Soft gelatin capsules

- The term 'soft gelatin capsules' is commonly abbreviated to 'softgels',
- Over recent years, **new drug molecules have tended to be more hydrophobic** and therefore less soluble in aqueous systems.
- In the case of drugs **for oral administration**, it is becoming more difficult to formulate poorly water-soluble drugs into products from which the drug is fully released and well absorbed.
- **One of the best methods to overcome this problem is to make a liquid formulation containing the drug.**
- **In order to convert this liquid formula into a solid dosage form, it may be encapsulated into soft gelatin capsules.**

DESCRIPTION OF THE SOFT GELATIN CAPSULE DOSAGE FORM (SOFTGELS)

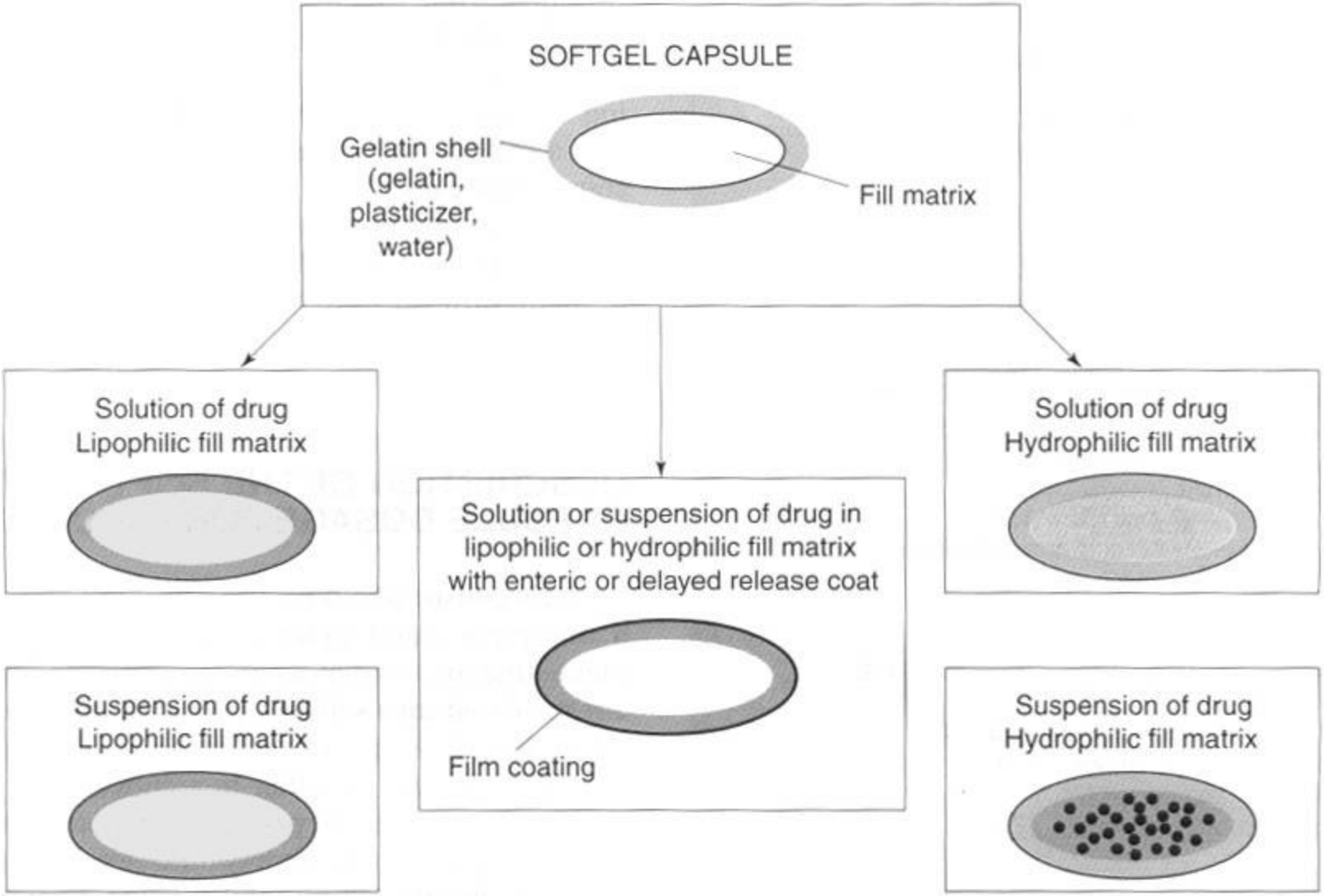
- Softgels consist of a liquid or semisolid matrix inside a one-piece outer gelatin shell.
- Ingredients that are solid at room temperature can also be encapsulated into softgels, provided they are at least **semisolid below approximately 45°C.**
- The **drug compound** itself may be either in **solution** or in **suspension** in the capsule-fill matrix.

- The characteristics of the **fill matrix may be:**
- **hydrophilic (for example polyethylene glycols) or**
- **lipophilic (such as triglyceride vegetable oils).**
- Indeed, in **many formulations**, **the matrix** may be a mixture of **both hydrophilic and lipophilic** ingredients.

- **Significant advances have been made in recent years** in the formulation of **softgel fill matrices**.
- These include **microemulsions** and **nanoemulsions** encapsulated as **preconcentrates in softgels.**

- The term '**preconcentrate**' means that the softgel fill matrix is a combination of lipophilic and hydrophilic liquids as well as surfactant components, which after oral administration disperse to form, for example, a microemulsion.

- **If the dispersion results in even smaller droplets in the nanoparticle range, then the dispersion is known as a nanoemulsion.**



different softgel formulations

Softgel capsule shell

- The softgel capsule shell consists of gelatin, water and a plasticizer.
- It may be transparent or opaque, and can be coloured and flavoured if desired.

- **Preservatives are not required** owing to the low water activity in the finished product.

- The softgel **can be coated** with enteric-resistant or delayed-release material.

- Although virtually **any shape softgel can be made**, **oval or oblong shapes are usually selected for oral administration**.

