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POSSIBLE STRATEGIES FOR THE FORMULATION OF ANTINEOPLASTIC DRUGS

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I. INTRODUCTION

Cancer, perhaps the most feared of all diseases, has become the second leading cause of death since the 1960s (Silverberg and Lubera, 1986; Statistical Abstract of the US, 1984). Silverberg and Lubera (1986) predicted that, in 1986, approximately 930,000

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Americans will have been diagnosed with cancer and 472,000 will have died of the disease. Due to the high mortality rate, the chemotherapy of cancer has been under vigorous investigation and important gains have been made in the treatment of some neoplasms such as testicular germ cell tumors, choriocarcinoma, Burkitt's lymphoma, Hodgkins disease, and several childhood cancers. However, progress in treating the three most common solid malignancies of the breast, lung and colon is less impressive. The majority of patients with these tumors die of metastatic disease (Poste, 1984).

A limiting factor of the effectiveness of cancer chemotherapy is the failure to differentiate the tumor cells from the normal cells. The cellular and subcellular differences between tumor cells and their normal counterparts appear to be quantitative rather than qualitative (Kato, 1983; Poste, 1986; Reiss et al.,1986). Thus the research for drugs that target entirely to tumor cells may be unrealistic. The recent investigation of oncogenes may provide measures to prevent the initiation, progression and metastasis of tumors (Newmark, 1983). However, it will be many years before drugs acting on these processes will be available for clinical use.

At present, successful chemotherapy is achieved either by the drug alone or by the so-called 'combined modality treatment' approach (Sartorelli, 1976). The latter, which is gaining in its importance in cancer treatment, is the combination of a chemical agent with surgery and/or irradiation. The basis for such a

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combined approach is to lessen the tumor cell burden of the host by the use of surgery and/or irradiation. This treatment is followed by chemotherapy designed to attack the metastatic or microscopic neoplastic cells. Thus the essential step of cancer chemotherapy is the elucidation of an effective chemotherapeutic agent.

Unfortunately, most antineoplastic agents possess a therapeutic index that is close to unity, i.e., these agents do not exhibit high selectivity towards tumor cells. Three strategies have been adopted to overcome the low selectivity of the antineoplastic agents (Poste, 1984). The first strategy is to improve the effectiveness of existing drugs by exploring their use in new combinations and dosing regimens in clinical studies. Secondly, pharmaceutical techniques are used to alter drug disposition, pharmacokinetics and/or dose-response relationships to achieve a higher therapeutic index of an existing drug. The final strategy involves the research for new drugs with entirely novel pharmacological actions. All three strategies are, more or less, hindered by the lack of qualitative biochemical differences between tumor and normal cells (Poste, 1984; Poste, 1986; Reiss et al., 1986).

Despite the progress made in synthetic chemistry, little success has been achieved for production of new molecular entities with desired pharmacological activities. Each year, the NCI chooses approximately 10,000 substances from the 40,000 or so that are available for possible inclusion in the new drug research

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program. Following a series of screening experiment using animal models, about 10 compounds have shown to be effective. Further toxicological studies permit only 5 to 8 drugs for clinical trials and filing for an INDA with the FDA (Gross, 1986). Of the rejected investigational new drugs, many face basic pharmaceutical formulation problems such as stability and solubility. Recent advances in polymer chemistry and the development of monoclonal antibodies may provide some solutions by targeting via the receptor-mediated reactions. It is our opinion that simpler drug delivery systems can be developed to solve some of the formulation problems of these potential antineoplastic agents. This review discusses some approaches for improving solubility and stability of these drugs.

II. PROBLEMS OF ANTINEOPLASTIC INVESTIGATIONAL DRUGS

Major formulations problems which inhibit the further development of many of the anticancer investigational drugs include the following: poor stability, poor aqueous solubility, poor membrane flux (NCI, 1984). Furthermore, these drug substances are available only in small quantities from NCI, and this severely impacts on preformulation evaluation. Of course, significant stability, aqueous solubility and membrane permeability are basic requirements for a successful dosage form.

In order to achieve the desired pharmacological actions, the bioavailability of the drug itself must be adequate. The drug must possess some limited aqueous solubility to enter the systemic circulation for therapeutic efficacy. Relatively insoluble

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compounds often exhibit incomplete or erratic absorption following oral administration. The drug must also possess a certain degree of lipophilicity to cross a biological membrane and enter a target cell to produce a biological response.

In addition to the basic formulation problems, many of the drugs under NCI investigation do not appear to be outstanding candidates for targeting to tumor cells. Widder et al. (1979) identified three stages of the biophysical targeting of anticancer drugs. First-order targeting involves the restricted distribution of a delivery system to the capillary beds of a pre-determined target site, organ or tissue. Second-order targeting refers to the selective direction of the drug-carrier complex or the drug to tumor cells relative to normal cells. Third-order targeting involves the carrier directed release of drug at selected intracellular sites. This implies that the drug-carrier complex enters the tumor cells by either phagocytosis or cell fusion.

Although a variety of innovative drug delivery systems have been proposed, none of them have completely solved the problems of first-order targeting. This is due to the physiological mechanisms of the body (Kato, 1983; Poste, 1986). Firstly, drug carriers which are small enough to avoid extensive embolization in the target organs and lungs are rapidly sequestered by phagocytosis of the reticuloendothelial system, mainly in the liver and spleen. Thus the drug concentration in tumor lesions is decreased much more than expected. Secondly, nearly all carriers must pass through the capillary endothelium before they reach the

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designated target. There is a rule of thumb that the majority of particles larger than 7 μm would been trapped in the lungs by capillary blockade, particles larger than 100 nm would normally be entrapped by the liver and spleen, and of particles less than 100 nm would be taken up by bone marrow and tumors (Illum and Davis, 1981; Tomlinson, 1982). Even the much focused monoclonal antibody delivery system could not bypass these mechanisms (Kato, 1983; Zalcberg, 1985).

Particles less than 100 nm will then have the possibility of leaving the systemic circulation through fenestrations in the cells lining the blood vessel. These fenestrations are of different sizes depending on the capillary beds considered. The capillary endothelium of pancreas, intestines and kidney has fenestrations of 50 to 60 nm while that of liver, spleen and bone marrow has fenestrations of about 100 nm. There is a suggestion that capillaries in tumor regions may have greater permeability because of tissue inflammation (Kato, 1983; Poste, 1984). These physiological mechanisms of size filtration can be coupled with route of administration to achieve first order targeting. Therefore, for large particles, intravenous injection is the route of administration when lung is the target organ; intra-arterial administration leads to entrapment in the liver, and local intramuscular injection into solid tumor leads to the selective targeting to the tumor capillaries.

In order to design an appropriate formulation to solve these problems, we need to consider the information regarding the drug

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itself and the factors involved in the formulation process. Micromethods must be employed during all processes due to the small quantities of these NCI investigational drugs.

III. PREFORMULATION CONSIDERATIONS

The development of a drug delivery system involves several important considerations related to the physicochemical properties of the drug, the biological properties of the drug, and patient/disease factors (Table 1) (Madan, 1985).

The most important properties of the active ingredient to be evaluated are stability, solubility and rate of dissolution. Additives in emulsions and suspensions, even in some forms of solutions, usually offer a protective environment to reduce the reactivity among solute molecules or between the solute and the medium. Factors which influence solubility include particle size, salt, ester or other chemical forms, solution pH, polymorphism, purity and hydrate formation (Boylan and Fites, 1979; Ravin, 1980). Manipulation of these factors may increase the solubility.

In order to provide efficacious, safe and elegant parenteral dosage forms, additives must frequently be incorporated into the formula. These substances include antioxidants, antibacterial agents, buffers, bulking materials, chelating agents, inert gases, solubilizing agents, and substances for adjusted tonicity.

In consequence, the effects of these additives to stability, solubility and rate of dissolution should be carefully monitored. Due to the extensive pharmacological and toxicological data required to obtain approval for any new additive, there is a

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Table 1. Factors influencing the formulation of drug delivery systems

FACTOR	CONSIDERATIONS
Physicochemical properties of the drug	Aqueous solubility of the drug
	Size of the dose
	Stability of the drug
	Molecular size and diffusivity of the drug
	Partition coefficient of the drug
	pKa of the drug
	Protein binding
	Type of dosage form
Biological properties of the drug	Absorption characteristics of the drug
	Biological half-life of the drug
	Body movement
	Distribution characteristics
	Duration of action of the drug
	Margin of safety of the drug
	Metabolism of the drug
	Role of circadian rhythm
	Role of disease state and tissue injury
	Drug administration route
	Side effects of the drug
Patient/disease factors	Acute or chronic therapy required
	Age and physiological state of the patient
	Ambulatory or bedridden patient
	Circadian changes in disease
	Duration of drug action desired
	Location of target area
	Pathology of disease state
	Route of drug administration

reluctance to use any currently unapproved parenteral product component. Thus, the formulator is restricted to a very few materials which have known acceptability (Davis et al., 1985; Boylan and Fites, 1979).

