

MICROENCAPSULATION OF DICLOFENAC SODIUM FOR ORAL SUSTAINED RELEASE

V.HANUMATH SASTRY^{1*}, P.AMARESHWAR², P.NIVETHITHAI¹ AND P.CHAKRAVARTI²

¹MESCO College of Pharmacy, Mustaeedpura, Karwan Road, Hyderabad-6

²University College of Technology, Osmania University, Hyderabad-44

ABSTRACT

With the recent advance of biotechnology and polymer chemistry, the use of microparticle systems will continue to grow for a variety of applications. The objective of this article is to provide an overview of the microencapsulation techniques that have been reported in developing oral sustained release (SR) dosage forms of diclofenac sodium, a widely used non-steroidal anti-inflammatory drug (NSAID) globally.

1. INTRODUCTION

The concept of microencapsulation has intrigued the pharmaceutical industry for many years, because it offers the possibility of providing a number of important new oral and parenteral dosage forms. Microcapsules in oral dosage forms can conceptually taste-mask bitter pharmaceuticals, provide extended release *in vivo*, provide enteric release, improve the stability of incompatible drug mixtures, provide resistance to oxidation, reduce volatility and distribute a drug in many small carrier particles so that effects of the drug on the sensitive walls of the stomach are minimized. Microencapsulated parenteral formulations can provide prolonged delivery of drugs with short half-lives *in vivo* and perhaps even achieve targeted drug delivery. For these reasons, microencapsulation has received much attention by pharmaceutical scientists and yielded a number of commercial pharmaceutical formulations (Thies, 1983).

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain and inflammation, particularly for different types of arthritis. Among the most popular NSAIDs worth mentioning is diclofenac sodium (DFS), which is approved in more than 120 countries across the globe since its introduction, 28 years ago, and is ranked 30th among the top 200 drugs with respect to new prescriptions (Bhandari, 2008). It exhibits antirheumatic, analgesic, antiosteoarthritis and antipyretic activities. It has a short half-life in plasma (1-2 hours). The daily dose varies between 75 and 200 mg/person, given in 3 or 4 divided portions depending on the route of

administration. The most common adverse effects of the drug are gastritis, peptic ulceration and depression of renal functions. Because of the short biological half-life and associated adverse effects, it is considered an ideal model drug for sustained drug delivery (Pimwipha, 2007). The here-presented article provides an overview of various techniques of microencapsulation utilized for the *oral* sustained release of DFS.

An Overview of Microencapsulation

Microencapsulation is a technique by which solid, liquid or gaseous active ingredients are packaged within a second material for the purpose of shielding the active ingredient from the surrounding environment. Thus the active ingredient is designated as the core material whereas the surrounding material forms the shell. This technique has been employed in a diverse range of fields from chemicals and pharmaceuticals to cosmetics and printing. For this reason, widespread interest has developed in microencapsulation technology (Dubey, 2009). At least eight industry segments routinely utilize microencapsulation to deliver improved performance of a variety of actives and benefit molecules. Table 1 provides some examples:

Table 1. Eight Market Areas for Microencapsulated Products

Personal Care
Household Care
Food Industry
Pharmaceuticals
Industrial Sector (Catalysts etc)
Paper Industry
Textile Industry
Agrochemicals

***Corresponding Author**

E-mail: vhsastry@rediff.com

The term microcapsule is used to describe particles with diameters between 1 and 1000 μm . Particles smaller than 1 μm are called nanoparticles; particles greater than 1000 μm can be called microgranules or macrocapsules. Many terms have been used to describe the contents of a microcapsule: active agent, actives, core material, fill, internal phase (IP), nucleus and payload. Many terms have also been used to describe the material from which the capsule is formed: carrier, coating, membrane, shell, or wall(Thies,1983).

Although virtually any coating material, conceptually, is a candidate microcapsule shell material, most commercial microcapsules produced to date utilize a relatively small number of different shell materials. Table 2 lists representative examples of these materials along with typical applications. Microcapsule shell material selection for a specific application is determined by a number of factors including cost, availability, processing ease and inherent barrier properties. Shell materials for pharmaceutical, food and personal care products are limited to materials that are approved by regulatory agencies responsible for such products(Thies,1983).