- Softgels can be formulated and manufactured to produce a number of **different drug delivery systems**:

1. Orally administered softgels containing solutions or suspensions that release their contents in the stomach in an easy to swallow, convenient unit dose form. This is the most common type of softgel, already described above;

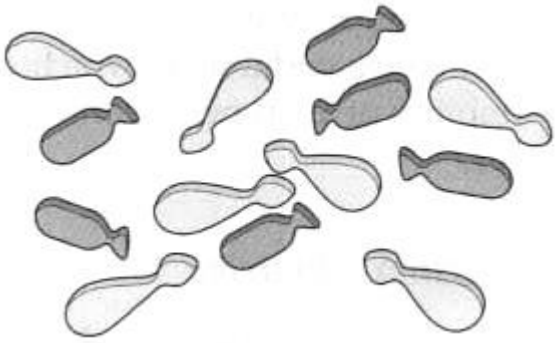
2. Chewable softgels, where a highly **flavoured shell** is chewed to release the drug liquid fill matrix.

- The drug(s) may be present in both the shell and the fill matrix.

3. Suckable softgels, which consist of a gelatin shell containing the flavoured medicament to be sucked and a liquid matrix or just air inside the capsule;

4. Twist-off softgels, which are designed with a tag to be twisted or snipped off, thereby allowing access to the fill material.

- This type of softgel can be very useful for unit dosing of topical medication, inhalations, or indeed for oral dosing of a paediatric product.



5. Meltable softgels, designed for use as 'patient friendly‘ pessaries or suppositories.

RATIONALE FOR THE SELECTION OF SOFTGELS AS A DOSAGE FORM

- In the majority of cases improved drug absorption is the primary reason.

Table 30.1 Summary of the key features and advantages of the softgel dose form

Features	Advantages
Improved drug absorption	Improved rate and extent of absorption and/or reduced variability, mainly for poorly water-soluble drugs
Patient compliance and consumer preference	Easy to swallow. Absence of poor taste or other sensory problem. Convenient administration of a liquid-drug dosage form
Safety – potent and cytotoxic drugs	Avoids dust handling problems during dosage form manufacture: better operator safety and environmental controls
Oils and low melting-point drugs	Overcomes problems with manufacture as compressed tablet or hard-shell capsules
Dose uniformity for low-dose drugs	Liquid flow during dosage form manufacture is more precise than powder flow. Drug solutions provide improved homogeneity over powder or granule mixtures
Product stability	Drugs are protected against oxidative degradation by lipid vehicles and softgel capsule shells

1. **Improved drug absorption**

- *Increased rate of absorption*
- One of the best methods is presentation of the drug to the gastrointestinal tract in the form of a solution from which it can be rapidly absorbed.

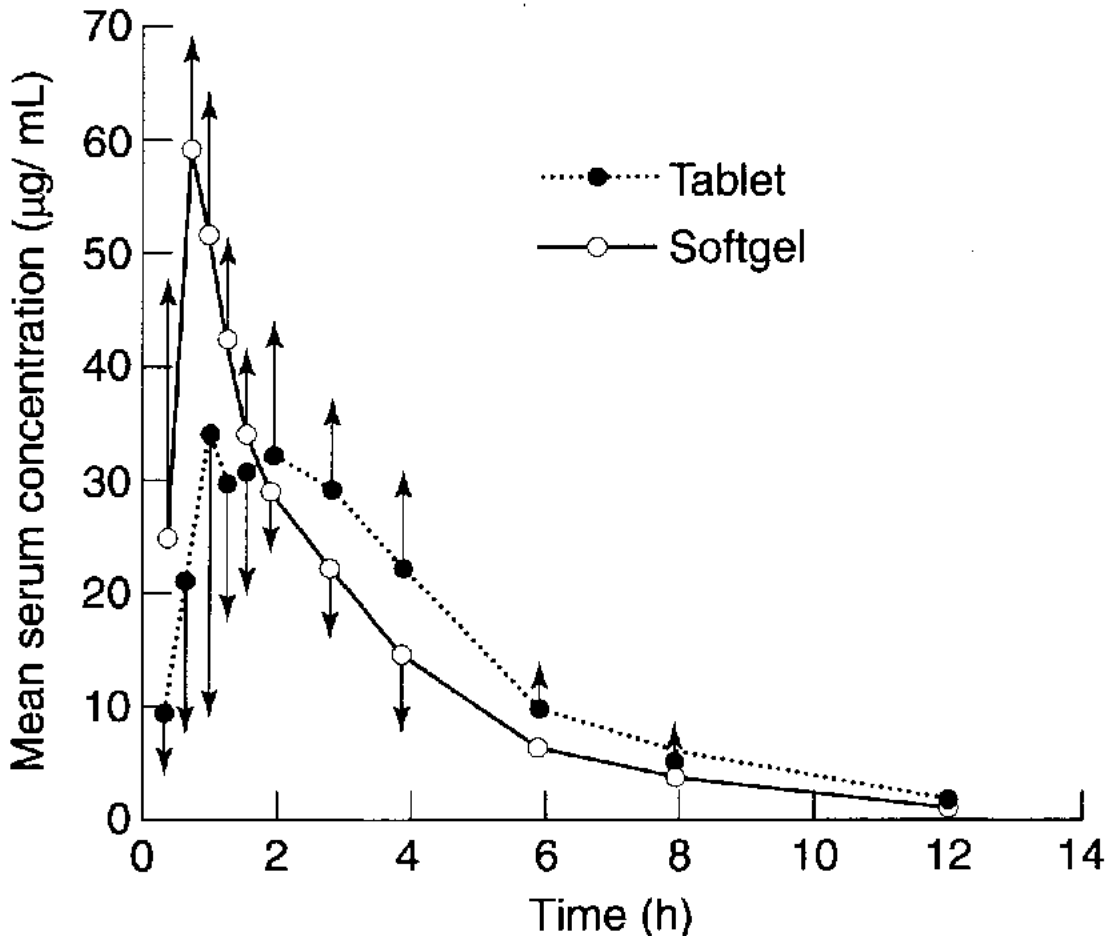
- This can be **achieved using a drug-solution matrix in a softgel** formulation whereby **absorption is significantly faster than from other solid oral dosage forms**, such as compressed tablets.
- This is because **absorption of a poorly soluble drug from a tablet formulation is rate-limited by the need for disintegration into granules, then drug dissolution into gastrointestinal fluid.**

- With the solution-softgel approach, the shell ruptures within minutes to release the drug solution, which is usually in a hydrophilic or highly dispersing vehicle that aids the rate of absorption.

