CHAPTER 1

INTRODUCTION
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1.1 Introduction, objectives and scope of the Investigation

The areas of current interest in pharmaceutical biotechnology which have a significant impact on clinical therapy are enhancement of dissolution rate and bioavailability of insoluble and poorly soluble drugs and development of controlled release drug delivery systems. Many of the modern drugs belong to the Class II category under Biopharmaceutical Classification System (BCS), which are characterized by low solubility and high permeability. These drugs are insoluble or poorly soluble in water and aqueous fluids in the pH range of g.i. tract i.e. pH 1.0 – 7.5 and exhibit low and variable dissolution and bioavailability. They also pose problems in the design of controlled release products due to their insoluble character. Hence there is a great need to develop technologies for these BCS – Class II drugs for enhancing their oral bioavailability as well as for obtaining controlled release. Sparfloxacin (antibacterial), nifedipine (antianginal and antihypertensive) and nimodipine (antianginal and antihypertensive) belong to BCS – Class II and require enhancement in solubility and dissolution rate for increasing their oral bioavailability and for development of controlled release drug delivery systems. The most effective option for increasing the dissolution rate is improvement of the solubility through formulation approaches such as use of salt forms, soluble products, surfactants, specific polymorphs and by complexation phenomena. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years for enhancing the solubility and dissolution rate. Cyclodextrins modify the physicochemical properties of the drug molecules by forming inclusion complexes enclosing insoluble drug molecules in their hydrophobic interior.

The present investigation, biotechnological studies on cyclodextrin complexation, has been undertaken with an overall objective of studying the complexation between two cyclodextrins, β-cyclodextrin (β-CD) and hydroxy propyl β-cyclodextrin (HPβ-CD) and the three drugs selected namely sparfloxacin (SPF), nifedipine (N) and nimodipine (NM). The feasibility of employing cyclodextrin complexation for enhancing the solubility, dissolution rate and bioavailability and for obtaining controlled release of these drugs was also investigated.
The specific objectives and scope of the investigation are as follows:

1. To study the complexation of SPF, N, and NM with β-CD and HPβ-CD by phase solubility studies.
2. To study the effect of cyclodextrins (β-CD and HP β-CD) and their concentrations on the solubility and dissolution rate of SPF, N and NM.
3. To prepare and evaluate the solid inclusion complexes of SPF, N and NM with β-CD and HP β-CD by different methods.
4. To evaluate the kinetics of dissolution of SPF, N and NM from the solid cyclodextrin inclusion complexes.
5. To evaluate the feasibility of formulating the solid cyclodextrin inclusion complexes of SPF, into compressed tablets and to evaluate the various characteristics of the resulting tablets including dissolution rate and dissolution efficiency.
6. To evaluate the stability of sparfl oxacin tablets formulated employing its cyclodextrin complexes as per ICH guidelines.
7. To evaluate the pharmacokinetics and bioavailability of sparfl oxacin from the tablets formulated employing SPF-βCD complexes in comparison to those formulated employing SPF as such.
8. To formulate and evaluate oral controlled release tablets of nimodipine.
9. To evaluate the application of cyclodextrin complexation in the design of oral controlled release tablets of nimodipine, an insoluble drug.

Extensive laboratory experimentation was carried out to achieve the above mentioned objectives and the results obtained are presented and discussed in the subsequent chapters.

1.2 Cyclodextrins

Cyclodextrins (CDs) are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose units that have a relatively hydrophobic central cavity and hydrophilic outer surface. The α,β- and γ-CDs are the most common natural or parent CDs consisting of six, seven and eight D-glucopyranose units respectively, linked by α-1,4-glycosidic bonds into a macro cycle. CDs are classical examples of compounds that form inclusion complexes.
1.2.1 Physicochemical properties

The structure of β-cyclodextrin is shown in Fig. 1.1. Each glucopyranose unit contains two secondary alcohols at C-2 and C-3 and a primary alcohol at C-6 position providing 21 sites for chemical modification and derivatisation. Numerous derivatives have been prepared and described in the literature. However, only the derivatives containing the hydroxy propyl (HP), methyl (M), sulfobutyl ether (SBE) and triethyl (TE) substituents in β-CD (Fig. 1.1) are in a position to be used as new pharmaceutical excipients. The characteristics of important CDs are summarized in Table 1.1.

