved in an organic solvent and emulsified into an aqueous drug solution to form a water in oil emulsion then reemulsified into an aqueous solution containing an emulsifier to produce a multiple w/o/w dispersion. The organic phase acts as a barrier between the two aqueous compartments, preventing the diffusion of the active material toward the external phase. The schematic diagram of w/o/w emulsification-solvent evaporation technique as shown in Figure 5.

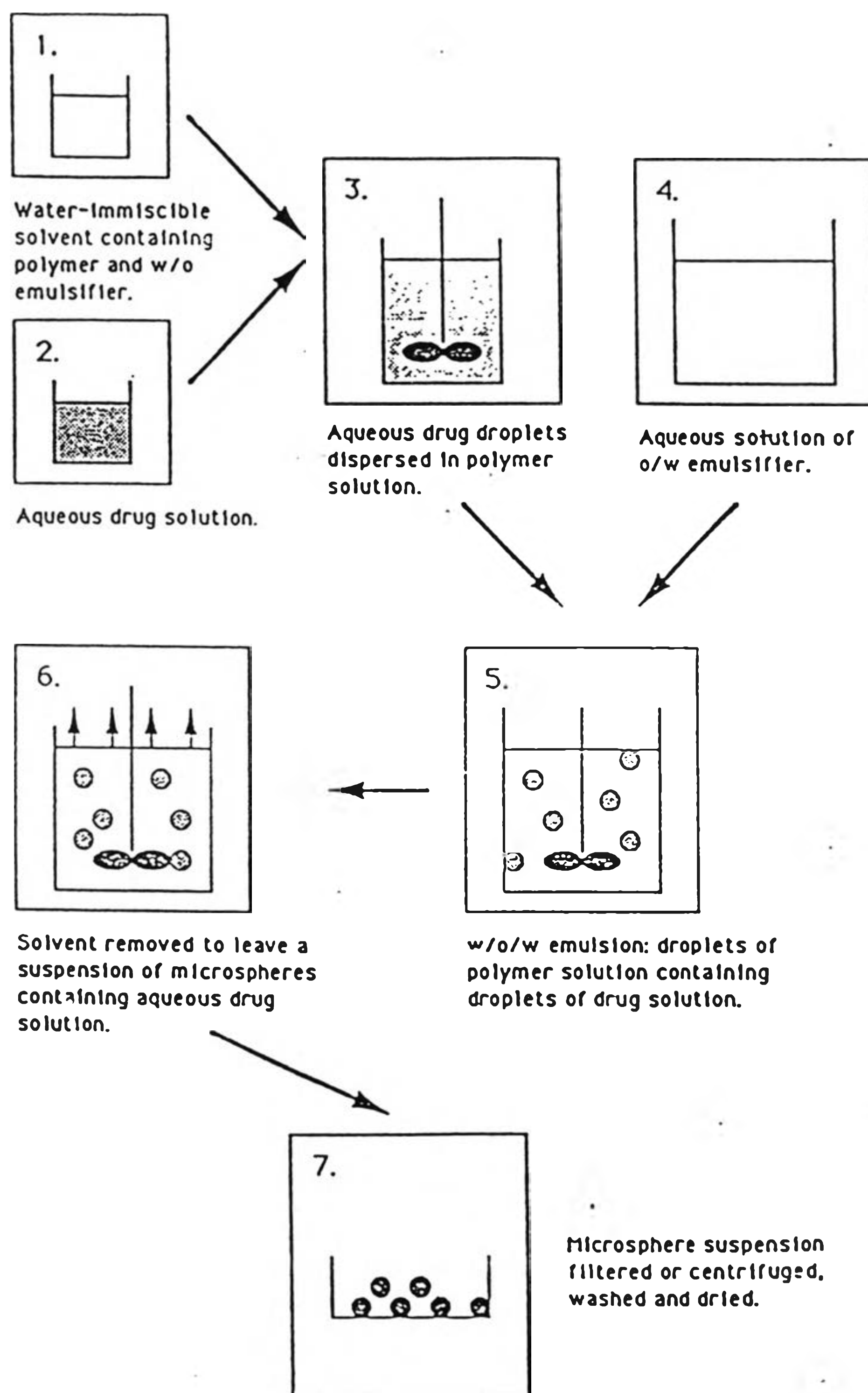

Figure 5 Schematic diagram of microsphere formation by a w/o/w technique .

(Watts, Devies, and Melia, 1990)

Hermann and Bodmeier (1995), for example, could not obtain acceptable encapsulation effciencies to encapsulate the water soluble peptide somatostatin acetate by o/w solvent evaporation method. Because of its high water solubility somatostatin acetate diffused into the external phase during microsheres preparation therefore they utilized w/o/w technique. In w/o/w technique, drugs or aqueous solution was dispersed in the organic polymer solution followed by emulsification into the external phase. Partitioning of the drug into the external phase was reported to be prevented.