The physicochemical properties of a drug determine the rate of release from the delivery system and the type of delivery

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system required for any given drug by that particular route of administration. Thus, the following information regarding the drug should be available: stability, aqueous solubility, partition coefficient, dissociation constants (pKa), particle size, and dissolution rate (Greene, 1979; Madan, 1985; Ravin, 1980). A thorough understanding of the physicochemical properties of the new drug substance is essential for the efficient development of stable and efficacious dosage forms. The type and depth of studies involved are influenced by both the nature of the drug substance, the anticipated route of administration, and amounts available for testing. To achieve reliable data fully validated micro-analytical methods are a prerequisite. These preformulation considerations will ensure that the available dosage forms for patients are manufacturable on a large scale, stable through the processing and storage conditions anticipated, and sufficiently bioavailable so as to give reasonable reproducibility of response.

For the anticancer investigational drugs, some of the major considerations are the appropriate route of administration and the properties of the drugs. The most common routes of administration of antineoplastic agents are either oral or parenteral. Although the gastrointestinal route of administration is the most popular for other types of drugs, some of its features can affect a drug's rate of absorption and duration of action. The successful transportation of an orally administered drug into the systemic circulation is often difficult to achieve because of chemical degradation in the lumen of the gut, the gut wall, or circulation,

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or because the properties of the drug such as pKa, partition coefficient, etc. adversely affect dissolution or membrane flux. Thus, many antineoplastic agents are administered by the parenteral route (Calabresi and Park, 1980; Harvey, 1980). Parenteral administration offers rapid, assured high blood and tissue levels without the incomplete or variable absorption from the gastrointestinal tract which may follow oral administrations. Safety requirements for a parenteral administration limit the injectable dosage forms to solutions, emulsions or suspensions. Components which are incorporated into parenteral dosage forms have very rigid specifications.

IV. PROPOSED STRATEGIES

Two possible approaches are suggested for the formulations for anticancer investigational drugs. The first is the use of classical solubility approaches which could result in an enhancement of the aqueous solubility of the various potential antineoplastic species. The second is the development of colloidal drug delivery systems such as liposomes, microencapsulation systems, fat emulsions and polyaphrons to achieve solubility and stability goals.

(A) Classical Solubility Approaches; Solubilization

For a solution of an antineoplastic agent, the most appropriate route of administration may often be parenteral, either intravenous or intra-arterial. Solutions have advantages over colloidal systems in physical stability, versatility and ease of sterilization. However, many of the investigational drugs have poor intrinsic aqueous solubility.

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Solubility is a dynamic process that results from the continuous making and breaking of cohesional and adhesional interactions between a solute and a solvent. The magnitude of solubility at equilibrium can be altered by the use of solubility sensitive parameters which increase the adhesional interactions. These parameters are pH, temperature, polarity, dielectric constant, additives, buffers, cosolvents, hydrotropic agents, etc. (Anderson and Pitman, 1980; Bosanquet, 1985; Flynn and Hagen, 1983; Martin et al., 1982). The techniques of solubilization that manipulate these solubility sensitive parameters can be summarized as follows: (1) forming micelles in surfactant systems, (2) solubilizing in cosolvents, (3) altering solubility through complexation, (4) solubilizing by the addition of a hydrotropic agent, (5) solubilizing by solid-state manipulation, (6) synthesizing derivatives. Past experience in dealing with low aqueous solubility drugs such as sulfonamides have shown that these approaches can achieve significant increase in solubility.

These solubility enhancement techniques, although useful for many compounds, typically allow for solubility enhancement of one or two fold to about two orders of magnitude (100 fold) depending on vehicle composition. Solubility enhancement that is several orders of magnitude (e.g., 1000 to 10,000 fold) require the combination of several of the above techniques.

The solubility and stability of a compound, especially complex organic molecules, can be increased by manipulating the solid-state forms, i.e., the crystalline or amorphous forms. This

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application, however, is limited by the physical properties of the drug itself. The magnitude of increased solubility is usually no greater than five fold (Behme et al., 1985; Haleblian, 1975; Lindenbaum et al., 1985; Shefter, 1981; Umeda et al., 1985). The derivatization approach offers dramatic increase in solubility e.g., the HCl salt of the dipropylamine N-Mannich base of carbamazepine has an aqueous solubility 10^4 fold greater than that of carbamazepine (Bundgaard et al., 1982). However, derivatization is most successful when a free hydroxyl, carboxyl, or amino functional group is available. Inactive derivative can be converted either by the spontaneous hydrolysis or the enzymatic degradation into an active form (Amidon, 1981; Anderson et al., 1985; Millership and Shanks, 1986). While derivatization has potential application in this area, it is a costly and difficult process. Furthermore, the prodrug approach usually changes the pharmacokinetic and pharmacological properties of the parent compound (Nagasawa et al., 1986; Repta et al., 1981a; Sasaki et al., 1984b). In developing a desirable formulation for an antineoplastic compound, we suggest that simpler approaches such as surfactant systems, cosolvent systems, hydrotropic agents and complex formation are more likely to be of general applicability since they are not as structurally specific.

(1) Surfactant Systems

Solubilization in a surfactant system is achieved by forming micelles around the solute when surfactant concentration is above the critical micelle concentration. Surfactant not only can

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increase the aqueous solubility of a drug, it can also increase its stability and dissolution rate. The transfer of a solute into micelles changes the molecular environment of the solute molecule. Reactivity among the solute molecules may decrease due to the change in proximity and orientation. The solute is protected from attacking species such as hydrogen ions or hydroxide ions and thus stabilization of the solute results (Cipiciani et al., 1985; Florence, 1981). In addition to the increase in solubility and stability, a surfactant lowers the surface tension of the solute and therefore increases the dissolution rate (Gander et al., 1985).

The limiting factors in the use of surfactant solubilizers as effective formulation aids are (1) the finite capacity of the micelles for the drug, (2) the possible short- or long-term adverse effects of the surfactants on the body, and (3) the concomitant solubilization of other ingredients such as preservatives and buffers in the formulation, with consequent alterations in stability and effectiveness (Florence, 1981; Lin and Kawashima, 1985; Schott, 1980).

Although micellar solubilization can increase solubility of griseofluvin from 2.8×10^{-5} M in water to 97×10^{-5} M in 5.5% cetomacrogol, it requires 15% cetomacrogol to achieve 257×10^{-5} M (Florence, 1981). This illustrates the limitation of the use of surfactants as solubilizers. Thus, there are few marketed products which could be considered as isotropic solutions of drug

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and surfactant. The surfactant, while limited as a sole agent, is more often used in conjunction with a cosolvent system or in an emulsion system (Florence, 1981; Schott, 1980). Recently, Azmin et al. (1985) proposed that the admixture of dicetyl phosphate, cholesterol and an non-ionic surfactant could form lamillar vesicles (niosomes) which act as alternative drug carries to liposomes.

(2) Cosolvent Systems

Cosolvents such as ethanol, propylene glycol, polyethylene glycol and glycerol are routinely used in either oral or parenteral dosage forms to aid in the solubilization of drugs in aqueous vehicles (Vromans and Moolenaar, 1985; Yalkowsky and Roseman, 1981; Yalkowsky and Rubino, 1985). The degree to which the solubility of a drug can be increased for a particular cosolvent is dependent upon the non-polarity of the drug and the non-polarity of the cosolvent. Thus the polarity scale of solvents provides a suggestion as to which solvent might be suitable for a particular solute system.

For example, 1.5 to 3.2 fold increase in solubility of a sulfonamide has been found in aqueous solution of urea, 10 to 100 fold in ethanol and polyethylene glycols, and 100 to 1000 fold in propylene glycol and PEG 400 (Robwald, 1975). While there may not be strict chemical similarity between sulfonamides and antineoplastics, many potential anticancer compounds are amines or nitrogen heterocycles. For example, NSC 261213 is a sulfonyl compound and NSC 24993 is a methane sulfonamide (NCI, 1984).

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Thus, it might be expected that some of NCI compounds could exhibit the same magnitude, of several orders, of solubility enhancement.

Practical considerations such as the availability of the cosolvent in the parenteral mixture and the possible precipitation upon dilution should be considered when a cosolvent system is used in a preformulation study.

(3) Complex Formation

The use of complexation to overcome pharmaceutical solubility problems has at least two advantages, i.e., the reversibility of the interactions and the physical stability of the system. Dissociation of the complexes to the individual reactants occurs rapidly and spontaneously upon dilution. Consequently, the biological effects of complexes can be predicted on the basis of knowledge of the pharmacological properties of each reactant (Mehdizadeh and Grant, 1984; Repta, 1981a). This characteristic of complexes is in contrast to chemically derived prodrugs which normally require some sort of 'triggering' to aid the release of the parent drug. Furthermore, a prodrug may exhibit pharmacological effects which are unrelated to the drug itself.