Fig. 1.1: Structures of β-CD and its derivatives
### TABLE 1.1

**CHARACTERISTICS OF IMPORTANT CDs**

<table>
<thead>
<tr>
<th>Property</th>
<th>α-CD</th>
<th>β-CD</th>
<th>γ-CD</th>
<th>HPβ-CD</th>
<th>MβCD*</th>
<th>SBE-β-CD*</th>
<th>TE-β-CD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of glucose units</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>972</td>
<td>1135</td>
<td>1297</td>
<td>1390</td>
<td></td>
<td></td>
<td>1723</td>
</tr>
<tr>
<td>Cavity diameter, Å</td>
<td>4.7-5.3</td>
<td>6.0-6.5</td>
<td>7.5-8.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solubility (20°C) (g/100 ml)</td>
<td>14.5</td>
<td>1.65</td>
<td>23.2</td>
<td>50.70</td>
<td>31-57</td>
<td>5-10</td>
<td>1.8x10-3</td>
</tr>
</tbody>
</table>

*: Derivatives will have different molecular weights depending on degree of substitution

The chemical structure of these CDs show that cyclic nature of the molecule and structure of CD takes the shape of a truncated cone. The hydroxyls located at C-2, C-3, and C-6 positions provide the hydrophilic exterior of the cone and are responsible for the aqueous solubility of CDs. The interior of cone is hydrophobic due to the presence of the glycosidic ether oxygen at O-4 and the hydrogens attached to C-3 and C-5 and thereby provides a cavity for the inclusion of hydrophobic compounds. Inclusion complexes are formed when a guest molecule (drug) is partially or fully included inside the hydrophobic cavity of CDs without covalent bonding. The cavity varies in size with different CDs. The inclusion of hydrophobic drugs inside the cavity of CD alters their physicochemical and pharmaceutical properties. CDs can improve properties such as solubility, dissolution rate and bioavailability of drugs by inclusion complexation and thereby potentially serving as novel drug carriers. Various complexes with different ratios of drug to CD molecules can be formed, depending on the type of CD used and the size and physicochemical characteristics of the drug molecule. In dilute solutions and/or if the drug fits entirely into CD cavity, a 1:1 complex results. However, if the cavity is large enough, two drug molecules may be accommodated resulting in the formation of 2:1 complex. Conversely, if the drug is very large, several CD molecules might enclose the drug for the formation of 1:2 or higher order complexes.
Complexation of drugs by CDs does not interfere with their activity because complexation is a rapidly reversible process.

1.2.2 Methods for Detection of Inclusion Complex Formation and Determination of Complex Stability Constant

One of the most interesting properties of CDs is their ability to form inclusion complexes with a wide variety of guest molecules. Molecular encapsulation may occur both in solution and in solid state. In solution there is equilibrium between complexed and non-complexed guest molecules, in solid state guest molecules can be enclosed within the cavity or may be aggregated to the outside of CD molecule. Upon inclusion within the CD cavity a guest molecule experiences changes in its physiochemical properties. These changes provide methods to detect whether guest molecules are really included in the CD cavity.

1.2.2.1 Detection of inclusion complexation in the solution state

Detection of inclusion complexation in solution state can be done by spectroscopic methods like Ultraviolet/visible (UVVIS), Fluorescence, Circular Dichroism, Electron Spin Resonance (ESR), and Nuclear Magnetic Resonance (NMR) methods. The $^1$H-NMR and $^{13}$C-NMR spectroscopic studies can also be used to determine the direction of penetration of guest molecules into the CD cavity. Other methods include Polarography, Conductivity measurement, Microcalorimetry and Solubility methods.

Phase solubility technique is the one of the widely used methods to detect the inclusion complexation in solution state.

The general experimental operation in studying molecular interactions by means of phase solubility method entails the addition of an equal weight (inconsiderable excess of its normal solubility) of a slightly soluble compound, S (substrate or guest) into each of several vials containing increasing concentrations of a relatively soluble compound, L (Ligand or host or complex agent), which are closed and brought to solubility equilibrium at constant temperature.
The solution phases are then analysed, by any suitable means, for their total concentration of compound S (guest), no matter what its molecular state may be.

A phase diagram is constructed by plotting, on the vertical axis, total molar concentration of S found in the solution phase against the molar concentration of L. The phase diagrams are observed to fall into two main classes, type A and type B with some variation within the classes (Fig. 1.2).