Table 2. Representative examples of Shell materials used in Microencapsulation

Shell material	Regulatory status	Chemical class	Encapsulation process	Applications
Gum arabic	Edible	Polysaccharide	Spray drying	Food flavors
Gelatin	Edible	Protein	Spray drying	Vitamins
Gelatin-gumarabic ^a	Nonedible ^b	Protein-polysaccharide complex	Complex coacervation	Carbonless paper
Ethylcellulose	Edible	Cellulose ether	Wurster process or polymer-polymer incompatibility	Oral pharmaceuticals
Polyurea or polyamide	Nonedible	Cross-linked polymer	Interfacial polymerization <i>in situ</i> polymerization	Agrochemicals and carbonless paper
Aminoplasts	Nonedible	Cross-linked polymer		Carbonless paper, fragrances, and adhesives
Maltodextrins	Edible	Low molecular weight carbohydrate	Spray drying and desolvation	Food flavors
Hydrogenated vegetable oils	Edible	Glycerides	Fluidized bed	Assorted food ingredients

^aTreated with glutaraldehyde.

^bFor intended application, ie, carbonless paper.

Microcapsules can be classified into three basic categories as monocored, polycored and matrix types as shown in Fig. 1. Monocored microcapsules have a single hollow chamber within the capsule. The polycore microcapsules have a number of different sized chambers within the shell.

The matrix type microparticle has the active ingredients integrated within the matrix of the shell material. However, the morphology of the internal structure of a microparticle depends largely on the selected shell materials and the microencapsulation methods that are employed.