- This may be a valuable attribute:

(a) for therapeutic reasons, such as the treatment of migraine or acute pain,

(b) where there is a limited absorptive region or 'absorption window' in the gastrointestinal tract.



Pharmacokinetic evaluation of softgels and tablets containing 400 mg ibuprofen (in 12 volunteers)

- ***Increased bioavailability:***

- As well as increasing the **rate** of absorption, softgels may also improve the **extent** of absorption.

- This can be particularly effective for hydrophobic drugs with a relatively high molecular weight.

- An example of such a product is the protease inhibitor saquinavir, which has been formulated as a solution-softgel product.

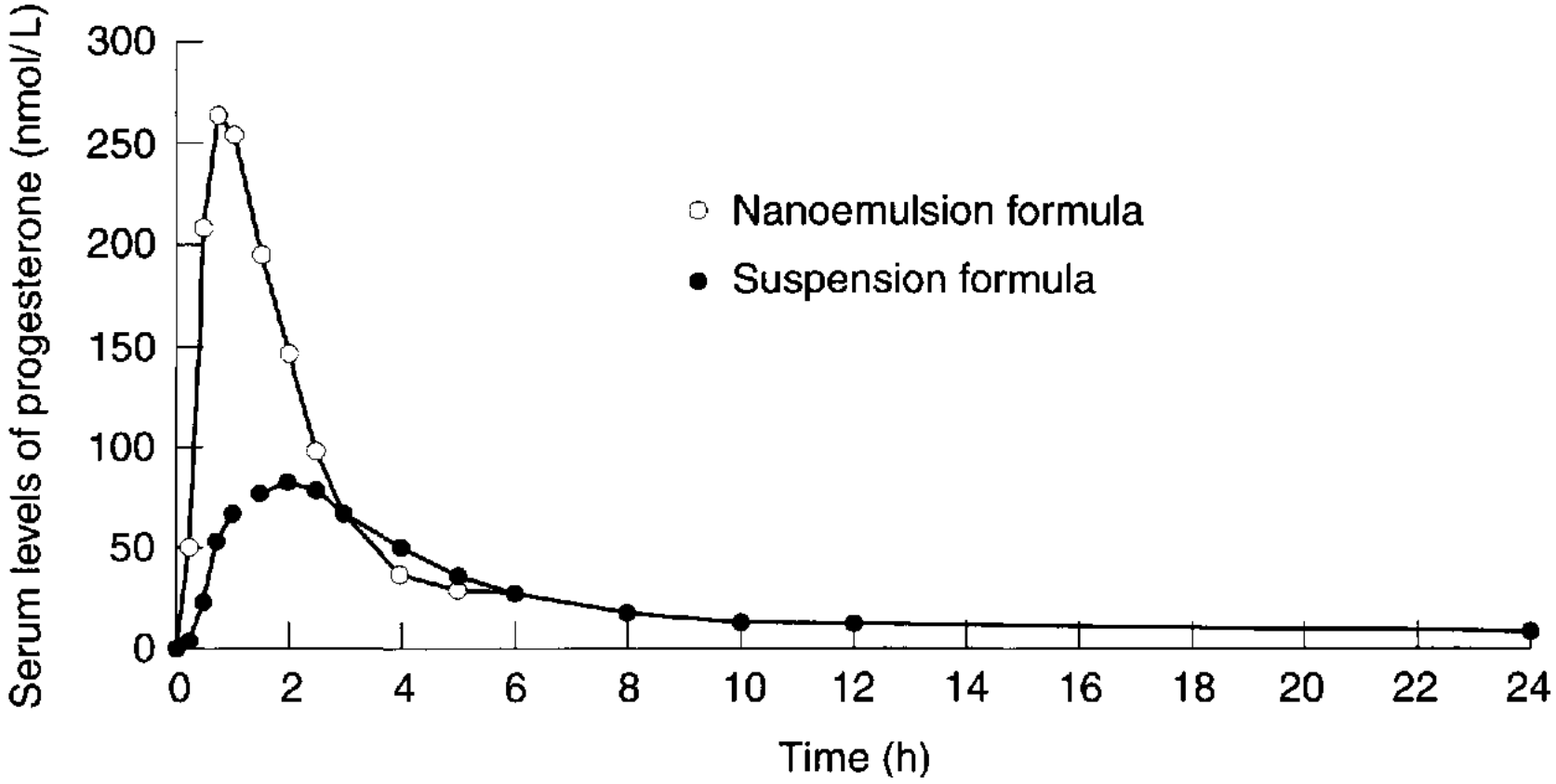
- **The solution-softgel formulation provided around three times the bioavailability of saquinavir** as measured by the area under the plasma-time curve (AUC), **compared to a hard-shell capsule formulation.**

- **In some cases a drug may be solubilized in a vehicle that is capable of spontaneously dispersing into an emulsion on contact with gastrointestinal fluid.**
- This is known as a self-emulsifying system.

- In other cases a drug may be dissolved in an oil/surfactant vehicle that produces a microemulsion or a nanoemulsion on contact with gastrointestinal fluids.

- **A nanoemulsion of progesterone** has been developed that provides a good example of this type of formulation.

- The vehicle, consisting of oils and surfactants in appropriate proportions, when in contact with aqueous fluids, produces an emulsion with an average droplet size less than 100 nm.



Pharmacokinetic evaluation of progesterone comparing a softgel nanoemulsion solution of progesterone with a softgel containing a suspension of the drug in an oil following single-dose administration in 12 healthy human volunteers

- *Decreased plasma variability*
- **High variability in drug plasma levels** is a common characteristic of **drugs with limited bioavailability**.

- By dosing drug optimally in **solution**, the plasma level **variability** of such drugs can be **significantly reduced.**

- The cyclic polypeptide drug cyclosporine (Sandimmun Neoral®) benefits from such an approach by using a microemulsion preconcentrate in a softgel

2. Patient compliance and consumer preference

- Compared to tablets and hard gelatin capsules, softgels were perceived to be appealing dosage forms to most consumers.

- Consumers expressed their preference for softgels in terms of
- (a) ease of swallowing,
- (b) absence of taste
- (c) convenience.