![Phase solubility diagram](image)

Fig. 1.2 Phase solubility diagram

The type A can be further classified in subtypes $A_L$, $A_P$ and $A_N$, where the guest solubility of first type increases linearly with cyclodextrin concentration while those of the second and third types deviate positively and negatively, respectively from the straight line. The complex formation with a $1:1$ stoichiometry gives the $A_L$ type diagram, whereas the higher order complex formation in which more than one-cyclodextrin molecules are involved in the complexation gives the $A_P$-type. The interaction mechanism for the $A_N$-type is complicated, because of significant contribution of...
solute-solvent interaction to the complexation. In the case of the B₃ type, the initial ascending portion of the solubility change is followed by a plateau region and then a decrease in the solubility at higher cyclodextrin concentrations accompanying a microcrystalline precipitation of the complex. The B₃-type diagram is indicative of the formation of insoluble complexes in water.

The stability constant (Kₐ) and stoichiometry of complexes are determined by analyzing quantitatively the phase solubility diagram.

1.2.2.2 Detection of inclusion complexation in the solid state

Detection of the inclusion complexation in solid state can be done by Powder X-ray diffractometry, single crystal X-ray structure analysis, Thermo analytical, Thin layer chromatography, paper chromatography, Infrared spectroscopy. Scanning electron microscopy and Dissolution study methods².

1.2.3 Pharmacokinetics of CDs

The parent CDs are poorly absorbed from the gastrointestinal tract (GIT). Oral absorption studies have shown ≤ 2%, 0.1 – 0.3% and ≤ 0.1% absorption respectively with α-, β-, and γ-CDs. The majority of an orally administered dose of α- and β- CD is metabolized in the colon, both in rats and man, by colonic bacteria. The derivatised CDs are generally more resistant to hydrolysis in the GIT than the parent CDs. Oral absorption of HP-βCD in dogs is 3.3%, ≤ 0.1% in rats and no absorption in humans. About 60% of the dose is excreted unchanged in faeces. The methylated derivatives have shown somewhat greater oral absorption in the range 6.3 – 9.6% in rats.

Intravenously administered CDs disappear rapidly from the systemic circulation and are excreted mainly through the kidneys. The t₁/₂ of HP-β-CD was 24 minutes in rats, 48 minutes in dogs and 72-108 minutes in humans, α- and β-CDs are excreted almost completely in their intact form, but some metabolism was observed with γ-CD. Little or no distribution of CDs into other tissues or storage compartments were observed.
1.2.4 Safety of CDs

Parent CDs are reported to be non-toxic and safe even at very high oral doses. Mortality was not observed even in animals treated with the highest possible oral doses. Therefore, the LD$_{50}$ in rats was reported to be greater than 12.5, 18.8 and 8.0 g/kg body weight for $\alpha$- and $\beta$- and $\gamma$-CD respectively. In another study $\alpha$- and $\beta$-CDs produced no toxic effects when fed to rats for 30-90 days at 1% of the diet or at 1 and 2 g/kg daily dose.

The safety of orally administered $\beta$-CD has been investigated in several studies with extensive evaluation of haematology, blood chemistry, urine analysis and Necropsy. No significant toxic effects were observed in any of these studies after oral administration of $\beta$-CD to mice, rats and dogs.

The oral safety of HP$\beta$-CD has been assessed in mice, rats and dogs for dosing periods upto 2, 2, and 1 year respectively. Doses reached as high as 5000 mg/kg/day. No adverse effects were noticed. The oral safety of SBE-$\beta$-CD derivative is currently under evaluation.

Numerous studies with the parent CDs have shown that their parenteral toxicity was observed primarily as renal and cytotoxicity (haemolysis and tissue irritation). The parenteral safety of CDs has not yet been established completely.

1.2.5 CDs as Drug Carriers

Cyclodextrins have several applications in pharmaceutical formulation as drug carriers, which are as follows:

1.2.5.1 Improvement of solubility

CD complexation results in improved solubility of hydrophobic, water insoluble or poorly soluble drugs when they are molecularly enclosed in the hydrophobic cavity of CDs. This property of CDs has important applications in solution formulations.
CD complexation provides an alternative to the use of non-aqueous solvents or large volumes. β-CD and its hydroxypropyl and sulfobutyl ether derivatives, which can be safely administered by parenteral routes, greatly enhances the aqueous solubility of drugs. These CDs can be used to replace co-solvents such as ethanol, propylene glycol and lipids as well as provide an alternative to the use of emulsions and suspensions. Some of the marketed liquid formulations based on CDs are as follows.