Factors Affecting on Microencapsulation Using Solvent Evaporation

1. Solvent Type

Central to the process of microencapsulation by emulsification/solvent evaporation is the selection of the two liquid phases, one to contain drug and polymer (dispersed phase) and one to contain the emulsifier (continuous phase) (Watts, Devies, and Melia, 1990).

Important criteria for dispersed phase solvent:

1. Ability to dissolve chosen polymer
2. Ideally, the solvent should be able to dissolve the drug
3. Immiscibility with the continuous phase solvent
4. Lower boiling point than continuous phase solvent
5. Low toxicity

Important criteria for continuous phase solvent:

1. Immiscibility with dispersed phase solvent
2. Inability to dissolve polymer
3. Low solubility toward drug
4. Higher boiling point than dispersed phase solvent
5. Low toxicity
6. Allows easy recovery and clean-up of microspheres

The final structure and composition of a microsphere will result from a complex interplay between polymer, drug, solvent, continuous phase, and emulsifier. Since the drug and polymer to be used are usually mixed, solvent choice can be of crucial importance. For example, in a detailed study of the effects of solvent properties on the preparation of poly (lactic acid) (PLA) microspheres a high efficiency of quinidine sulfate entrapment was favored by dissolving the drug and polymer in water-immiscible solvents with significant water solubility. It was considered that such solvents cause rapid precipitation of polymer at the droplet interface, thereby creating a barrier to drug diffusion out of the forming microsphere. The solvent able to achieve the highest drug loading, 23% w/w (theoretical 30%), was methylene chloride (dichloromethane), which had the highest water solubility (2% w/w), whereas insignificant loading (0.4%) was achieved using chloroform, which has a solubility of only 0.8% w/w. If water-miscible solvents were used to dissolve the drug and polymer, large polymer agglomerates were formed on mixing, although it was possible to produce discrete microspheres using a dispersed phase containing 30% of a water-miscible solvent such as acetone (Bodmeier and McGinity, 1988).

Methylene chloride is the most widely used solvent for producing microspheres by the emulsification/solvent evaporation method. This solvent has high volatility that facilitates easy removal by evaporation, and also shows good solubility toward a range of encapsulation polymers (Watts, Devies, and Melia, 1990).

2. Emulsifier

The emulsifier (stabiliser) is an important parameter that provides a thin protective layer surrounding the oil droplets and reduces the coalescence and coagulation of microparticles during the solvent evaporation process. Due to a gradual decrease in volume and subsequent increase in viscosity of dispersed oil droplets, these affect the droplet size equilibrium and droplets tend to coalescence and produce agglomerates during the early stages of solvent removal. As the solvent is removed, the emulsifier continues to maintain the spherical shape of the oil droplets and prevents the

หอสมุดกลาง สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

aggregation, until the microspheres are hardened and isolated as discrete particles (Jain et al., 1998).

The emulsifiers used in this process are the hydrophilic polymeric colloids and anionic or nonionic surfactants. The most commonly emulsifier as PVA is used in o/w emulsion. Others include poly (vinylpyrolidone), alginate, gelatin, methylcellulose, hydroxyalkyl cellulose, hydroxypropylmethycellulose, polyoxyethylene derivative of sorbitan fatty esters (Tweens), cetyltrimethyl ammonium bromide, and fatty acid salts such as sodium oleate. For o/o emulsion, oil soluble emulsifiers such as polyoxyethylene fatty acid ethers (Brijs), Spans, and lecithins have been used (Jain et al., 1998).

Physicochemical properties and concentration of emulsifier or stabiliser influence morphology and encapsulation efficiency. Esposito et al. (1997) found that tetracycline microcapsules prepared by the w/o/w solvent evaporation technique using gelatin as stabiliser of the primary emulsion gave better result than pectin and pemulen, both in terms of microparticle morphology and encapsulation efficiency. Furthermore, Schugens et al. (1994) found that drug entrapment of indigocarmine microcapsules prepared by using bovine serum albumin as stabiliser increased with increasing concentration of bovine serum albumin.

3. Core to Wall Ratio

As the core to wall ratio decreased, the microcapsule size distribution shifted to the smaller size (Ruiz, Sakr and Sprockel, 1990). The similar result was obtained with preparation of ascorbic acid microcapsules that a high core to wall ratio resulted in an increase of both microcapsule size and drug release rate (Vanichtanunkul, Vayumhasuwan and Nimmannit, 1998). In addition, Herrmann and Bodmeier (1995) found that increasing the amount of polymer increased the encapsulation efficiency.