3. Safety for potent and cytotoxic drugs

- The mixing, granulation and compression/filling processes used in preparing tablets and hard-shell capsules can generate a significant quantity of airborne powders.

- This can be of great concern for highly potent or cytotoxic compounds in terms of the operator and environmental protection required for satisfactorily safe product manufacture.

- By preparing a solution or suspension of drug, where the active component is essentially protected from the environment by the liquid, such safety concerns can be significantly reduced.

4. Oils and low melting-point drugs

- When the pharmaceutical active is an oily liquid, has a melting point less than about 75°C or proves difficult to compress, liquid filling of softgels is an obvious approach to presenting a solid oral dosage form.

- If the drug is an oily liquid, then it can be encapsulated directly into a softgel **without adding a further diluent**.

- Other low melting-point drugs may be formulated **with a diluent oil** in order to ensure satisfactory liquid flow and dosing into softgels.

5. Dose uniformity of low-dose drugs

- In pharmaceutical manufacture **liquid dosing avoids** the difficulties of **poor powder flow** and therefore poor content uniformity.

- **This is an important benefit for formulations containing drug doses in the microgram region.**

- Attempts to produce adequate mixtures of small quantities of a low-dose drug in larger quantities of powdered excipients for tabletting or hard-shell filling are often unsatisfactory.

- In contrast, **improved homogeneity is achieved by dissolving** the drug in a liquid and then encapsulating the liquid matrix in a softgel.

6. Product stability

- If a drug is subject **to oxidative or hydrolytic** degradation, the preparation of a liquid-filled softgel may prove beneficial.

1. The liquid is prepared and encapsulated **under a protective nitrogen atmosphere** and **the subsequently dried shell has very low oxygen permeability.**

2. By formulating in **a lipophilic vehicle** and packaging in well designed blister packs using materials of low moisture transmission, the drug can be protected from moisture.

- **Conversely, it is well accepted that, in a solution, the drug may be more reactive than in the dry state and therefore potentially less stable.**

- **The appropriate choice of excipients, an understanding of the drug degradation pathways and appropriate preformulation studies are vital to achieving a stable product**

MANUFACTURE OF SOFTGELS

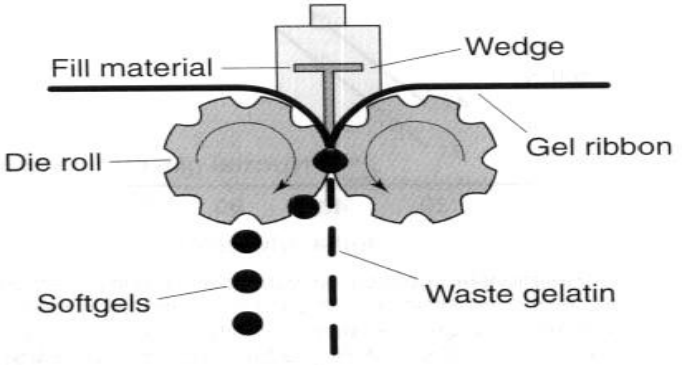
- Softgel capsules were used in the 19th century as a means of administering bitter-tasting or liquid medicines.
- These were manufactured individually by preparing **a small sack of gelatin** and allowing it to set.
- Each sack, or gelatin shell, was then filled with the medication and heat-sealed.

- This method of manufacture was improved using a process that involved **sealing two sheets of gelatin film between a pair of matching flat brass dies.**

- **Each die contained pockets** into which the gelatin sheet was pressed and into which the medication was filled.

- **The pressure between the two plates** enabled individual capsules to be cut out from the die mould, and these capsules were subsequently dried.