Since complex formation involves attainment of equilibrium, the behavior of the formed complexes is reproducible and predictable. This feature is in contrast to the solid-state modification method which is often thermodynamically unstable and therefore may undergo time-dependent changes which can lead to changes in solubility behavior (Shefter,1981; Rowe and Anderson,1984).

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Kreilgard et al. (1975) have demonstrated the solubility enhancement of hexamethylene, an antineoplastic, by complexation with gentisic acid. The increase in solubility is about five fold at pH 3.5 to about 90 fold at pH 5.0 Another cytotoxic agent, acronine, showed a solubility increase of about 25 fold by complexation with 2-methylgentisic acid and to 160 fold for ethylgentisic acid-acronine complexes (Repta and Hincal, 1980). Truelove et al. (1984) showed significant increase in solubility of some investigational antineoplastic agents as a result of complexation with nicotinamide. Collett et al. (1976) described the effect of urea on the solubility of salicylic acid, while McGinity (1984) evaluated the complexation of urea on the solubility of tolbutamide. Pitha and Szente (1984) reported increased solubility of some organic materials (up to 400 fold) with digitonin, which is capable of forming inclusion compounds.

However the complexation system is not without disadvantages. The rapid and total reversibility previously presented as an advantage may cause the precipitation of the active ingredient upon dilution. This problem may be serious when an intravenous infusion route is used. The choice of ligand may be primarily dictated by the strict requirements of the parenteral dosage forms. These limiting factors should be carefully evaluated when designing the dosage form (Repta, 1981a).

Complexation with cyclodextrins is presently attracting renewed interest from pharmaceutical scientists (Hegde and Rhodes, 1985). A number of groups are presently investigating the

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possible use of cyclodextrin complexes for antineoplastic agents. The possibility of using monoclonal antibody drug complexes as a means of delivering anticancer drugs has also got exciting possibilities (Edmond et al. 1986; Paynton et al., 1984; Zalcberg, 1985).

(4) The Hydrotropic Agents

The use of hydrotropic agents as solubilizing agents has not been fully explored in the literature. They would be of interest for anticancer drugs because there is a wide variety of agents which exhibit this effect; many are biocompatible, and a number of them are accepted for human use. Compounds which have shown this effect include fatty acids, amino acids, amides, salicylates and related compounds. These compounds, although some of them may form complexes with a drug, are referred to as hydrotropic agents because the solubilization mechanism is not complexation. Klevens (1950) prepared an extensive list of hydrotropic materials, and Lindstrom (1979, 1980) reported on the degree to which chemical structure affects the solubilizing ability of selected hydrotrope analogs. Hamza and Paruta (1985) showed an increase in solubility of paracetemol in the presence of several of these compounds (sodium gentisate, sodium glycinate, sodium salicylate, and nicotinamide). It would be expected that amino acids as a class would provide a variety of hydrotropes with a range of solubilizing effectiveness.

In addition to the above mentioned agents, there exist a few materials having exceptional solubilizing ability.

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Dimethylsulfoxide (DMSO) is a unique solvent in that it associates with a diverse number of neutral molecules and ionic substances. Particularly interesting is its ability to carry a drug into cells without precipitation of materials (Schultz, 1976). DMSO has been approved for human use on a limited basis as an analgesic agent, and is used as a solvent in drug formulations for osmotic pumps (Alza, 1976). The solubility of many of the investigational antineoplastic agents in DMSO are reported (NCI, 1984). Recently, Pitha et al. (1983) discussed the relative biological inertness and solubilizing potential of the l-methionine derivative of DMSO. It is our opinion that a more extensive evaluation of these types of agents should be included in the preliminary evaluation of the drugs in this area since their use might well be applicable to a wide variety of anticancer drugs.

The utilization of the above methods to alter solubility properties of a drug definitely has a place in pharmaceutical formulation, but it is not a universal panacea. Each approach has its own advantages and limitations and usually offers limited solubility enhancement when employed alone. Thus the formulator must understand each approach and evaluate its potential use, relative to the needs and constraints of the drug and the formulation desired, either in single usage or in combination. Careful screening of these methods in a preformulation program is likely to provide valuable insight into potential delivery systems.

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(B) Colloidal Systems

Colloidal systems such as liposomes, microcapsules, microspheres, nanoparticles, polyaphrons and macromolecule complexes may enhance the solubility and stability of a drug due to the changes in molecular environment of the drug molecules. Reacting species such as hydroxyl ions, hydrogen ions or oxygen molecules may be shielded away from the drug molecules by the encapsulation or inclusion mechanism. In addition, these drug delivery systems may alter the pharmacokinetic and pharmacological properties of a drug. Therefore a sustained release form with lower dosage, higher therapeutic index and better targeting may be achieved. These merits are especially important for antineoplastic agents.

In general terms, the delivery of drugs using colloids will be governed by the same physicochemical principles and physiological processes common to other approaches. Many colloidal systems are thermodynamically unstable, and the formulation process should not endanger the stability of the dosage forms. The additives that are needed for an elegant pharmaceutical product are under the strict requirements for parenteral administrations. The method of sterilization should be carefully chosen so that the colloidal systems will still be physically intact. The pyrogenicity should also be carefully monitored. Thus their potential advantages may be counter-balanced by an increased complexity of the dosage form, attendant problems of optimal formulation and acceptable stability.

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The biological fate of particles in the colloidal system following the intravenous administration is basically the same as that of foreign particles in the body (Illum and Davis, 1982; Kato, 1983; Poste, 1984; Tomlinson, 1982). The initial process is the uptake of blood components onto the surface of colloidal particles. This process, opsonization, occurs right after the particles reach the blood stream. The nature of the adsorbed blood component will depend upon the surface characteristics of particles. Various protein and glycoproteins have been implicated in this process. Thus, manipulation of the surface charge (Wilkins et al., 1966; Wilkins, 1967) or the hydrophobicity (Van Oss et al., 1975) of the particles can modify the blood clearance rate and organ deposition pattern. Following the route of blood circulation, particles that are greater than 7 μm in diameter will be trapped by mechanical filtration in the capillary beds in the lung. There has been an incidence of death by pulmonary embolism which occurred following the injection of aggregated liposomes (Yatvin and Lelkes, 1981)

Particles that are less than 7 μm in diameter will normally pass through the lungs and deposit in the reticuloendothelial system (RES). The RES, (mainly liver and spleen) is well supplied with fixed macrophages to engulf foreign particles with or without opsonization. Such uptake into liver and spleen can be extremely efficient and provides a means of selective delivery of drugs to the liver. Of a sample labeled albumin microspheres, 90% of the radioactivity was located in the lung and 0.1% in the liver 10

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minutes after an intravenous injection of microspheres of 12 - 44 μm, while 86% of radioactivity was found in the liver and 0.4% in the lung 10 minutes after an injection of microspheres of about 1 μm Marty and Oppenheim, 1977). Particles less than 100 nm will then have the possibility of leaving the systemic circulation through fenestrations in the cells lining the blood vessel. These fenestrations are of different sizes depending on the capillary beds considered. They offer another filtration blockade before these particles can reach the target cells (Illum and Davis, 1982; Poste, 1984).

The successful exploitation of colloidal systems for drug delivery requires a full understanding of the basic physical and biological processes. Thus an optimal formulation for the drug delivery system can be designed to exert the pharmacological activities of the drug.

(1) Liposomes

Liposomes consist of one or more lipid bilayers enclosing a central core. Since they were first described by Bangham et al. (1965), extensive research into their properties has been reported. Liposomes have received considerable attention with respect to their potential use as drug delivery systems for antineoplastic agents (Brassinne, 1983; Freytag, 1985; Gregoriadis, 1984; Weinstein, 1984; Yatvin and Lelkes, 1982). Although no longer considered to be the 'magic bullet' they may once have been, liposomes still show substantial potential for providing targeted drug delivery (Fildes, 1981; Gregoriadis, 1984;

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Mayhew and Papahadjopoulos, 1983; Ryman et al., 1982; Ryman and Tyrrell, 1980;).

Liposomes are made from natural constituents such as phospholipids and cholesterol. Thus they are biodegradable, quite non-toxic and of low immunogenic capacity, although toxicities were reported when charged phospholipids were used (Weinstein, 1984; Yatvin and Lelkes, 1982). No physiological damages, caused by antigenicity or toxicity, were detected through a long term intravenous injection treatment (Gregoriadis, 1978) and through a large volume infusion treatment (Coune et al., 1983).