- PGE, - αCD – an intra-arterial infusion (Prostandin of M/s Ono, Japan and Prostavasin of M/s Schwarz Pharma, Germany and Italy).
- Ziprasidone – SBEβ-CD – an intramuscular injection (Zeldox of M/s Pfizer, Sweden and USA).
- Itraconazole – HPβ-CD – oral and i.v. solutions (Sporanox of M/s Janssen, USA and Belgium).
- Piroxicam-β-CD – oral liquids in several countries under various trade names.
- Iodine β-CD – gargling solution (Mena-Gargle of M/s Kyushin of Japan).
- Chloramphenicol – Mβ-CD – an eye drop solution (Clorocil of M/s Oftalder of Portugal).
- Diclofenac-HPβ-CD – an eye drop solution – (M/s Ciba-Vision of Switzerland).

1.2.5.2 Enhancement of dissolution rate and bioavailability

The drug-CD complexes often exhibit improved dissolution rate due to enhanced solubility when compared to other formulations of the drug. These two features can provide for an improvement in oral bioavailability when the solubility and the rate of dissolution are limiting the availability of the drug for absorption. Several hundred studies with a broad range of CDs and therapeutic agents have described the enhancement of dissolution rate and bioavailability of poorly soluble drugs from solid dosage forms.
Some of the important therapeutic agents studied in recent years for enhancement of their dissolution rate and bioavailability through CD complexation include piroxicam, tenoxicam, celecoxib, rofecoxib, meloxicam, nimesulide, nifedipine, nimodipine, nicardipine, miconazole, griseofulvin, itraconazole, paclitaxel, acyclovir and doxorubicin.

Some of the marketed solid formulations based on CDs are as follows:

- Cefotiam Hexetil HCl - αCD tablets – Pansporin T of M/s Takeda, Japan.
- Piroxicam-β-CD tablets and suppositories in several countries under various trade names.
- PGE₂-βCD sublingual tablets – Prostarmon E of M/s Ono, Japan.
- Benexate-β-CD capsules – Ulgut of M/s Teikoku, Japan.
- Cephalosporin-βCD tablets – Melact of M/s Meiji Seika, Japan.
- Nimesulide-βCD tablets – Nimedox of M/s Ital Farmaco, Italy and Mesulid Fast of M/s Novartis, Switzerland.
- Chlordiazepoxide βCD tablets – Transilium of M/s Gador, Argentina
- Omeprazol-βCD capsule – M/s Hexal, Germany.
- Cisapride-HPβCD suppository – prepulsid of M/s Janssen-Cilag, Belgium.

1.2.5.3 Reduction of unpleasant side effects and bitter taste

CD complexation also reduces the contact time between the drug and the tissue mucosa, thereby, minimizing tissue irritation produced by drugs. CD formulations of non-steroidal anti-inflammatory drugs such as naproxen, diclofenac and piroxicam caused fewer gastric lesions than produced by the drug alone. Formulations containing CDs have also shown less irritation than non-CD containing formulations for ophthalmic, intravenous, and intramuscular administration. Complexation with CDs can also have the effect of reducing the amount of contact with taste receptors that results in taste masking. Complexation has been used to mask the unpleasant bitter
taste of a number of drugs such as oxyphenonium bromide, propantheline, acetaminophen.

1.2.5.4 Improvement of drug stability

CDs have been shown to stabilize drugs to hydrolysis, hydrolytic dehalogenation, oxidation, decarboxylation and isomerization, both in solution and in solid state. The nature of stabilization or destabilization depends on the CD used and on the position of the drug inside the CD. Enhanced stability usually results when the area or site of instability of the drug is located fully within the CD cavity. In the solid state, stabilization of drugs to degradation has been reported for drugs such as nicardipine, colchicines, prostaglandin E, diclofenac, and sulfamethoxazole.

1.2.5.5 Reduction in volatility

CD complexation has been shown to reduce the volatility and improve the stability of many compounds. Examples include lemon oil and other flavouring agents, clofibrate, isosorbide-5-mono nitrate and nitroglycerine.

1.2.5.6 As sustained release carriers

While the hydrophilic CDs (β-CD, HP-β-CD) enhance the solubility, dissolution and bioavailability of the drugs; the hydrophobic CD derivatives such as alkylated and acylated CDs are useful as sustained release drug carriers for water-soluble drugs and peptides because they tend to decrease the solubility of the guest molecules. Hydrophobic CD derivatives such as diethyl-β-CD, triethyl-β-CD, tributanoyl-β-CD, triacetyl-β-CD, aluminium-β-CD sulphate, carboxymethyl, ethyl-β-CD have been evaluated as carriers for sustained release. Sustained release formulations of several drugs such as diltiazem, buserelin acetate, flufenamic acid, nitroglycerine, isosorbide dinitrate, salbutamol, and captopril have been tried employing hydrophobic CD derivatives mentioned above and the results obtained are promising and showed that the hydrophobic CDs have great potential to act as carriers for sustained release.