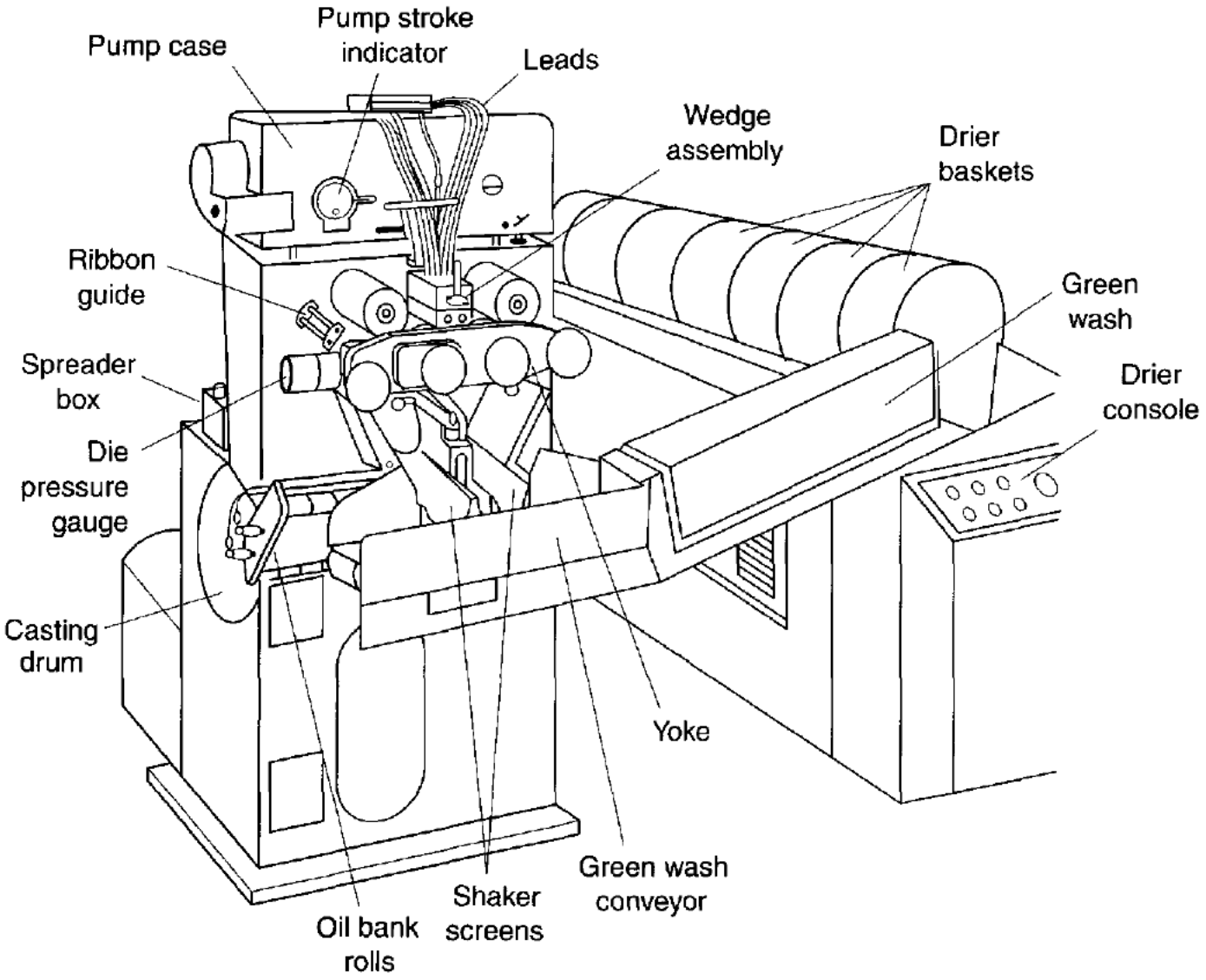
rotary die encapsulation machine



- it was not until the invention of **the rotary die encapsulation machine** by Robert Pauli Scherer in 1933 that liquid-fill capsules could be manufactured on a production scale.

- The rotary die process involves **the continuous formation of a heat seal between two ribbons of gelatin, simultaneous with dosing of the fill liquid into each capsule**.

- Although the speed and efficiency of the manufacturing process have improved greatly in recent years, the basic manufacturing principle remains essentially unchanged.


Pump case
Pump stroke indicator
Leads
Wedge assembly
Drier baskets
Ribbon guide
Green wash
Spreader box
Drier console
Die pressure gauge
Casting drum
Yoke
Green wash conveyor
Shaker screens
Oil bank rolls

- Before the encapsulation process takes place, there are **two sub-processes** that are often carried out simultaneously, yielding the two components of a softgel.

- These are:

- (a) the gel mass which will provide the softgel shell,

- (b) the fill matrix for the contents.

the gel mass

- The gel mass is prepared by:
- dissolving the gelatin in water at approximately 80°C and under vacuum,

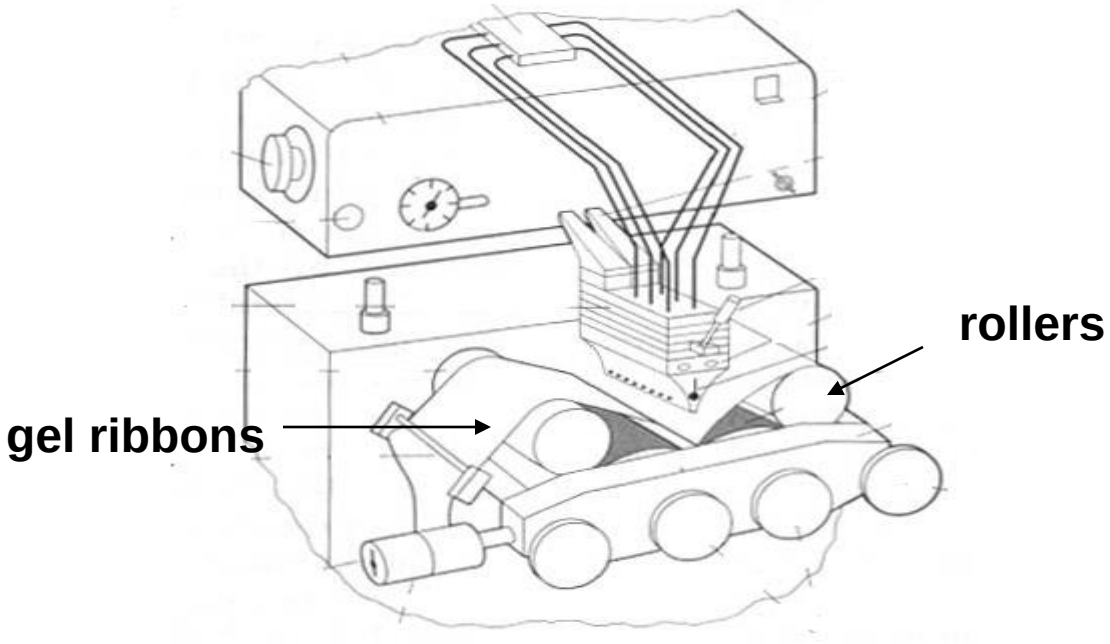
- followed by the addition of the plasticizer, for example glycerol.

- Once the gelatin is fully dissolved then other components, such as colours, opacifier, flavours and preservatives, may be added.

- The hot gel mass is then supplied to the encapsulation machine through **heated transfer pipes** by a **casting method** that **forms two separate gelatin ribbons**, each approximately **150 mm wide**.

- During the casting process the gelatin passes through the **sol-gel transition** and the **thickness** of each gel ribbon is controlled to **± 0.1 mm**, in the range of about **0.5-1.5 mm.** The thickness is checked regularly during the manufacturing process.

- The two gel ribbons are then carried through **rollers** (at which a small quantity of vegetable oil lubricant is applied) and onwards to the rotary die encapsulation tooling.
- Each ribbon provides one half of the softgel.
- It is possible to make bicoloured softgels using gel ribbons of two different colours.



The liquid fill matrix

- The liquid fill matrix containing the active drug substance is manufactured separately from preparation of the molten gel.

- Manufacture of the active fill matrix involves **dispersing or dissolving** the drug substance in the non-aqueous liquid vehicle using conventional mixer-homogenizers.

- **A number of different parameters are controlled during the preparation of the active fill matrix**, depending on the properties of the drug substance.

- For example:

1. oxygen-sensitive drugs are protected by mixing under vacuum and/or inert gas; and in some cases an antioxidant component may be added to the formulation.

2. Also, if the drug substance is present as a suspension in the liquid fill matrix then it is important to ensure that particle size of the drug does not exceed approximately 200 µm.

Why?