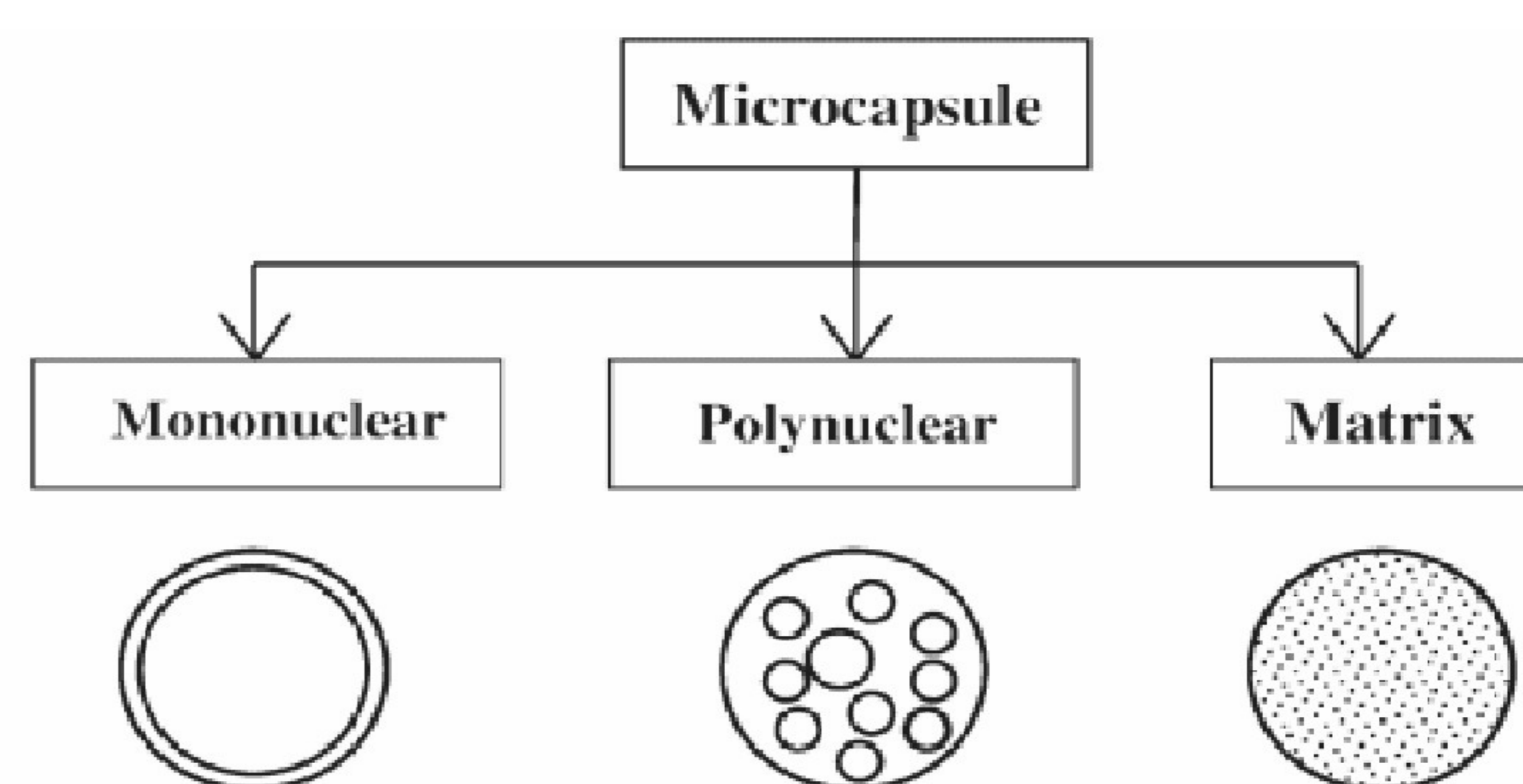


Fig. 1. Morphology of Microcapsules

In addition to these three basic morphologies, microcapsules can also be mononuclear with multiple shells, or they may form clusters of microcapsules. Schematic diagrams of these types of microcapsules are shown in Figures 2 and 3. Morphological control is important and much effort has been given to controlling internal structures, which largely depend on the protocol and the microencapsulation methods employed.

The most significant feature of microcapsules is their microscopic size that allows for a huge surface area, for example, the total surface area of 1 μm of hollow microcapsules having a diameter of 0.1 μm has been reported to be about 60 m^2 . The total surface area is inversely proportional to the diameter. This large surface area is available for sites of adsorption and