Several reviews describe the physico-chemical aspects and applications of cyclodextrins.²⁻¹¹
1.3 Dissolution rate and bioavailability – methods of enhancement

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Together with the permeability, the solubility behaviour of a drug is key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole and chloramphenicol come immediately to mind. With the recent advent of high throughput put screening of potential therapeutic agents, the number of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

The most important property of a dosage form is its ability to deliver the active ingredients to its site of action in an amount sufficient to elicit the desired pharmacological response. This property of the dosage form has been variously referred to as its physiological availability, biologic availability or bioavailability. Bioavailability is defined more precisely as the rate and extent of absorption of a drug from its dosage form into the systemic circulation. Accordingly, the absorption of an intravenously administered drug is instantaneous and complete. However, for reasons of convenience and stability most drugs are administered orally after first being formulated into dosage forms usually tablets or capsules. The rate and extent of absorption from such dosage forms is usually not precisely known as it is affected by a number of factors related to the drug, dosage form and patient.

Dosage form related factors which can produce profound differences in drug bioavailability include formulation and manufacturing. Variables such as particle size, the chemical form and solubility of the drug, the type and quantity of the excipients used, the compaction pressure etc. Among the patient related factors those over which the physician and/or the patient can exert some control include the time of administration of the drug relative to meals, coadministration of other drugs which may influence the absorption and compliance of the patient with the instructions of the physician, pharmacist or nurse. The patient related factors which
normally cannot be controlled but for which some allowance (or adjustment can be made include age, disease state, abnormal genital characteristics and/or gastrointestinal physiology. The active ingredient in a solid dosage form must undergo dissolution before it is available for absorption in the gastrointestinal tract. Dissolution forms the rate limiting step in the absorption of drugs from solid dosage forms especially when the drug is poorly soluble.

1.3.1 Dissolution and absorption of drugs from solid dosage forms

When a drug is administered in a solid dosage form in order for the drug to be absorbed, it must be first available in solution. The usual steps involved in the absorption process are represented in Scheme 1.1.

Scheme 1.1

Scheme 1.1 indicates the processes involved in the absorption of drugs after oral administration in the form of a tablet or capsule. Dissolution of the drug occurs not only from the fine particles of the drug ultimately produced but also to a small degree from intact dosage form before its disintegration and from fragments and agglomerates produced after disintegration.
In vivo process 4 (Scheme 1.1) involves the absorption of the drugs. The drug dissolved in the gastrointestinal contents must diffuse in the aqueous fluids to the gastrointestinal barrier and then be transported through the barrier to the circulation. When the dissolution process is very much lower than the other processes, the dissolution essentially completely controls absorption rate. There is adequate evidence now available to conclude that the dissolution rate often partially or totally controls the rate of absorption. This is particularly true in the case of poorly soluble drugs. Examples of drugs for which dissolution rate limited absorption was observed include aspirin, tolbutamide, spiranolate, prednisone, methyl prednisone, ampicillin, griseofulvin, sulphamethazine and salicylamide. The rates of the process of disintegration, deaggregation and dissolution are all dependent upon the composition and method of preparation of the dosage form. These rates are all largely dependent upon pharmaceutical factors which the formulator can alter. A more quantitative description of the dissolution rate is given by the Noyes-Whitney equation based on diffusion layer model:

\[
\frac{dc}{dt} = \frac{D}{h} \times S \times (C_S - C) \quad \ldots \quad (1)
\]

where

- \( \frac{dc}{dt} \) = rate of dissolution
- \( S \) = surface area available for dissolution
- \( D \) = diffusion coefficient of the compound
- \( h \) = thickness of the diffusion layer
- \( C_S \) = saturation solubility
- \( C \) = concentration of drug in solvent at time \( t \).

In dissolution rate limited absorption 'C' is negligible compared to \( C_S \). Under well defined conditions of use, \( D \) and \( h \) are relatively constant values that are not conveniently altered to any degree by product formulation. Hence,

\[
\frac{dc}{dt} = k \cdot S \cdot C_S
\]
i.e. dissolution rate \( \propto \) surface area \( \times \) solubility. Apart from the physical features of the drug, many physiological parameters can also play a role in determining the dissolution rate. The physical and physiological parameters relevant to drug dissolution are tabulated in Table 1.2.