- By doing this it is possible to ensure that **drug particles do not become trapped within the capsule seal**, **potentially leading to loss of integrity of the softgel.**

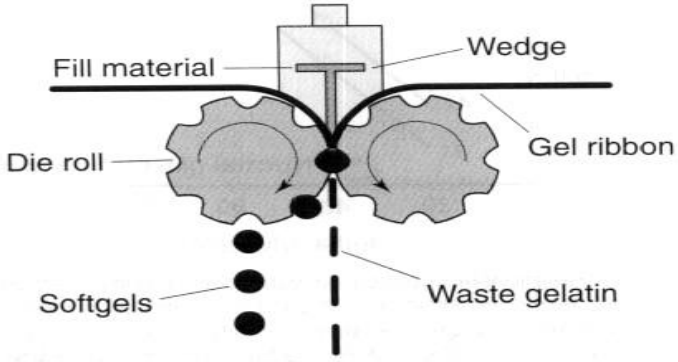
- **Rotary die encapsulation** is **the process by which the gel ribbon and the unit dose of liquid fill matrix are combined to form the softgel.**

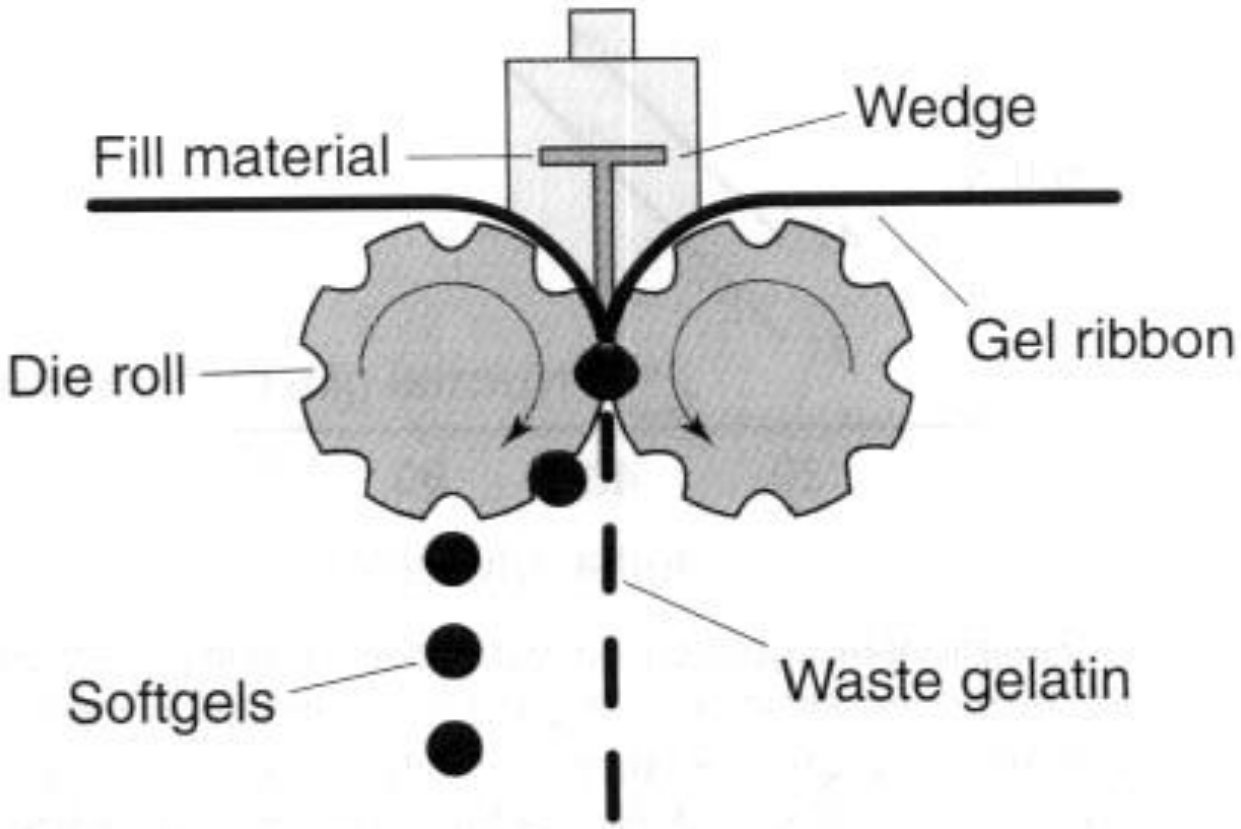
- **The process involves careful control of three parameters:**

1. **Temperature**. This controls the heat available for capsule seal formation.

2. **Timing**. The timing of the dosing of unit quantities of fill matrix into the softgel during its formation is critical.

3. **Pressure**. The pressure exerted between the two rotary dies controls the softgel shape and the final cut-out from the gel ribbon.





a simplified diagram representing the mechanism of softgel formation using contrarotating dies and the wedge-shaped fill-matrix injection system.

- Accurately **metered volumes of the liquid fill matrix are injected** from the **wedge device** into the space between the gelatin ribbons as they pass between the die rolls.

- The wedge-shaped **injection system** is itself heated to approximately **40°C**.

- The injection of liquid between the ribbons forces **the gel to expand into the pockets of the dies**, which govern the size and shape of the softgels.

- **The ribbon** continues to flow past the heated wedge injection system and is then **pressed between the die rolls.**
- Here the two softgel capsule halves are **sealed together by the application of heat and pressure**.

- The capsules are cut automatically from the gel ribbon by raised rims around each die on the rollers.

- After manufacture the capsules are passed through a **tumble drier** and then, to complete the drying process, **spread on to trays and stacked in a tunnel** drier that supplies air at 20% relative humidity.

- The tunnel drying process may take 2 or 3 days, or possibly as long as 2 weeks, depending on the specific softgel formulation.

- Finally, the softgels are **inspected and packed** into bulk containers in order to prevent further drying and for storage.

FORMULATION OF SOFTGELS

- **Gelatin shell formulation:**
- *Gelatin:*
- A large number of different gelatin shell formulations are available, depending on the nature of the liquid fill matrix.

- Most commonly the gelatin is alkali- (or base-) processed (**type B**) and it normally constitutes **40%** of the wet molten gel mass.

- Type A acid-processed gelatin can also be used.