4. Stirring Rate

Stirring rate is a parameter of primary importance in emulsification steps. In the forming droplets, the energy and the surface active agent decrease the interfacial tension between the organic droplets and the aqueous phase. The stirring rate providing the energy which is appropriate for the division of the organic phase, so if high energy, small particle and narrow particle size distribution are obtained (Sansdrap and Moes, 1993).

5. Polymer Type

The type of polymers used in solvent evaporation technique was designed on the purpose of study, physicochemical properties of polymers such as molecular weight, hydrophilic properties influenced the microcapsules. Polard et al. (1996) reported the effect of molecular weight (MW) on the characteristics of microparticles that drug content of polylactide (MW 2000) microparticles was higher than of poly lactide-co-glycolde (MW 9000 and 12000) and polylactide (MW 9000) microparticles due to rapid rate of polymer precipitation at the droplets surface. In addition, polymer type also effected on the drug release. Esposito et al. (1997) found that tetracycline released from poly (L-lactide) (MW 171000) slower than poly (DL-lactide) (MW 86400) microcapsules due to its high molecular weight and polymer nature. This result is consistent with a study by Lacasse et al. (1997) in which the release of angiotensin receptor antagonist increased with increasing percentage of low molecular weight poly (L-lactide).

Polylactic acid

Polylactic acid, a biodegradable polymer of lactic acid, has been extensively investigated for its use as an absorbable suture, as a material for (i) implants, (ii) in sustained and controlled drug delivery systems, and (iii) microcapsules. Polylactic acid

was reported that non-toxicity and non-tissue reactivity of polylactic acid (Lalla and Chugh, 1990). Further, it was reported that none of its metabolites were retained in any of the vital organs of the body, they were eliminated from the body as carbon dioxide and water thus making it biodegradable (Jain et al., 1998).

Poly (L-lactide) and Poly (DL-lactide)

Poly (L-lactide) and poly (DL-lactide) are insoluble in water (Arshady, 1991). Polymer structures are shown in Figure 6 (Brannon-Peppas, 2000).

Poly (L-lactide) is found to be semicrystalline because of the high regularity of its polymer chain, and poly (DL-lactide) is an amorphous polymer because of irregularities in its polymer chain structure (Jain et al., 1998).

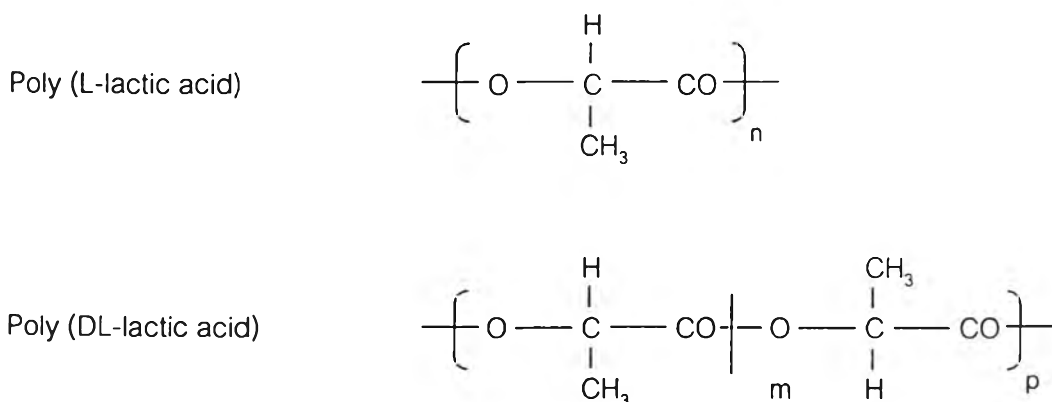

Figure 6 Structure of Poly (L-lactide) and Poly (DL-lactide). (Brannon-Peppas, 2000)

When stored at 0.12% RH and 80% RH at 4°, 40°, 50° and 60°C the polymer showed both temperature and humidity dependent hydrolysis. At 0.12% RH and at temperatures ranging from 4-60°C, PLA did not show any hydrolysis. The results on samples stored at 80% RH show significant influence of humidity on the stability of the polymer. The results indicate the susceptibility of the polymer to degrade under acclerated conditions of temperatures and humidity. As regards the influence of pH, the

results indicate that the material is relatively stable in acidic and neutral medium, but almost all the polymer got hydrolysed in 0.1N NaOH in 15 days.

When immersed in enzyme compositions simulating the gastrointestinal milieu, the polymer remained practically unaffected (Lalla and Chugn, 1990).