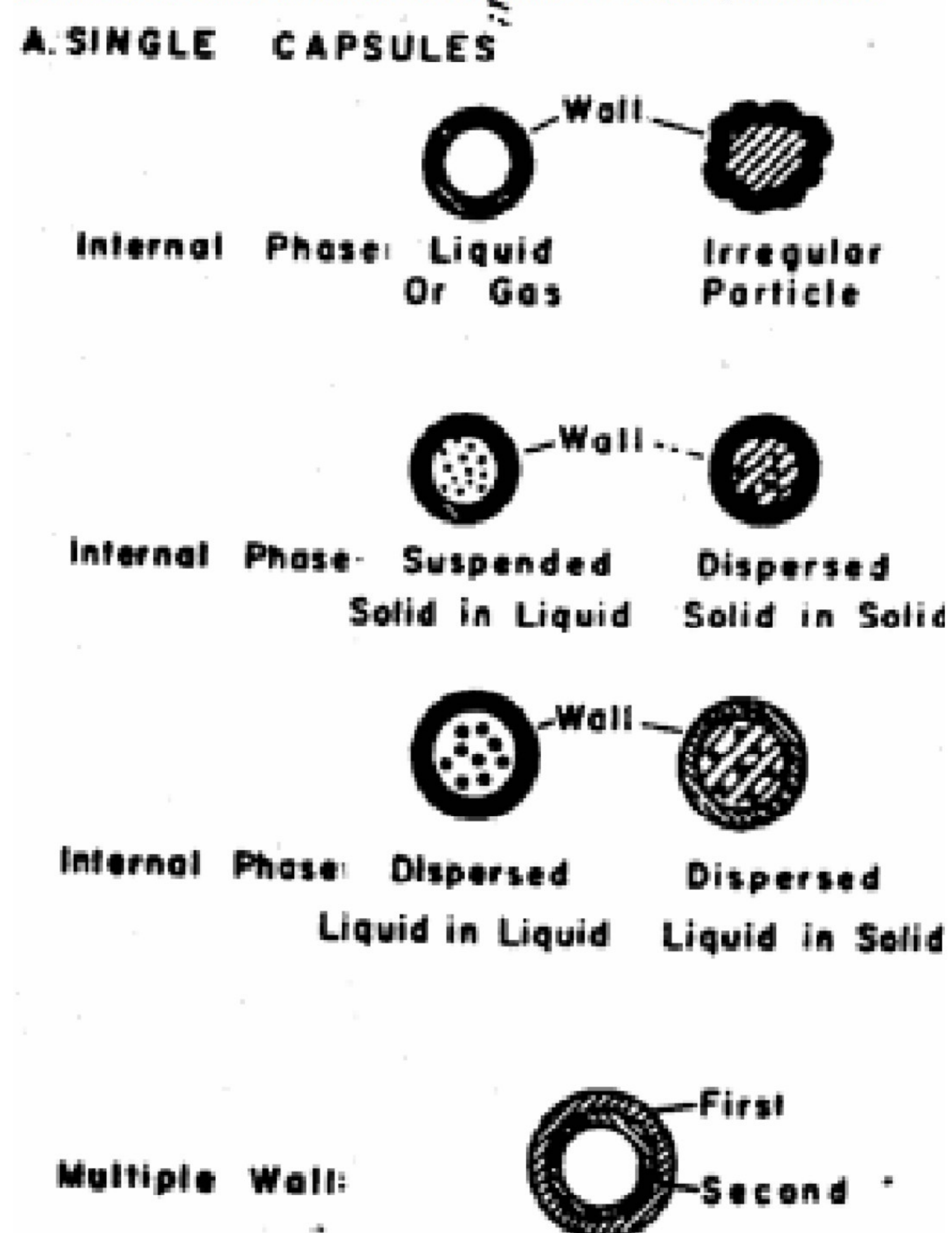


Fig.2. Single microcapsule system

B. MULTIPLE CAPSULES (AGGREGATE)

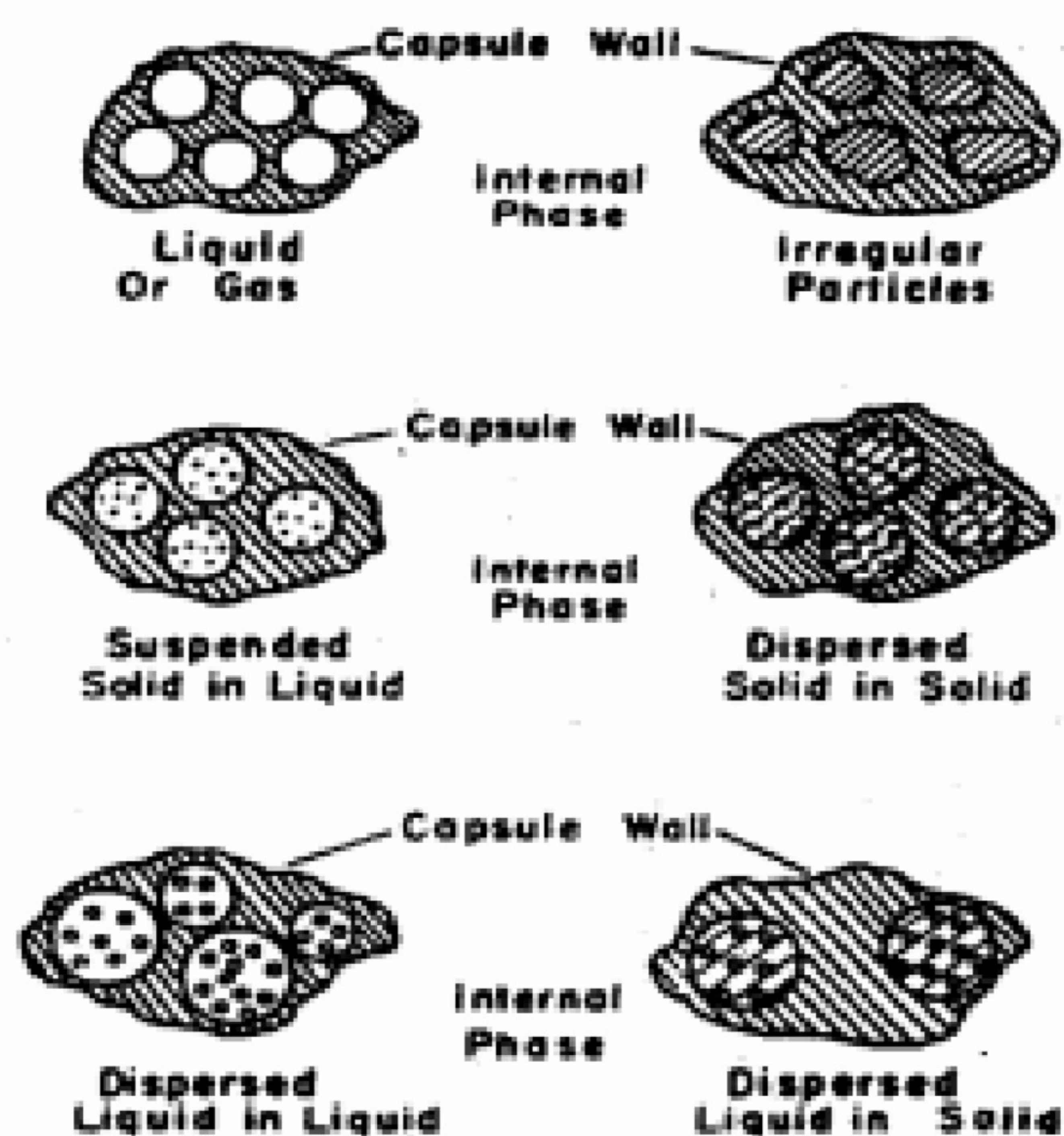


Fig. 3. Multiple microcapsule system

desorption, chemical reactions, light scattering, etc. More detailed features of microcapsules are summarized in books by Gutcho(1976) and Arshady(1999).

Although a variety of techniques have been reported for microencapsulation, they can broadly be divided into two main categories (Table 1) (Dubey,2009). The first category includes those methods in which starting materials are monomers/prepolymers. In these methods chemical reactions are also involved along with microsphere formation. The second category consists of those methods in which starting materials are polymers. Hence, in these methods no chemical reactions are involved and only shape fabrication takes place. Description of these techniques may be found elsewhere (Dubey,2009; Gutcho, 1976; Arshady,1999).

Chemical Methods	Physical / Mechanical Methods
Suspension Polymerization	Suspension crosslinking
Emulsion Polymerization	Solvent Evaporation/Extraction
Dispersion Polymerization	Coacervation/ Phase separation
Interfacial Polymerization	Spray Drying
Polycondensation	Fluidized Bed Coating
Ionic Gelation	Melt Solidification
Polyelectrolyte Complexation	Precipitation
	Co-extrusion
	Layer-by-Layer deposition
	Sol-gel encapsulation
	Supercritical fluid expansion
	Spinning disk
	Centrifugal techniques
Vacuum encapsulation	
Electrostatic encapsulation	

Profile of Diclofenac Sodium

Diclofenac sodium (Fig.4) is a phenylacetic acid derivative that is a white to off-white, virtually odorless, crystalline powder. Diclofenac sodium is freely soluble in methanol, soluble in ethanol and practically insoluble in chloroform and in dilute acid. Diclofenac sodium is sparingly soluble in water. Its chemical formula and name are: $C_{14}H_{10}Cl_2NO_2Na$ [M.W. = 318.14] 2-[(2, 6-dichlorophenyl) amino] benzeneacetic acid, monosodium salt(Medication guide,2009).