There are three types of liposomes which are classified according to their size differences; multilamellar vesicles (MLV), large unilamellar vesicles (LUV) and small unilamellar vesicles (SUV). MLV are liposomes with sizes in the range of 400 to 3500 nm. Due to the characteristic of being multiple layers, MLV liposomes have a low capture volume (4.1 μl of aqueous phase/mg of phospholipids) despite being the largest liposomes. They have the potential to be sustained release dosage form. LUV liposomes have the largest capture volume (12.7 μl/mg) and thus usually act as the carrier system for macromolecules. The sizes of LUV liposomes range from 200 to 1000 nm. SUV liposomes have the lowest capture volume (0.5 μl/mg) and their sizes range from 20 to 50 nm. They have great potential as a carrier system for antineoplastics due to their small sizes. Particulates that are smaller than 150 nm have been shown to have a reduced uptake in liver and spleen. Consequently, SUV show an increased carcass disposition and an

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increased half-life in blood (Hauser, 1982; Poste, 1984; Szoka and Papahadjopoulos, 1978).

The majority of liposomes are prepared by the following methods (Connor et al., 1985; Deamer and Uster, 1985; Hauser, 1982; Szoka and Papahadjopoulos, 1978, 1980):

(i) Mechanical disruption

Liposomes can be made from hydrating a thin film of lipid coating on a flask. Thus, MLV liposomes can be made by simple agitation. SUV liposomes can be prepared by sonication. The extrusion of an aqueous dispersion of lipids through a polycarbonate membrane can be applied to make all three types of liposomes. Liposomes are obtained by a high pressure through a French pressure cell (Mayhew et al., 1984; Mayhew et al., 1985) or a Microfluidizer (Hamilton and Guo, 1984; Barenholzt et al., 1984).

(ii) Emulsion Reversal

After forming a W/O emulsion of phospholipids and buffer in an excess organic phase, the subsequent removal of the organic phase under reduced pressure will form LUV. This method also called reverse phase evaporation can be used to prepare LUV liposomes with a high encapsulation efficiency. The LUV liposomes made in this manner are therefore called reverse-phase-evaporation vesicles (REV).

(iii) Solvent Injection

The solvents often used are ethanol and ether. Lipids dissolved in a solvent are rapidly injected into a buffer solution where SUV are spontaneously formed. In addition to the low encapsulation

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efficiency and size heterogeneity, the process has to be performed at a high temperature, i.e., the boiling point of the solvent used.

(iv) Detergent Removal

A detergent (e.g., desoxycholate, octylglucoside) is used to disperse the phospholipids and thus temperature-labile compounds can be encapsulated into SUV liposomes. However, extensive dialysis is needed for the removal of the detergent and the encapsulation efficiency is low.

Table 2 lists the parameters that should be carefully monitored during manufacture of liposomes to ensure quality and reproducibility (Connor et al., 1985; Deamer and Uster, 1985; Hauser, 1982; Szoka and Papahadjopoulos, 1978, 1980).

Among the methods of preparation, the Microfluidizer (Mayhew et al., 1984; Mayhew et al., 1985) and French pressure cell (Hamilton and Guo, 1984; Barenholzt et al., 1984) have great potential in the manufactured liposomes on an industrial scale. Both methods are extensions from the mechanical extrusion method by the addition of a device to recycle the processed sample. The main differences is that the French pressure cell uses 20,000 p.s.i. to extrude the phospholipid mixture, the Microfluidizer uses 10,000 p.s.i.. They are both reproducible and highly efficient. The encapsulation efficiency of the Microfluidization was 75% compared with 8% of sonication and 24.9% of reversed phase evaporation (Barenholzt et al., 1984; Hamilton and Guo, 1984; Mayhew et al., 1984, 1985). The stability of the liposomes

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Table 2. Critical formulation factors for liposomes

1. purity of phospholipids
2. encapsulation efficiency
3. capture volume
4. transition temperature of liposomes
5. ionic strength and pH of buffer during preparation
6. particle size distribution
7. lipid peroxidation
8. lipid hydrolysis (i.e., monitor the hydrolysed products such as fatty acids and lysophosphatides)
9. stability of liposomes in the presence of human plasma
10. stability of liposomes upon storage
11. sterility
12. pyrogenicity

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produced by the French pressure cell and Microfluidizer is better than in those produced by the traditional methods. These methods, however, are by no means perfect. Sample volume only up to 40 ml was tested which indicates further scale-up is needed toward commercial mass production (Hamilton and Guo, 1984). In addition, the loss of biological activity of proteins was detected after prolonged exposure to high pressure (Hamilton and Guo, 1984; Lelkes, 1984).

Numerous antitumor drugs have been incorporated into liposomes. Among them are actinomycin D (Gregoriadis, 1973),

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alkylating agents (Rutman et al., 1976), methotrexate (Colley and Ryman, 1975), L-Asparaginase (Neerunjun and Gregoriadis, 1976), bleomycin (Gregoriadis and Neerunjun, 1975), cytoarabinoside (Mayhew et al., 1976), doxorubicin (Rahman et al., 1986), vinblastine (Juliano and Stamp, 1978) and etc.. The major advantages of using liposomes as drug delivery systems for antineoplastics are biodegradability, low toxicity, low immunogeneity, ease of preparation in a variety of forms, ability to trap drugs without the necessity of covalent bonding, high potential for drug stability enhancement and the potential for high drug load capacity.

In general, drugs are trapped without covalent bonding either in the internal aqueous space of liposomes (water-soluble drugs) or in the lipid bilayers (lipid-soluble drugs). The incorporation of highly soluble compounds such as methotrexate aspartate (Heath et al., 1983) and Ara-CTP (Mayhew et al., 1978) into liposomes can bypass the membrane barrier by endocytosis and thus the drug can enter the cytoplasm to exert cytotoxicity. Brassinne et al., (1983) administered a water-insoluble quinazolone derivative (NSC 251635) as a liposome preparation and enhanced therapeutic efficacy without marked toxicity. In addition, higher stability and encapsulation efficiency of liposomes made from lipophilic drugs have been demonstrated by Juliano et al., (1981) and Inaba et al. (1981).

The incorporation of biological labile compounds such as cytosine arabinoside (Mayhew et al., 1976), macrophage activating

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factor (Filder et al., 1980) and maramyl peptide (Sone et al., 1981) into liposomes have significantly lengthened the plasma half-lives and thus enhanced the bioavailability toward cancer cells. Although there are presently few, if any, published reports on attempts to encapsulate physicochemical labile compounds, this approach may prove to be very useful. The improved stability, solubility and partition coefficient indicate that liposome carrier systems may solve the formulation problems of many anticancer investigational drugs. In addition, liposomes do not accumulate in normal heart and kidneys to the same extent as do many free drugs. Hence, it has been proposed that liposomes may be useful with cardiotoxic and nephrotoxic agents, for instance, to reduce the cardiotoxicity of doxorubicin (Jensen, 1986; Juliano and Stamp, 1978; Maslow et al., 1980; Rahman et al., 1986).

However, liposomes are not without any disadvantages as drug carriers. The major limitations of liposomes for wide clinical application are stability, scale-up, and targeting.

Previous limitations of physicochemical stability and large scale production problems have been greatly reduced in recent years. Enhanced in vitro stability is demonstrated by selection of saturated phospholipids, by incorporating _-tocopherol (Hunt and Tsang, 1981), cholesterol, inert atmosphere and protection from light and oxygen, and elevated temperature to decrease lipid peroxidation (Szoka, 1985; Gregoriadis, 1984). Other approaches such as storing the liposomal preparation at pH 6.5 in a medium of

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low ionic strength at 4°C (Frokjoer et al., 1982), frozen preparation (Machy and Leserman, 1984), PEG block preparation (Olliff et al., 1985), or lyophilized preparation, i.e., proliposomes (Gordon et al., 1982; Payne et al., 1985; Schneider and Lamy, 1979; Shulkin et al., 1984), may allow the development of possible dosage forms for commercial use. The disruption of the intact liposomes, i.e., in vivo stability, may be due to lipid or cholesterol exchange between liposomes and cell membranes or lipoproteins in the biological fluids. It may also be caused by the protein adsorption onto the lipid bilayers of liposomes. The liposomes can be strengthened against these influences by inclusion of cholesterol (preferably more than 30 mol %), by use of shingomyelin, by polymerization of lipid bilayers, and by use of saturated phospholipids below their phase transition temperature (Gregoriadis, 1984; Regen et al., 1981; Weinstein et al., 1979; Yatvin et al., 1978). These approaches in structure manipulation have shown promising results.

Among the preparation methods, the French pressure cell and the Microfluidizer have the potential of preparing liposomes on an industrial scale. The advantages of using either one are time-saving, size homogeneity, high reproducibility, high encapsulation efficiency, and ease of scale-up while maintaining stability and versatility of liposomes (Hamilton and Guo, 1984; Mayhew, et al., 1985).