Poly (DL-lactide-co-glycolide) 75:25 and 50:50

Poly (DL-lactide-co-glycolide) 75:25 and 50:50 are insoluble in water (Arshady, 1991). Lactic acid is more hydrophobic than glycolic acid and hence lactide rich poly (lactide-co-glycolide) (PLGA) copolymers are less hydrophilic, absorb less water, and subsequently degrade more slowly and they are amorphous (Jain et al., 1998). Structure of poly (lactide-co-glycolide) is shown in Figure 7.

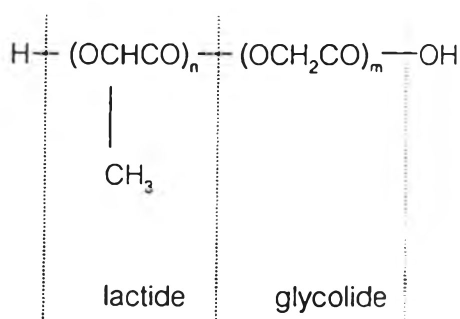

Figure 7 Structure of Poly (lactide-co-glycolide). (Hutchinson and Furr, 1990)

The degradation of PLGA polymers in contact with aqueous *in vivo* fluids or media has been the subject of many discussions aimed at deciding whether the mechanism is purely chemical or enzyme-dependent. Currently, the degradation of aliphatic polyesters in contact with living tissues or with enzyme-containing body fluids is regarded by most people as resulting from abiotic hydrolysis of ester bonds only. However, enzymatic degradation of aliphatic polyesters should not be claimed unless mass loss and dimensional change without molar mass decrease are conclusively shown to exist since enzymes can hardly penetrate deep in a dense polymer matrix.

For any reason, surface degradation occurs because the rate of degradation is greater than the rate of diffusion of water into the polymeric mass, surface erosion is observed and thus confusion is possible between enzymatic surface degradation and abiotic, hydrolytic surface degradation (Brannon-Peppas, 2000).

The Release of Drug from Microcapsules

Model of delivery achieves by a controlled release system can vary over a wide range, but most release profiles are categorized into three types (Baker, 1987; Washington, 1990):

1. Zero-order release model
2. First-order release model
3. Square root of time release model or Higuchi model

1. Zero-Order Release Model

An ideal drug release of controlled release dosage form device is one which can deliver the drug at a constant rate until the device is exhausted of active agent.

Mathematically, the release rate from this device is given as:

$$\frac{dM_t}{dt} = k \quad (1)$$

where k is a constant, t is time, and M_t is the mass of active agent released. This model of release is called zero-order release model.

Zero-order model can be predicted by plotting the percentage of drug released against time. The release of drug is the zero order model if the linear relationship is obtained.

2. First-Order Release Model

The release rate is proportional to the mass of active agent contained within the device. The rate declines exponentially with time approaching a release rate of zero as the device approaches exhaustion.

On the assumption that the exposed surface area of matrix decreases exponentially with time, It is suggested that the drug release from most sustained release matrices can be described by first order kinetics as follows:

$$A_t = A_0 e^{-k_1 t} \qquad (2)$$

where k_1 = first order release constant

A_0 = initial amount of drug

A_t = amount of drug remaining in the matrix at time t.

Taking the logarithm of the above equation yields

$$\ln A_t = \ln A_0 - k_1 t. \qquad (3)$$

First-order model can be predicted by plotting logarithm of the percentage of drug remaining against time. The release of drug is the first order model if the linear relationship is obtained. The initial curvature of the plot may be obtained because of the presence of surface drugs and they suggested to ignore it.

3. Square Root of Time Release Model or Higuchi Model

The release model of this type can be described by Higuchi equation (Higuchi, 1963).

$$Q = [(D\varepsilon/\tau)(2A - \varepsilon C_s) C_s t]^{1/2} \quad (4)$$

where Q = weight in grams of drug released per unit surface area

D = diffusion coefficient of drug in the release medium

ε = porosity of the matrix

τ = tortuosity of the matrix

C_s = solubility of drug in release medium

A = concentration of drug in the microcapsules, expressed as g/mL.

The assumptions made for equation (4) are as follows:

1. A pseudo-steady state is maintained during the release.
2. $A >> C_s$, i.e., excess solute is present
3. The system is in a perfectly sink condition in which concentration of solution is approximately equal to zero at all time.
4. Drug particles are much smaller than those in the matrix.
5. The diffusion coefficient remains constant.
6. No interaction between the drug and the matrix occurs.

For purpose of data treatment, the equation (4) is usually reduced to

$$Q = k_h t^{1/2} \quad (5)$$

where k_h is Higuchi constant. Therefore, the plot of amount of drug released from matrix versus the square root of time should be increased linearly if drug released from the matrix is diffusion controlled. Although the above equation was based on the release from a single face, it may be used to describe diffusion-controlled release from all surface matrix.