Plasticizers:

- Plasticizers are used to **make the softgel shell elastic and pliable.**
- They usually account for **20-30%** of the wet gel formulation.

- The most common plasticizer used in softgels is **glycerol**, although **sorbitol and propylene glycol** are also frequently used, often in combination with glycerol.

- The **amount and choice of the plasticizer** contribute to **the hardness** of the final product and may even affect its **dissolution or disintegration characteristics**, as well as its **physical and chemical stability**.

- Plasticizers are selected on the basis of their **compatibility** with the fill formulation, **ease of processing**, and **the desired properties of the final softgel**, **including hardness**, **appearance, handling characteristics and physical stability**.

- One of the most important aspect of softgel formulation is to ensure that there is minimum interaction or migration between the liquid fill matrix and the softgel shell.

- The choice of plasticizer type and concentration is important in ensuring optimum compatibility of the shell with the liquid fill matrix.

Water

- Water usually accounts for **30-40% of the wet gel** formulation

- its presence is important to ensure proper processing during gel preparation and softgel encapsulation.

- Following encapsulation, excess water is removed from the softgels through controlled **drying**.

- In **dry softgels** the equilibrium water content is typically in the range **5-8% w/w**, which represents the proportion of water that is bound to the gelatin in the softgel shell.

Colourants/opacifiers:

- Colourants (soluble dyes, or insoluble pigments or lakes) and opacifiers are typically used at **low concentrations** in the wet gel formulation.
- Colourants can be either synthetic or natural, and are used to impart the desired shell colour for product identification.

- An opacifier, usually **titanium dioxide**, may be added to produce an opaque shell:

1. when the fill formulation is a suspension,
2. or to prevent photodegradation of light-sensitive fill ingredients.

- Titanium dioxide can either be used:

1. alone to produce a white opaque shell
2. or in combination with pigments to produce a coloured opaque shell.

Formulation of softgel fill materials

- In terms of formulation requirements, the softgel should be considered as **a biphasic dosage form**: a solid-phase capsule shell and a liquid-phase fill matrix.

- Although it is possible to incorporate a drug in the shell of a softgel, the overwhelming majority of products have the active ingredient(s) within the fill matrix.

Lipophilic liquids/oils

- **Triglyceride oils**, such as **soya bean oil**, are commonly used in softgels.

- When used alone, however, their capacity to dissolve drugs is limited.

- Nevertheless, active ingredients such as **hydroxycholecalciferol and other vitamin D analogues, plus steroids such as oestradiol**, can be formulated into **simple oily solutions** for encapsulation in softgels.

Hydrophilic liquids

- Polar liquids with a sufficiently **high molecular weight** are commonly used.

- Polyethylene glycol (**PEG**) is the most frequently used, for example PEG 400, which has an average molecular weight of approximately 400 Da.

- **Smaller hydrophilic molecules**, such as **ethanol or indeed water**, can be incorporated in the softgel fill matrix in low levels, typically **below 10%** by weight.

Self-emulsifying oils

- A combination of a **pharmaceutical oil and a non-ionic surfactant** such as **polyoxyethylene sorbitan mono-oleate** can provide an oily formulation which **disperses rapidly in the gastrointestinal fluid**.

- The resulting oil/surfactant droplets enable rapid transfer of the drug to the absorbing mucosa and subsequent **drug absorption**.

Microemulsion and nanoemulsion systems

- A **microemulsion** of a **lipid-surfactant-polar liquid system** is characterized by its **translucent single-phase appearance**.
- The droplet size is in the submicrometre range, and light scattering by these droplets results in a **faint blue colouration known as the Tyndall effect.**
- A **nanoemulsion** is a similar system but contains emulsion droplets in the **100 nm size range**.
- Microemulsion and nanoemulsion systems have the advantage of a **high capacity to solubilize drug** compounds and to **retain the drug in solution even after dilution** in gastrointestinal fluids.

- In order to produce a microemulsion or nanoemulsion in the gastrointestinal tract a '**preconcentrate**‘ is formulated in the softgel fill matrix.

- In other words, the preconcentrate fill matrix contains **a lipid component and one or more surfactants**, which spontaneously form a microemulsion or a nanoemulsion on dilution in an aqueous environment, such as in gastrointestinal fluid

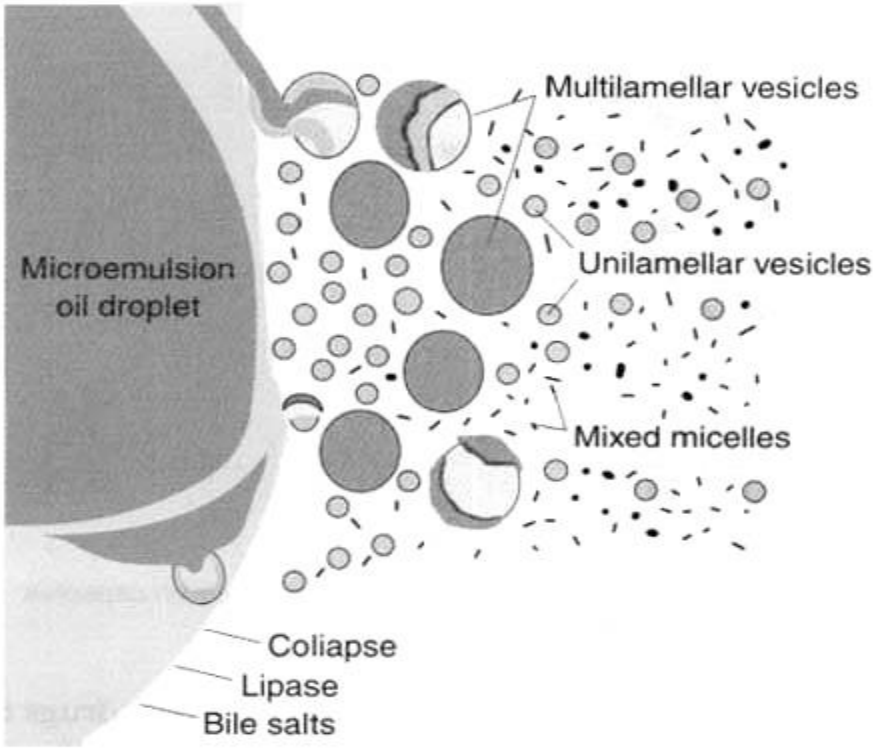


Diagram of proposed nanoemulsion/microemulsion dissolution mechanism.