Drug-loaded liposomes are taken up by the reticuloendothelial system, mainly liver and spleen, just as any other type of

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particulate carriers are. Thus targeting to tumor cells is hard to achieve by administering drug-loaded liposomes. Techniques have been developed to target liposomes to particular cell types or anatomical locations. There are four strategies developed to improve targeting (Gregoriadis, 1984; Poste, 1984; Weinstein and Leserman, 1984).

(1) Passive (natural) targeting

The uptake of liposomes by physiological processes such as filtration by lung capillaries or phagocytosis by cells of the RES can be decreased to a limited degree by the manipulation of surface characteristics, the charge and the size of liposomes, or by predosing with carbon particles, dextran sulfate (Bradfied et al., 1974;), methylpalmitate (Tanaka et al., 1975), polystyrene microspheres (Illum et al., 1986) and empty liposomes (Gregoriadis and Neerunjun, 1974) to block the uptake. These approaches, however, have not produced significant improvement in vivo. Another approach is to reduce the affinity of liposomes to cells of the RES by a coating of sialic acid (Jancik et al., 1978; Utsumi et al., 1983). The effectiveness of sialic acid coating needs further in vivo testing.

(2) Compartmental targeting

The localization of liposomes in specific anatomical compartments can be achieved by intra-arterial or by local administration in joint, lung (aerosol) and peritoneal cavity. Compartmental targeting has shown promise for delivering antineoplastic agents to peritoneal and lymphatic sites (Szoka, 1985; Hirano and Hunt, 1985; Poste et al., 1984).

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(3) Active (ligand) targeting

Better targeting can be obtained by attaching a ligand to the liposome surface specific for a determinant on the target cell. Antigen, immunoglobulins, glycoproteins, glycolipids and lectins have all been used in this way. Immuno-potentiating agents have been delivered selectivity to phagocytes in the lung and have significantly retarded the development of pulmonary metastasis (Yatvin and Lelkes, 1982). However, specific binding of liposomes to cells does not guarantee that the contents of the liposomes will reach the cytoplasm, i.e., endocytosis. The resulting immuno-conjugates are usually antigenic, and the subsequent neutralization of the conjugates by the antibodies generated may decrease the bioavailability to tumor cells. In addition, the presence of endothelial or other histological barriers between liposomes and the binding site provide another filtration blockade to reach the target sites. Actually, the majority of the ligand-liposome complexes are still taken up by the liver and spleen (Connor et al., 1985; Gregoriadis, 1984; Poste, 1984; Yatvin and Lelkes, 1982).

(4) Physical targeting

There are reports of the use of an external influence such as temperature or a magnetic field to direct particles to desired sites (Kato, 1983) or to achieve site specific release of drug-loaded liposomes. Due to the small size of liposomes, liposomes containing ferromagnetic particles requires a much stronger external magnetic field for targeting to solid tumors.

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Thus, targeting of ferromagnetically loaded liposomes may be feasible only if an external magnetic field is combined with arterial catheterization technique to achieve initial delivery to the organ of interest (Poste,1984; Poste et al.,1984; Szoka, 1985). Selective release can also be obtained through the injection of the temperature-sensitive or pH-sensitive liposomes. Liposomes engineered to have a reasonably well defined transition temperature (+ 2°C) demonstrated an increased targeting when local hyperthermia (42-44°C) was coupled with the treatment. A similar approach is to design pH-sensitive liposomes which are addressed to the treatment of the metastatic lesion where lower ambient pH have been demonstrated. Both the temperature and pH approaches are based on the fact the tumor cells have a local hyperthermia and lower ambient pH than normal tissue. The practical limitations on the application of temperature-sensitive liposomes is that local hyperthermia can only be applied for a limited time period. However, pH-sensitive liposomes, can remain effective for a much longer time (Connor et al., 1985; Gregoriadis, 1984; Weinstein, 1984; Yatvin and Lelkes, 1982). The temperature-sensitive and magnetically loaded liposomes are limited to solid tumors, not to metastases, because the necessity of the localization of targeted organ (Poste,1984; Szoka, 1985). More in vivo testing is needed before these approaches can be clinically applied.

At present, the clinical application of liposomes as carriers for antineoplastic agents is limited somewhat by the large uptake

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of the RES system. However, one must bear in mind that none of the particulate carrier systems can escape this physiological barrier. Liposomes, being so versatile in structure, may improve the efficacy of antineoplastic agents. For the anticancer investigational drugs that are unstable and highly insoluble in water, liposomes may be the carrier to solve the formulation problems.

The above review suggests possible ways to overcome the problems in formulation and targeting. The manipulation of the phospholipid composition (preferably those can be made into temperature- and pH-sensitive liposomes), size, the dosage form, and preparation method offer possible means to provide a pharmaceutical acceptable dosage form and to improve the therapeutic efficacy of anticancer compounds.

(2) Microencapsulation Systems

Microencapsulation involves the application of a thin film of material around micronized solid, liquid or gas to produce discrete units ranging in sizes from less than 1 m to several millimeters. The products of microencapsulation, according to size differences, are nanoparticles, microspheres and microcapsules. Nanoparticles are usually defined as particles with a diameter between 200 and 500 nanometers. The microspheres range in diameter from well below 1 μm to well over 100 μm. Microcapsules are usually referred to when particles are larger than 100 μm. The terms 'microcapsules and microspheres' are sometimes somewhat ambiguous (Marty & Oppenheim, 1977; Thies and

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Bissery, 1984). Significant tissue necrosis due to embolization was observed after the administration of large microspheres (224.6 ± 54.9 μm) (Kato, 1983). Hence, the microencapsulation systems proposed for the investigational drugs are limited to those of less than 125 m in diameter (Poste, 1984; Tice and Cowsar, 1984).

Microencapsulation processes have been used by the pharmaceutical industry since the 1960's to alter the physical, chemical and physiological effect of drugs and biomaterials. Microparticles can be low in toxicity and immunogeneity therefore they have been developed as drug carrier system. Numerous techniques for preparing these microparticles have been used when parenteral preparations are involved (Marty and Oppenheim, 1977; Thies and Bissery, 1984; Zour, 1984). In the following section a discussion of these methods according to the biodegradable polymer used in forming the microparticles is given. Nonbiodegradable carriers have little merit in the therapy of cancer or other chronic diseases in which accumulation of the carrier with repeated dosing over extended period will pose a potential toxicity hazard (Wallace, 1984).

(i) Lactide/Glycolide Microspheres

Poly (dl-lactide) and lactide/glycolide copolymers rich in lactide have been fabricated into biodegradable microspheres by a solvent evaporation process (Beck et al., 1979; Juni et al., 1985) and a coacervation process (Thies and Bissery,1984). In the solvent evaporation method, a methylene chloride (other organic solvent or solvent mixture can also be used) solution of the drug

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and poly(dl-lactide) are emulsified in excess 5% aqueous poly(vinyl alcohol). Once the desired emulsion droplet size is formed, the agitation rate is reduced and evaporation of methylene chloride from the system begins. Evaporation can be achieved at atmospheric or reduced pressure. The temperature of evaporation may also be varied. Once a significant portion of the methylene chloride has been evaporated, the partially solidified microspheres are allowed to settle, and the aqueous poly(vinyl alcohol) solution is replaced with water. The evaporation of methylene chloride continues until it is complete. The microparticles are then isolated and dried (Beck et al., 1979; Juni et al., 1985).

In the low temperature phase-separation, i.e., coacervation, the micronized drug particle are dispersed in a solution of poly(dl-lactide). The addition of an incompatible polymer, in this case, polybutadiene, will cause phase separation of the poly(dl-lactide) which spontaneously engulfs the drug particles. The poly(dl-lactide)-rich phase is desolvated and solidified by adding excess nonsolvent to the system. The microspheres are then isolated and dried (Thies and Bissery, 1984).

Good yield of biodegradable microspheres of less than 100 _m are obtained from both methods. The dry, free-flowing microspheres from the solvent evaporation method should be easily dispersed in aqueous injection media due to the residual poly(vinyl alcohol). The microspheres prepared from the phase separation method, however, can form a uniform suspension in

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aqueous injection medium only if a water soluble surfactant is added (Thies and Bissery, 1984).

(ii) Poly(alkyl α-cyanoacrylate) Microparticles

Because alkyl α-cyanoacrylate monomer polymerizes spontaneously at oil/water interfaces, it can be used to prepare microspheres (Florence et al., 1979; Wood et al., 1981; Thies and Bissery, 1984) or nanoparticles (Kante et al., 1980; Marty et al., 1978; Speiser, 1976). The procedure involves forming a W/O emulsion with the drug to be encapsulated dissolved in the aqueous phase. Alkyl α-cyanoacrylate monomer is added to the oil phase. Spontaneous polymerization occurs at the water/oil interface thereby depositing a poly(alkyl α-cyanoacrylate) film or wall at the interface. The affect of various conditions on the interfacial polymerization process has been examined (Wood et al., 1981). Mildly basic conditions in the aqueous phase increase the rate of polymerization. The microspheres obtained are transferred to aqueous media with the aid of a water-soluble emulsifier, polysorbate 20 (Thies and Bissery, 1984).