### TABLE 1.2

**PHYSICAL AND PHYSIOLOGICAL FACTORS IMPORTANT TO DRUG DISSOLUTION**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Physical factor</th>
<th>Physiological factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface area</td>
<td>Particle size</td>
<td>Native surfactants</td>
</tr>
<tr>
<td>Diffusion coefficient</td>
<td>Molecular size</td>
<td>Viscosity</td>
</tr>
<tr>
<td>Boundary layer thickness</td>
<td>Hydrophilicity (crystal structure)</td>
<td>Motility patterns, flow rate</td>
</tr>
<tr>
<td>Solubility</td>
<td></td>
<td>pH, buffer capacity, Bile, food components</td>
</tr>
<tr>
<td>Concentration of drug in solution</td>
<td></td>
<td>Permeability</td>
</tr>
<tr>
<td>Volume of GI contents</td>
<td></td>
<td>Secretions administered fluids</td>
</tr>
</tbody>
</table>

The main possibilities for improving dissolution according to Eq. 1.1 are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions. Of these possibilities changes in the hydrodynamics are difficult to invoke in vivo and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the lumenal fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution, the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media. However the most
attractive option for increasing the release rate is improvement of the solubility through formulation approach.

The following are the various formulation and chemical approaches that can be taken to improve the solubility or to increase the available surface area for dissolution.

1. Physical modification
   - Particle size
   - Micronization
   - Nanosuspensions
   - Modifications of the crystal habit
   - Polymorphs
   - Pseudopolymorphs (including solvates)
   - Complexation/solubilisation
   - Use of cyclodextrins
   - Use of surfactants
   - Drug dispersion in carriers
   - Eutectic mixtures
   - Solid dispersions
   - Solid solutions

2. Chemical modifications
   - Soluble prodrugs
   - Salts

The different methods available to enhance the dissolution and absorption rates of poorly soluble drugs are summarized in table 1.3.
TABLE 1.3

METHODS AVAILABLE TO ENHANCE THE DISSOLUTION AND ABSORPTION RATES OF POORLY SOLUBLE DRUGS

<table>
<thead>
<tr>
<th>Method</th>
<th>Examples of drugs for which increased dissolution and absorption is reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Methods which increase the solubility of the drug</td>
<td>Buffered aspirin\textsuperscript{13,14,15}, theophylla\textsuperscript{16} sulphanethoxazole\textsuperscript{17} and co-trimoxazole\textsuperscript{18}</td>
</tr>
<tr>
<td>2. Use of salts of weak acids and weak bases</td>
<td>Sodium, potassium and calcium salts of p-amino salicylic acid\textsuperscript{19}, sodium tolbutamide\textsuperscript{20}, tetracycline HCl\textsuperscript{21}, sodium and potassium salts of penicillin V\textsuperscript{22}, sodium phenobarbitone\textsuperscript{23}, theophylline isoprenolamine\textsuperscript{24}, and choline theophylline\textsuperscript{25}</td>
</tr>
<tr>
<td>3. Use of solvates and hydrates</td>
<td>Ampicillin anhydrate\textsuperscript{26}, theophylline, caffeine and glutethimide anhydrous forms\textsuperscript{27}, solvated forms of succinyl sulphathiazole and hydrocortisone\textsuperscript{27}</td>
</tr>
<tr>
<td>4. Use of selected polymorphic forms</td>
<td>Novobiocin\textsuperscript{28}, chloramphenicol palmitate\textsuperscript{29} and succinyl sulphathiazole\textsuperscript{30,31}</td>
</tr>
<tr>
<td>5. Complexation</td>
<td>Benzocaine-caffeine complex\textsuperscript{32}, digitoxin-hydroquinone complex\textsuperscript{33} and caffeine-ergot alkaloids\textsuperscript{34}</td>
</tr>
<tr>
<td>6. Prodrug approach</td>
<td>Prodrugs of ampicillin in pirampicillin\textsuperscript{35}, hetacillin\textsuperscript{36}, prodrugs of erythromycin\textsuperscript{37} in erythromycin-2'-N-alkylsuccinate and 2'-N-alkylglutaramate, prodrugs of carbenicillin\textsuperscript{38}, lincomycin and clindamycin\textsuperscript{39}</td>
</tr>
<tr>
<td>7. Use of surfactants</td>
<td>Hydrocortisone – Tween 80\textsuperscript{40}, amphotericin-(\beta)-Biosurfactants\textsuperscript{41} (sodium taurocholate and sod. Cholate) tolbutamide – Tween 20 and Tween 80\textsuperscript{42} sulphathiazole, prednisolone and chloramphenicol – polysorbate 80\textsuperscript{43}.</td>
</tr>
</tbody>
</table>
1. Methods which increase the surface area of the drug