Suspensions

- Drugs that **are insoluble in softgel fill matrices** are formulated as suspensions.
- The **continuous phase** may be **any of the vehicles** described above.
- Suspension formulations provide significant advantages for certain **low-solubility drugs** which are very poorly absorbed after oral administration.
- With the **appropriate choice of excipients**, softgel suspensions can have **improved bioavailability**.

Lipolysis systems

- The advantage of the **microemulsion** approach lies in the **high surface area** presented by the microemulsion particles, which are essentially **surfactant micelles swollen with solubilized oil and drug.**

- This high surface area facilitates the **rapid diffusion of drug from the dispersed oil phase into the aqueous intestinal fluids**, until an equilibrium distribution is established.

- Thereafter, as drug is removed from the intestinal fluids via enterocyte absorption, it is quickly replenished by the flow of fresh material from the microemulsion particles.

- the lipid components of a softgel fill matrix, which comprise **triglycerides or a partial (mono-/di-) glyceride**, are often subject to **intestinal fat digestion** or lipolysis.

- Lipolysis is the term used to describe the action of the enzyme **pancreatic lipase** on triglycerides and partial glycerides, to form 2-monoglycerides and fatty acids.

- These **2-monoglycerides and fatty acids, known as lipolytic products**, then **interact with bile salts to form small droplets, or vesicles.**

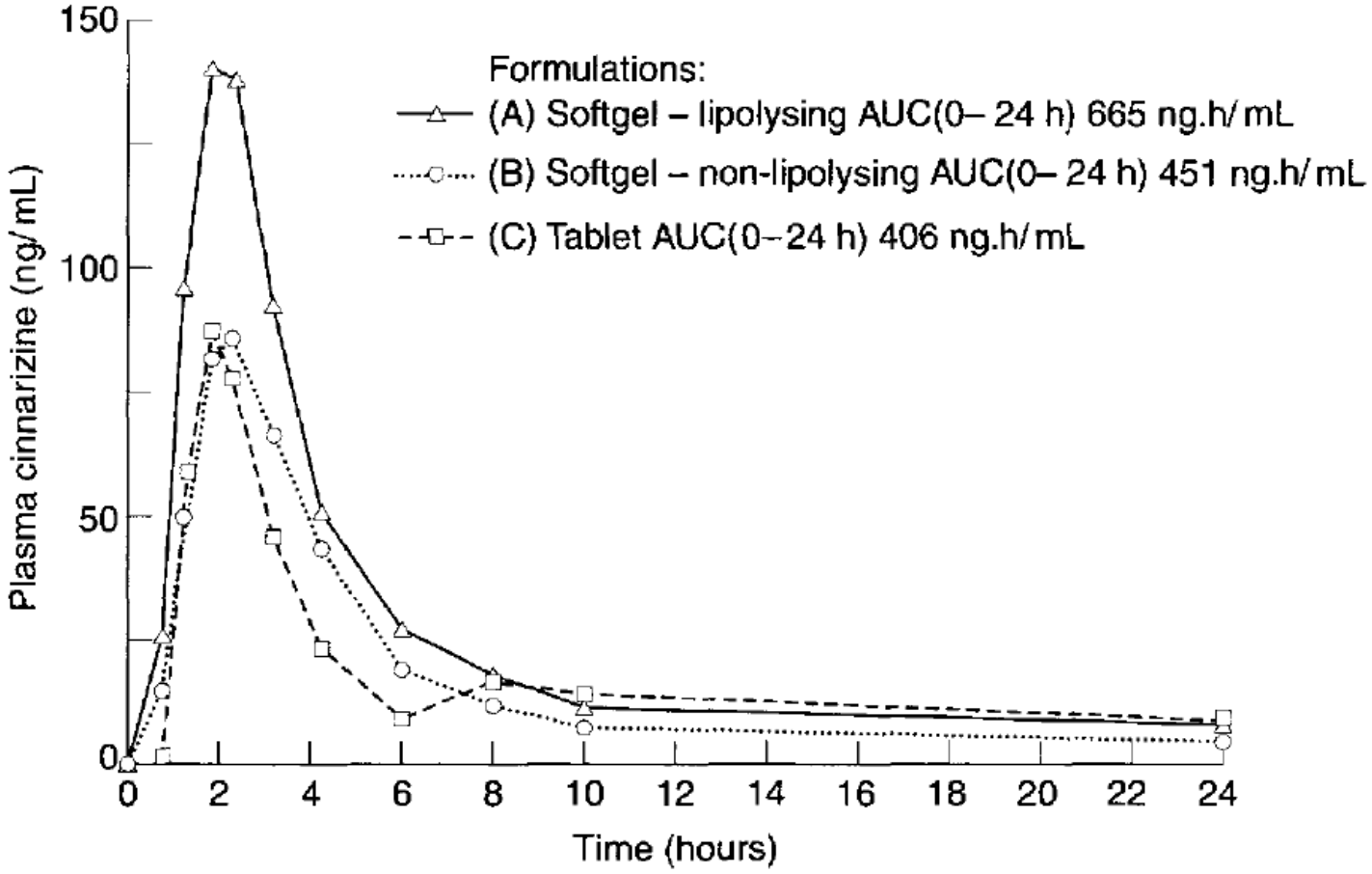
- These **vesicles are broken down into smaller and smaller vesicles**, ultimately resulting in the **formation of mixed micelles that are approximately 3-10 nm in size**.

- If a drug compound possesses **higher solubility in lipolytic products than in triglyceride oils**, then it is advantageous for lipolysis to occur in the intestinal lumen.

- In this way, the process of lipolysis promotes the formation of an **excellent dissolution medium for the drug**, namely **lipolytic products.**

- On the other hand, the absorption of a drug compound may be adversely affected by the **presence of bile salt**, and in such a case it may be advantageous for **lipolysis to be reduced or blocked completely.**

- It has been found that certain **hydrophilic and lipophilic surfactants** have the ability to **block or promote** lipolysis respectively



Plasma concentration versus time curves for three formulations of cinnarizine in the dog (n=6)

End of lecture