Poly(butyl α-cyanoacrylate) nanoparticles have been prepared under acidic conditions by adding butyl α-cyanoacrylate monomer to an aqueous solution containing a surfactant and the drug. Because of their small size, dispersion of nanoparticles in water appeared non-turbid or slightly opalescent and particle sedimentation was imperceptible (Marty et al.,1978; Speiser,1976).

(iii) Polyacrylamide Microparticles

Polyacrylamide microparticles are prepared by polymerizing droplets of aqueous monomer solution emulsified in an organic

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solvent. The monomer solution is a mixture of acrylamide and N-N'-methylenebisacrylamide dissolved in sodium phosphate buffer. A polymerization accelerator is added to the aqueous phase after emulsification.

Microspheres of sizes below 10 μm in diameter and nanoparticles can be obtained by this procedure (Marty and Oppenheim, 1977; Thies and Bissery, 1984).

(iv) Microparticles Formed by Natural Polymers

A number of workers have prepared microspheres and nanoparticles from natural polymers such as gelatin, serum albumin and starch. The first step of the basic manufacturing process is to create a W/O emulsion. The water phase is a solution of the polymer and drug, and this phase is usually smaller in volume than that of the oil phase. If an emulsifier is needed, it normally is added to the oil phase (Desoize et al., 1986; Oppenheim et al., 1978; Thies and Bissery, 1984).

Once the desired W/O emulsion is formed, desolubilization of the polymer is accomplished by some type of cross-linking process. In the case of gelation, the cross-linking process is by rapid chilling of the emulsion thereby forming a gel network structure (Hashida et al., 1979, 1980). The gel structure is labile and readily destroyed by moderate temperature increases. A stable chemical cross-linkage can be formed by heat denaturation of a polymer such as serum albumin. Drug degradation caused by high temperature, usually over 100° C, must be carefully controlled during the heat denaturation process. A third approach is to add

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a chemical cross-linking agent such as glutaraldehyde (Thies and Bissery,1984).

Microparticles formed by natural polymers if not cross-linked by chemical, are monolithic type. There is no drug-free shell to separate the drug particles from the environment. The model for drug release for monolithic microparticles is quite different from that of the reservoir-type (Thies and Bissery, 1984; Tice and Cowsar, 1984).

Other methods such as covalent attachment of drug to Schiffs base in forming polyglutaraldehyde microspheres (Tokes et al., 1984; Desoize et al., 1986), coacervation in forming gelatin-walled microspheres (Thies and Bissery, 1984), ionic attachment of drug to DEAE in forming the nonbiodegradable DEAE-cellulose microspheres (Illum and Davis, 1982), and polymerization by γ-radiation in forming the nonbiodegradable polystyrene microspheres (Rembaum, 1984) have also been used.

The microspheres made from any method usually can be sedimented by themselves or by centrifugation. They are generally dried and stored as dried powder or as a suspension after being resuspended. The nanoparticles obtained are usually isolated by freeze-drying and stored in the lyophilized form (Desoize et al., 1986; Thies and Bissery, 1984).

Below are listed pharmaceutical and biopharmaceutical parameters which should be considered in the development of a microencapsulation system (Tomlinson, 1983). Some of the parameters interact with each other (as stated in the parentheses)

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and it is advisable to have a full understanding of these parameters before formulating a microencapsulation system.

1. core material (preferably biodegradable)
2. route of preparation with respect to (3-7)
3. size (related to 1-3)
4. drug incorporation
5. drug load capacity
6. drug release in vitro and in vivo
7. drug stability during (2) and (9)
8. stability of the microencapsulation system in vitro and in vivo
9. effect of storage on (6-8)
10. surface properties as they related to (4), (6) and (11)
11. presentation (e.g., free-flowing, freeze-dried powder or emulsified suspension)
12. antigenicity
13. biofate and toxicity of the microencapsulation systems
14. biokinetics of drug and the microencapsulation systems

Depending on the microencapsulation processes used, one of the three types of internal structure will result and it will affect drug release characteristics. Reservoir-type microparticles have a central core of drug coated with a polymeric membrane. In monolithic microparticles, the drug is homogeneously dispersed throughout a polymeric matrix. The third type is the

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combination of both (Thies and Bissery, 1984; Tice and Cowsar, 1984). The reservoir-type microparticles act as membrane reservoir devices and provide a constant rate of drug release. Nixon (1984) reviewed the diffusion mechanisms of different microparticles and described them with mathematical models. In monolithic microparticles, no drug-free shell of finite thickness separates the drug particles from the environment in which the microspheres are placed. Hence, microspheres will not give constant release over a prolonged period. Drug/polymer interactions, in this case, can significantly affect drug release rate. The monolithic microparticles are sometimes exclusively called "microspheres" (Marty & Oppenheim, 1977; Tice & Cowsar, 1984; Thies and Bissery, 1984). Tomlinson et al., (1984) described the drug release of the albumin microspheres by a biexponetial model. The first (fast) phase is accompanied by a burst effect of the albumin microspheres, which can be reduced by ultrasonication. Seventy percent of drug can be released during this first phase period. The release mechanism of the third combination type have not been determined (Desoize et al., 1986; Thies and Bissery, 1984). Hoffman et al. (1985) investigated other factors such as the size, the content, the wall properties, shapes of the microparticles that may affect the release profiles.

Drugs can be incorporated into microparticles by entrapment inside the polymetric excipient, (either reservoir or monolithic-type), or by sorption on albumin, gelatin, polyacrylamide and polycyanoacrylate microparticles (El-Egakey and Speiser, 1982; Couvreur et al., 1979). A recent survey by

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Tomlinson (1983) has shown that for all microsphere systems, over 90 drugs have been incorporated. Yapel (1979) has studied the incorporation of more than 40 drugs into human serum albumin microspheres. Oppenheim (1981) has briefly reviewed the possible use of nanoparticles as delivery system for viruses, vaccines, diagnostic agents, cytotoxics, flukicides and anti-arthritics. In general, hydrophilic drugs will be less well incorporated (Thies and Bissery,1984; Tomlinson,1983). However, methods for improved encapsulation efficiency have been developed for acrylic nanoparticles (Birrenbach and Speiser, 1976; Sjoholm and Edman, 1979), for protein nanoparticles (Scheffel et al., 1972; Kramer, 1974; Widder et al., 1979; Yoshioka et al., 1981), for gelatin-nylon microcapsules (McGinity et al., 1975), and for ethylcellulose microcapsules (Samejima et al., 1982).

The rationales for using microparticles in delivering antineoplastic agents are basically the same as those of liposomes. The major advantages of using microencapsulation systems are biodegradability, low toxicity, low immunogeneity, versatility in formulation, high drug load capacity and high potential for drug stability enhancement (Thies and Bissery, 1984; Tice and Cowsar, 1984). El-Samahagy and Rhohdewald (1982) showed the controlled release characteristic of triamcinolone diacetate-loaded nanoparticles. Boag (1979) has demonstrated that additional drug could be co-solubilized with the albumin microspheres.

Microparticles can protect the biologically labile compounds from their environment such as L-asparaginase (Edman and Sjoholm,

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1979, 1982), insulin (Couvreur et al., 1980). In addition to reduced cardiac uptake, albumin microspheres containing doxorubicin significantly prolonged the survival times of rats bearing liver metastasis (Morimoto et al., 1981). Poste (1976) has suggested the usefulness of drug-loaded nanoparticles to treat tumor cells which have become resistant to the uptake of free drug. Ryser and Shen (1980) have demonstrated that the cellular uptake of methotrexate-poly(L-lysine) conjugates was about 200 times that of free drug when tested on a methotrexate-resistant cell lines.

The major advantages of microencapsulation systems over the liposomes are the larger drug load capacity, the stability of dosage form, the relative ease of sterilization, and the controlled release over a longer period of time (Thies and Bissery, 1984; Tomlinson, 1983). After one year of storage, freeze-dried nanoparticles have been successfully dispersed in aqueous systems with the original in vitro and in vivo properties (Oppenheim et al., 1982). They are also more stable in the biological fluid in vivo and the leakage problems are not as dramatic as those of liposomes. Some polymers can be polymerized and sterilized by γ-irradiation (Kreuter et al., 1983). Gelatin nanoparticles were autoclaved at 121^{o}C for fifteen minutes with no gross changes detected by the scanning electron microscopy (Oppenheim et al., 1982).