<table>
<thead>
<tr>
<th></th>
<th>Methods which increase the surface area of the drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Micronization (particle size reduction to increase surface area)</td>
</tr>
<tr>
<td>2</td>
<td>Use of surfactant (to increase effective surface area by facilitating proper wetting)</td>
</tr>
<tr>
<td>3</td>
<td>Solvent deposition (deposition of poorly soluble drugs on inert materials)</td>
</tr>
<tr>
<td>4</td>
<td>Solid dispersions (dispersion of poorly soluble drug in a solid matrix of water soluble carrier)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Griseofulvin$^{44,45}$, digoxin$^{46,47}$, phenacetin$^{48}$ and sulphadiazine$^{49}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phenacetin$^{50}$</td>
</tr>
<tr>
<td></td>
<td>Oxyphenbutazone$^{51}$, prednisolone$^{52}$, tolbutamide$^{53}$, indomethacin$^{54}$, phenylbutazone$^{55,56}$ and hydrochlorothiazide$^{54}$</td>
</tr>
<tr>
<td></td>
<td>Griseofulvin-PVP$^{57}$, reserpine-PVP$^{58}$, tolbutamide-PEG$^{59}$ and chloramphenicol-Urea$^{60}$</td>
</tr>
</tbody>
</table>

1.3.2 **Cyclodextrin complexation**

Cyclodextrins (CDs) and their derivatives are receiving more and more attention both in pharmaceutical formulations and as drug carrier systems. Cyclodextrins are cyclic ($\alpha,1,4$)-linked oligosaccharides of $\alpha$-D-glucopyranose containing a relatively hydrophobic central cavity and hydrophilic outer surface. Cyclodextrins are able to form inclusion complexes with poorly water soluble drugs. These inclusion complexes have been shown to improve pharmaceutical properties like stability, solubility, dissolution rate and bioavailability.

They can also reduce side effects associated with same drugs. The improvement in hydrophilicity obtained either through the formation of inclusion complexes of host/guest type, as a function of the dimension of the oligosaccharide ring or by means of highly homogeneous
assembly between the CD and the drug in the solid state. In most cases, this association yields a better solution behaviour of poorly soluble drugs.

In the present research work three poorly water soluble drugs namely sparfloxacin, nifedipine and nimodipine were complexed with β and HP-β-CDs with an objective to improve their pharmaceutical properties like solubility, dissolution rate and oral bioavailability.

1.4 Introduction to controlled release drug delivery systems

In recent years, considerable attention has been focused on the development of new drug delivery systems. There are a number of reasons for the intense interest in new systems. First, recognition of the possibility of repatenting successful drugs by applying the concepts and techniques of controlled release drug delivery systems, coupled with the increasing expense in bringing new drug entities to market, has encouraged the development of new drug delivery system. Second, new systems are needed to deliver the novel, genetically engineered pharmaceuticals i.e. peptides and proteins to their sites of action without incurring significant immunogenicity or biological inactivation. Third, treating enzyme deficient diseases and cancer therapies can be improved by better targeting. Finally, therapeutic efficacy and safety of drugs, administered by conventional methods, can be improved by more precise spatial and temporal placement within the body, thereby reducing both the size and number of doses.

In general controlled delivery attempts to

1. Sustain drug action at a predetermined rate by maintaining a relatively constant effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern.

2. Localise drug action by spatial placement of a controlled release system (usually rate-controlled) adjacent to or in the diseased tissue or organ.

3. Target drug action by using carriers or chemical derivatization to deliver drugs to a particular “target” cell type.
In most cases, the release system creates constant concentration of drug within the body over an extended period of time. The assumption is that there is a steady state drug levels in plasma and in target tissues or cells are correlated. Ideally, it is desirable to place the drug at the target, be it a tissue, a population of cells or receptors, leaving the rest of the body drug free. This would be quite difficult.

In order to maintain a constant drug level in either plasma or target tissue, release rate from the controlled release system should be equal to the elimination rate from plasma or target tissue. Various designations such as ‘smart’, ‘targeted’, ‘intelligent’, ‘novel’ and therapeutic systems have been given in controlled release systems.