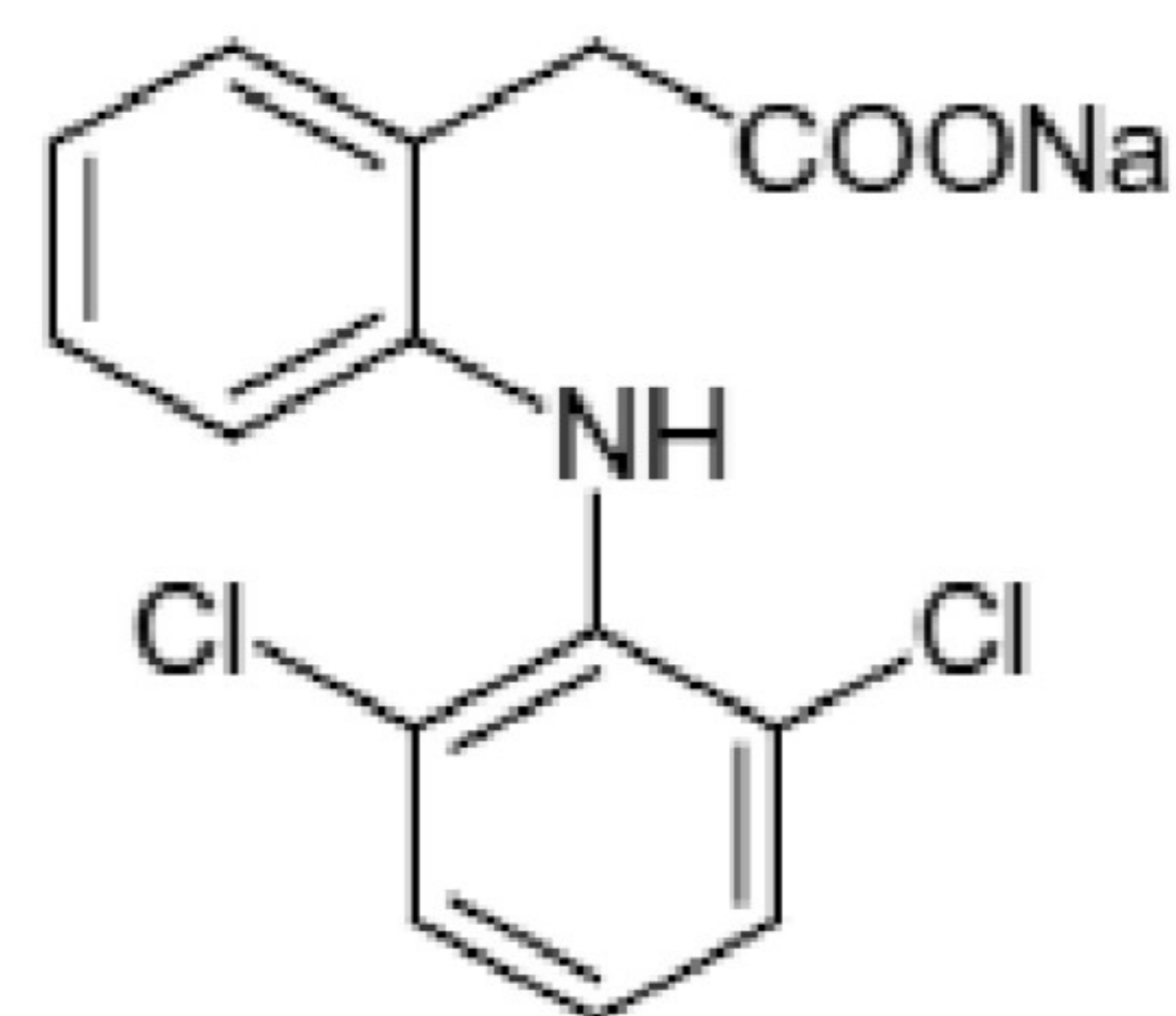


Fig.4. DFS Chemical Structure

Diclofenac sodium is one of the widely prescribed NSAIDs. In pharmacologic studies, diclofenac sodium has shown anti-inflammatory, analgesic and antipyretic properties. The mechanism of action of diclofenac sodium, like other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. Diclofenac sodium is completely absorbed from the GI tract after fasting, oral administration.

Only 50% of the absorbed dose is systemically available due to first pass metabolism. Peak plasma levels are achieved in 2 hours (range 1–4 hours) and the area under the plasma concentration curve (AUC) is dose proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose-proportional and are approximately 1.5 and 2.0 mcg/mL for 50 mg and 75 mg doses, respectively.

Plasma concentrations of diclofenac sodium decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of distribution are about 350 mL/min and 550 mL/kg, respectively. More than 99% of diclofenac sodium is reversibly bound to human plasma albumin.

Diclofenac sodium is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine and 35% in the bile.

Conjugates of unchanged diclofenac account for 5–10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. Conjugates of the principal metabolite account for 20–30% of the dose excreted in the urine and for 10–20% of the dose excreted in the bile.

Conjugates of three other metabolites together account for 10–20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life = 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of Diclofenac metabolites is unknown. Some of the metabolites may have activity. DFS may cause Cardiovascular Thrombotic Events, Hypertension, Congestive Heart Failure and Edema, Gastrointestinal Effects - Risk of Ulceration, Bleeding and Perforation, Advanced Renal Disease, Hepatic effects, Anaphylactic reactions, Skin Reactions. In late pregnancy, as with other NSAIDs, DFS causes premature closure of the ductus arteriosus and therefore, should be avoided.

Literature Review of DFS Oral SR Dosage Forms

Extensive review of literature reveals that DFS was microencapsulated for SR studies employing the following techniques: Coacervation/Phase separation, Emulsification, Ionotropic gelation, Solvent evaporation, Spray drying and Wurster process.

Coacervation/Phase separation may be of simple or complex type. Simple coacervation involves the use of a single polymer such as gelatin or ethyl cellulose, in aqueous or organic media, respectively. Complex coacervation involves two oppositely charged polymeric materials such as gelatin and acacia, both of which are soluble in aqueous media. In both the cases, coacervation is brought about by gradual desolvation of the fully solvated polymer molecules (Dubey, 2009). Shell materials used include ethyl cellulose (Sajeev, 2002; Hasan, 1992), ethyl vinyl acetate (Hanan, 2002), chitosan (Gohel, 1994).