Extended controlled release of nanoparticles can be tailored to cover a period of two months to 44 weeks (Kreuter, 1983). This is done by manipulating the choice of different materials and

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methods during manufacture to achieve different degradation or elimination rates (Kreuter, 1983). This is a great advantage over other colloidal carriers. Microparticles may have a very short half-life in the body such as the gelatin nanoparticles made by Oppenheim et al., (1978); they may have a medium fast degradation and elimination rate if made into albumin or the short-chained polycyanoacrylate microparticles, or a longer degradation rate if made into long-chained polycyanoacrylate microparticles; or they may have a very long half-life in the body if made into the polymethacrylate microparticles (Kreuter, 1983).

However, microparticles are not without disadvantages. The use of albumin microspheres has carried the risk of anaphylaxis (Littenberg, 1975). Residual monomers of methylmethacrylate and acrylamide have been blamed for toxicity of prosthetic materials (Dillingham et al., 1975). The biodegradability problems of polyacrylamide and polymethacrylate microparticles have stimulated many scientists to develop delivery systems based on other monomers (Oppenheim, 1982). The LD_{50} was 230 mg/kg for polybutylcyanoacrylate nanoparticles and 196 mg/kg for polyisobutylcyanoacrylate nanoparticles. These values are significantly higher than that of liposomes which is 5 g/kg (Kreuter, 1983; Szoka, 1985). The LD_{50} of microparticles is also closely related to their particle size (Szoka, 1985).

Because of the very considerable uptake by RES, the same strategies of passive, compartmental, active and physical targeting for liposomes have been applied to microencapsulation systems in order to increase the selectivity of the tumor cells

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toward the antineoplastic agents. Local injections and intra-arterial administrations have been used to achieve compartmental targeting (Kato, 1983; Tomlinson et al., 1982). Homing the microparticles with antibodies and magnetic particles has been under vigorous investigation (Davis and Illum, 1985; Poste, 1984). More in vivo testing is needed before conclusions can be drawn from these targeting approaches.

Nanoparticles and microspheres generally have the same applications when used as a drug carrier system for antineoplastic agents except in chemoembolization. Chemoembolization can be regarded as a new approach for compartmental targeting for anticancer treatment. This treatment is based on the combination of two effects; a mechanical effect due to the obstruction of the feeder vessels of a tumor by large microparticles, i.e., microspheres, and a chemotherapeutic effect due to the local diffusion of a microencapsulated active ingredient inside the pathological area (Madoule et al., 1984; Kato et al., 1981; Benita et al., 1984). In this approach, short-term biodegradability of these microspheres is needed to avoid tissue necrosis (Benita et al., 1984).

Due to the biodegradability, low toxicity and pharmaceutical acceptability and stability in formulation, microencapsulation systems have great potential in solving the formulation problems of the anticancer investigational drug. Careful selection of the materials and methods for microencapsulation should produce the drug-loaded microparticles with desired release rate. Toxicity,

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antigenicity and biodegradability should be carefully monitored at all times.

(3) Fat Emulsions

Emulsions have great potential as drug delivery systems. Compared with other colloidal systems, their advantages include high drug loading capacity and extensive experience from clinical use in parenteral nutrition. Emulsions can be used as vehicles for lipid-soluble material, as drug carrier for controlled release, and as a carrier system for targeting to specific sites in the body (Davis et al., 1985).

Formulation problems can arise in the parenteral administration of drugs that have low water solubilities. The normal types of solution formulation comprise various cosolvents and/or surfactant mixtures (e.g., polyethylene glycol, propylene glycol, Cremophor, Pluronic) (Israel et al., 1978). Such systems may be painful when injected and the drug may precipitate upon dilution of the administered solution by the blood or tissue fluid. Furthermore, the various formulation additives are not without their own pharmacological or immunological effects (Davis et al., 1985; Yalkowsky and Valvani, 1977). An alternative approach is to administer the water insoluble compounds via the intravenous route by the use of the natural fat particles already in the blood, the chylomicrons. Artificial chylomicrons have been developed in the form of emulsions for use in parenteral nutrition (e.g., Intralipid®, Lipofundin S®, Lipofundin®, Liposyn®, Travemulsion®) and such fat emulsions have been considered as

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vehicles for the administration of pharmacological agents (Davis et al., 1985; West et al., 1985).

On thermodynamic grounds, the two-phase emulsion systems have an advantage over a solubilized system in that the drug contained therein are much less likely to precipitate as solid (harmful) particles when diluted. Furthermore, the presence of the bulk of the drug in a nonaqueous environment may lead to an increased stability of the drug (e.g., reduced hydrolysis) and offers the possibility of a controlled release system. All the above advantages are potentially very useful for solving the formulation problems of anticancer investigational drugs.

Forstner et al. (1975) and Litterst et al.(1974) have explored the possible use of lipid emulsions for the administration of anticancer agents, and this idea has been developed further by Repta (1981b). Valinomycin has been formulated in an emulsion by using the commercially available lipid emulsion, Intralipid 10% (Repta, 1981b). Tests in animals showed equivalent therapeutic effects but the emulsion formulation required a 20 fold lower dose to produce these effects. Repta (1981b) also discussed the effect of enhanced stability, which can arise when a drug is formulated into an emulsion system. The commercial products Liposyn® and Intralipid® was used as a vehicle to enhance the solubility and stability of the investigational drug NSC 278214. The rate constant of first-order degradation decreased from 2080 x 10^2 hr^{-1} in acetone-water (3:1) to 6.8 x 10^2 hr^{-1} in 1% DMA-Intralipid® mixture (El-Sayed and Repta, 1983).

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It has been noted that interstitially injected particles, such as dyes and artificial oil droplets, are readily taken up from the tissue by the lymphatics, but not by the blood capillaries (Yoffey and Courtice, 1970). Considering this fact and also the feasibility of drug entrapment, various types of lipid emulsions were introduced as lymphotropic carriers of anticancer drugs (Hanaue et al, 1986; Hashida et al., 1977a,b; Nakamoto et al., 1975a,b; Takahashi et al., 1973, 1976, 1977). Anticancer drugs such as mitomycin C, bleomycin, 5-fluorouracil, N_1-(2-tetrahydrofuryl)-5 fluorouracil, and sodium-o-iodohippurate have been formulated into various emulsion systems for parenteral administrations. Injections were given by intramuscular, intraperitoneal, and intragastric routes. Using mitomycin C and bleomycin, Nakamoto et al. (1975a, b) and Hanaue et al. (1986) noted that the W/O emulsion produced a much greater specific delivery of drugs into the lymphatic systems than did an O/W emulsion. The lymphotropic property of lipid emulsions is expected to be an effective adjuvant for preventing or minimizing lymph node metastases. Takahashi et al. (1973, 1976) showed that the direct administration of anticancer drugs into tumors by using W/O emulsions as vehicles has demonstrated antitumor activity, prevention of lymphatic metastasis and sustained release effect of such a formulation. A subsequent clinical trial in which 121 patients with gastric carcinoma received oral administration of 5-fluorouracil emulsion showed encouraging results (Takahashi et al., 1977). Though long-term follow-up has not been reported, clinical and histological observations suggested that emulsions

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given orally also enhance the therapeutic effects of the drug on regional lymph node metastases. Sasaki (1984b) demonstrated that O/W emulsion, in addition to lymphotropic property, delivered a prodrug of Mitomycin C in the same controlled released fashion as liposomes would.

More complex emulsion systems have also been used. Multiple emulsions such as W/O/W or O/W/O emulsion can be made by re-emulsifying the appropriate single emulsion system. They are of much lower viscosity, are thus easier to inject, and produce less local reactions (Herbert, 1965; Florence and Whitehill,1982; Taylor et al., 1969). They can also be used as depot systems (Davis et al., 1985). However, the complexity of the multiple emulsions creates formulation difficulties. Methods for the assessment of the stability of multiple emulsions for pharmaceutical use have been described (Davis and Burbage, 1977, 1978; Burbage and Davis, 1980, Florence and Whitehill, 1982). The potential advantages of multiple emulsions in drug delivery are counterbalanced by an increased complexity of the dosage form and the attendant problems of optimal formulation and acceptable stability. Methods for improved stability, however, have been developed by Florence and Whitehill (1982) and Chang (1976). The kinetics of drug transport in complex "liquid membrane" (W/O/W emulsions) have been explored by Chilamkurti and Rhodes (1980), Yang and Rhodes (1980) and Panaggio and Rhodes (1984).

The combination of the microencapsulation system and lipid emulsions proved to have superior pharmaceutical characteristics The microsphere-in-oil emulsions showed increased stability

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against phase separation under various storage conditions, and stable incorporation of the drug into the oil droplets (Hashida et al., 1977a, b; Sezaki et al., 1982; West et al., 1985). The microsphere-in-oil emulsions not only retain the antitumor activity of the microspheres, but they also have a sustained release mechanism and a lymphotropic property to prevent lymphatic metastases.