Microparticles can be produced from emulsion of two or more immiscible liquids. Depending on the method of solidifying the discontinuous droplets, the emulsion method can be classified as solvent evaporation, solvent extraction and cross-linking method. In Solvent Evaporation/Solvent Extraction, the polymer is dissolved in a water immiscible volatile

organic solvent like dichloromethane or chloroform, into which the core material is also dissolved or dispersed. The resulting solution is added dropwise to a stirring aqueous solution having a suitable stabilizer like poly(vinyl alcohol) or polyvinylpyrrolidone, etc. to form small polymer droplets containing encapsulated material. With time, the droplets are hardened to produce the corresponding polymer microcapsules. This hardening process is accomplished by the removal of the solvent from the polymer droplets either by solvent evaporation (by heat or reduced pressure), or by solvent extraction (with a third liquid which is a precipitant for the polymer and miscible with both water and solvent) (Dubey, 2009). A number of hydrophilic polymers from natural origin, such as gelatin, albumin, starch, dextran, hyaluronic acid and chitosan, can be solidified by a chemical or thermal cross-linking process. Most proteins are cross-linked using glutaraldehyde, but its toxicity remains a problem for pharmaceutical applications (James, 2007). Shell materials used include Sequential interpenetrating network (IPN) of poly(vinyl alcohol) (PVA) and poly(acrylic acid) (PAA) (Mahaveer, Tejraj, 2004), chitosan (Kumbar, 2002), poly(vinyl alcohol) (PVA) (Viney, 2000), alginic acid (Gursoy, 2000), acacia/ethylcellulose/acacia (three-plywalled) (Bhatnagar, 1995), hydroxypropyl methylcellulose phthalate (HPMCP) (Torres, 1995), Eudragit RL (Satturwar, 2002), poly(L-lactic acid) (PLA)/ copoly(lactic acid/glycolic acid) (PLGA) / poly(delta-valerolactone) (PV) (Lin, 2000), polymerized rosin (Fulzele, 2004), ethyl cellulose (Gohel, 1999).

Ionic gelation involves cross-linking of polyelectrolytes in the presence of multivalent counter ions. Ionic gelation is often followed by polyelectrolyte complexation with oppositely charged polyelectrolytes. This complexation forms a membrane of polyelectrolyte complex on the surface of the gel particles, which increases the mechanical strength of the particles (James, 2007). DFS dispersed in: Gelucire® matrix and encapsulated in calcium alginate shell, polyvinyl pyrrolidone and mannitol (Solid dispersions) and encapsulated in alginic acid/chitosan/agar (Manjunatha, 2007), Compritol 888 and encapsulated in calcium alginate shell (Amani, 2000) were reported. DFS was also encapsulated using alginate/chitosan (Gonzalez, 2002) and sodium alginate (Gohel, 1998).

Microencapsulation by spray drying is a low cost commercial process, which is mostly used for the encapsulation of fragrances, oils and flavors. In this

process, an emulsion is prepared by dispersing the core material, usually an oil or active ingredient immiscible with water, into a concentrated solution of wall material. The resultant emulsion is atomized into a spray of droplets by pumping the slurry through a rotating disc into the heated compartment of a spray drier. There the water portion of emulsion is evaporated, yielding dried capsules containing core material (Dubey, 2009). Sweet potato starch (Cheng, 2007) and chitosan (Kashappa, 2006) were investigated as shell materials. In Wurster's process, solid particles to be encapsulated are suspended in a jet of air and then covered by a spray of liquid coating material. The capsules are then moved to an area where their shells are solidified by cooling or solvent vaporization. The process of suspending, spraying and cooling is repeated until the capsule walls are of the desired thickness (Dubey, 2009). Hydroxypropyl cellulose/ Eudragit L30D/ Eudragit RS30D (Hideki, 1997) and Aquacoat® / Eudragit® RS30D (Hideki, 2001) were studied as shell materials by this technique.

2. CONCLUSION

The microencapsulation technology, which started as a way of encapsulating dyes and flavors, has now become one of the most intriguing fields in the area of controlled drug delivery systems. This article presented an overview of the microencapsulation techniques reported for the design of SR dosage forms of DFS.

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