Though the use of emulsions in parenteral systems is well-documented, parameters such as particle size, stability, emulsifying agent and ionic strength must be carefully monitored to quantify any toxicity. Large oil droplets could give rise to blockade (emboli) in the body, particularly in the fine capillaries of the lungs. In general, particles greater than 5 m are excluded from intravenous use. More recently, data on fat emulsions administered to rats indicates that there is a rise in toxicity (as measured by LD_{50}) when the mean particle size rises above 1.5 μm (Davis et al., 1985).

Stability was the foremost problem in the early development of intravenous fat emulsions (Panaggio et al., 1979). There was a conflict between the requirements for good stability and low toxicity, and these requirements are to some extent incomparable. Changes in the stability of fat emulsions may be manifested in a number of different ways; physical stability such as change in particle size of oil droplets, creaming, coalescence, and oil separation; and chemical stability such as hydrolysis of emulsifier, change in bulk pH, release of free fatty acids, and rancidity of the oil. Such stability changes can occur during

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preparation (particularly upon autoclaving), during storage, or through the addition of electrolytes and drugs. The manufacturers of commercially available products warn against the addition of drugs to intravenous fat emulsions. Special formulation may be needed to retain the stability and to prevent the cracking of the emulsions (Davis et al.,1985; Florence and Whitehill,1982).

The small lipid droplets in emulsions may be taken up by the reticuloendothelial system rather than the lymphatic system. The size, composition, structure and charge of the particles is considered relevant to their biological fate. Jeppsson and Rossner (1975) have reported that emulsion particles may have very different rates of clearance from the plasma if the nature of the emulsifier is changed. The selection of the appropriate emulsifying agent is very important for the removal of the emulsion from the blood stream.

The incorporation of an antineoplastic agent into a commercially available fat emulsion, a simple emulsion (W/O or O/W/O) or a microsphere-in-oil emulsion may enhance its stability, solubility and therapeutic efficacy. Although fat emulsions usually are lymphotropic which is very useful in metastatic tumors, this property can be reduced by the nature of emulsifier, and the size, composition, structure and charge of the oil droplets. The most important formulation factor is the stability of the emulsion. The factor that may influence the stability is well-documented and methods for stability improvement have been developed (David et al., 1985; Florence and Whitehill, 1982).

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(4) Polyaphrons

A polyaphron is a biliquid foam that has been created by the replacement of the gas phase of a microfoam (gas aphron) by an immiscible liquid. The initial component of the polyaphron system, a colloidal gas aphron, was first investigated by Sebba (1971). These systems were initially called microfoams, gas foams, or microgas dispersions because it was generally thought that they were foams comprised of very small bubbles (Sebba and Barnett, 1981). Further studies showed the bubbles to consist of a volume of gas encapsulated in a thin shell of water. Due to the small size of the bubbles, colloidal behavior was exhibited, and suspensions of these bubbles could last for long periods of time.

Colloidal gas aphrons (CGAs), the initial component of the polyaphron system, were first made by Sebba using a modified Venturi apparatus (Sebba, 1971), which provides a point of high velocity and low pressure in a moving stream of water containing a solution of surface active agent (Sebba, 1971; Gregory et al., 1980; Sebba, 1975). By repeated re-circulation of the materials, a dispersion of the resulting bubbles can be made to contain as much as 65% gas by volume.

It is essential that the surfactant used to generate the foam have appropriate surface active characteristics (Shea and Barnett, 1979). Surfactants having high HLB values work best. The resulting CGAs can range in size from 2 to 100 micrometers in diameter. They are generally stable and can be made at a variety of viscosities. Coalescence of the bubbles appears to be negligible, indicating that the shell which is essentially a

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double soap film, is very elastic and strong (Sebba and Barnett, 1981). The most useful and most investigated function of CGAs is the application in separation and flotation operations.

When the gas cells of the colloidal gas aphrons are replaced by a liquid not miscible with the liquid comprising the aqueous film, polyaphrons or biliquid foams are thus obtained (Sebba, 1972, 1984). The best result can be obtained when a surfactant is added to the oily liquid before the incorporation into the CGAs system. These systems are relatively stable, homogeneous, and typically display a 'honeycomb' structure. The preparation of a polyaphron requires several essential components. Most important is a volume of colloidal gas aphron which provides a highly expanded surface area of water. Secondly, the internal phase, also called the oil phase, must have a sufficient concentration of oil soluble surfactant. Lastly a reasonable degree of restraint must be exercised while adding the oil phase into the gas aphron. Too rapid addition will swamp the interface, thus preventing complete encapsulation of the oil. Slow addition with appropriate agitation will insure more effective production of the polyaphrons (Montalto, 1984). The maximum concentration of oil that can be used to produce a very stable system is about 95%.

Due to the encapsulation of the oil phase by an aqueous film, it is highly possible that polyaphrons may offer protection to physicochemical unstable compounds against attacking species such as hydrogen ions, hydroxyl ions and oxygen molecules. The encapsulation by the aqueous film can also increase the solubility of an oil-soluble and water-insoluble compounds. The high

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percentage of oil, e.g., 95%, that can be incorporated into the polyaphron systems demonstrated that a high drug load is possible for this system. Recently Montalto and his associates have disclosed the successful formulation of a pharmaceutical aphron system (Montalto, 1984). It was found that stable polyaphron systems could be made with sodium lauryl sulfate and mineral oil, materials which have been used in pharmaceutical industry for many years.

The application of polyaphrons as drug carrier system for antineoplastic agents in parenteral administration has not yet been developed. The nature of biliquid films may offer better improvement in stability and solubility than the simple fat emulsions. Thus the full potential of polyaphrons in pharmaceutic formulation has yet to be explored. The authors feel that, as long as the surfactants of the oil phase and the aqueous phase can pass the strict requirements of the parenteral administrations, polyaphron may solve the formulation problems of many investigational anticancer compounds and may improve the therapeutic efficacy of these compounds.

V. SUMMARY

This paper has provided brief reviews of several drug delivery systems which may solve the formulation problems of many investigational anticancer compounds. A summary of these approaches can illustrate the advantages and disadvantages of each system.

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(1) Solubilization Approaches

The solubilization approaches are technically the easiest ones. Usually one or more additives are added to the aqueous solution of a drug. A sufficiency of literature data are available for this solubilization approach. It is possible to find additives than can pass the strict requirements of parenteral administration. The disadvantages are: the limited improvement in solubility and stability, the pain that may be inflicted on patients, the possibility that drug may precipitate upon dilution of the administered solution by the blood or tissue fluids, and the pharmacological and immunological effects of the additives themselves. Therefore the authors propose that the use of colloidal systems to combat these problems is more attractive.

(2) Colloidal Systems

Table 3. summarizes the advantages and limitations of liposomes, microencapsulation systems, fat emulsions and polyaphrons.

Careful evaluation of advantages and disadvantages of these drug delivery systems is necessary before a suitable choice for a specific compound can be made. Although the advantages and limitations of each delivery system are important factors, properties regarding the drug itself are the most important parameters, and information regarding its physicochemical properties should be available before choosing a delivery system for it. A simple and effective approach is more desirable since the present knowledge regarding tumor cell kinetics have not made the first-order targeting possible yet.

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Table 3. Characterictics of liposomes, microencapsulation systems, fat emulsions and polyaphrons

	Liposomes	Microencapsulaion systems	Fat emulsions	Polyaphrons
Technology				
range of composition	excellent	good	poor	poor
size range	0.02-5 um	0.1-100um	0.1-0.4 um	2-100um
size distribution	± 20%	± 10%	± 20%	± 20%
ability to adjust restricted	excellent	excellent	restricted	
stability of carrier on drugs	>1 year	≫1 year	2 years	3 years
aggregation	excellent	excellent(with surfactant)	excellent	excellent
lyophylizable information	yes	yes	maybe	no
ability to carry water-soluble drugs	excellent	fair	no	no
efficiency of encapsulation of water-soluble drugs	excellent	fair	ISI	ISI
encapsulaion ratio (W/W)	0.02-4	depends on size, for 1 um, 0.01-0.2	0.01-0.1	ISI
ability to carry lipid-soluble drugs	excellent	excellent	excellent	excellent
sterilization by autoclving	yes	yes	yes	maybe
In Vivo Performance				
toxicity, single IV dose	low 5 g/Kg	high 200 mg/Kg	very low 25 g/Kg	NI
toxicity, IM	good	fair	excellent	NI
ability to be metabolized	good	fair	excellent	NI
stability in vivo	good	fair	fair	NI
controlled release of water-soluble drugs	good	fair	NA	NA
half-live in the bloodstream	size dependent	short	15 min - 3 hrs	NI
immunogenicity	low	depends on composition	low	NI
Available Knowledge/Data				
success in animal model for therapy	good many papers	good few papers	good very few papers	NI
success in human therapy	excellent	excellent	?	NI
scientific knowledge to guide future development	excellent	good	good	fair

Note: NA: non-applicable; NI: no information; ISI: insufficient information

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