1.4.1 Advantages of controlled release dosage forms

They provide one or more of the following benefits or advantages.

1. Controlled administration of a therapeutic dose at a desirable delivery rate.


3. More consistent and prolonged therapeutic effect is observed.

4. Maximization of efficiency – dose relationship

5. Reduction of adverse side effects

6. Minimization of the need for frequent dose intake

7. Enhancement of patient compliance

8. More efficient drug utilization by the body.

1.4.2 Disadvantages of controlled release dosage forms

1. Increased variability among dosage units.
2. Stability problems are observed

3. Toxicity due to dose dumping occurs when more than usual fraction is being released

4. Increased cost

5. More rapid development of tolerance

6. Need for additional patient education and counseling.

1.4.3 **Characteristics of drugs suitable for controlled release**

1. Exhibit moderate rates of absorption and excretion.

2. Uniform absorption throughout the GI tract

3. Administered in relatively small doses.

4. Poses good margin of safety

5. For the treatment of chronic therapy

1.4.4 **Characteristics of drug unsuitable for controlled release**

1. Not effectively absorbed in the lower intestine (riboflavin).

2. Absorbed and excreted rapidly: short biological half-lives, <1 hr. (penicillin G, furosemide).

3. Long biological half-lives > 12 hr (diazepam, phenytoin).

4. Large doses required, 1g (sulfonamides).

5. Drugs with low therapeutic index (Phenobarbital, digoxin).

6. Precise dosage titrated to individuals required (anti coagulants, cardiac glycosides).

7. No clear advantage for sustained release formulation (griseofulvin).
Fig. 1.3 shows comparative blood drug level profiles obtained from administration of conventional, controlled as well as prolonged released dosage forms. The conventional tablet or capsule provide only a single and transient burst of drug. One of the main purposes of controlled release is to improve safety and minimize side effects of the drug by reducing fluctuations in drug level. This is achieved by releasing a small burst of drug over a prolonged period of time.

1.4.6 Factors influencing the design and performance of controlled release products

To establish criteria for the design of controlled release products, a number of variables must be considered.

1.4.6.1. Drug properties

The physico-chemical properties of a drug including stability, solubility, partitioning characteristics, charge and protein binding propensity play a dominant role in the design and performance of controlled release systems.
1.4.5.2. Route of drug delivery

The area of the body in which drugs will be applied or administered can be restrictive on the basis of technological achievement of a suitable controlled release mechanism or device. Performance of the controlled release systems may also be influenced by physiological constraints imposed by the particular route, such as first pass metabolism, GI motility, blood supply and sequestration of small foreign particles by the liver and the spleen.

1.4.5.3. Target sites

In order to minimize unwanted side effects it is desirable to maximize the fraction of applied dose reaching the target organ or tissue. This can be partially achieved by local administration or by the use of carriers.

1.4.5.4. Acute or chronic therapy

Consideration of whether one expects to achieve cure or control of a condition and expected length of drug therapy are important factors in designing controlled release systems. Moreover, long-term toxicity of rate controlled drug delivery systems is usually different from that of conventional dosage forms.\(^1\)

1.4.5.5. The disease

Pathological changes during the course of a disease can play a significant role in the design of a suitable drug delivery system.

1.4.5.6. The patient

Whether the patient is ambulatory or bed ridden, young or old, obese or gaunt etc. can influence the design of a controlled release product for example, single unit controlled release products are particularly prone to intra and inter subject variation because of variabilities in individual GI motility.\(^2\)

To establish the influence of drug properties and the route of administration on controlled release product design, it is worthwhile focusing on:

1. Behaviour of the drug in its delivery system.
2. Behaviour of the drug and its delivery system in the body.

For conventional drug delivery systems, the rate limiting step in drug availability is usually absorption of drug across a biological membrane such as the gastrointestinal wall (scheme 1.2).

![Scheme 1.2](image)

Scheme 1.2

In a controlled release product, one aims for release of drug from the dosage form as the rate limiting step. Drug availability is controlled by the kinetics of drug release rather than absorption. It is shown in scheme 1.3.

![Scheme 1.3](image)

Scheme 1.3

To control drug release one can employ a variety of approaches, such as dissolution, diffusion, swelling, osmotic pressure, complexation, ion-exchange and magnetic field.

Behaviour of the drug and its delivery system in the body is extremely complex, that involves the fate of the drug during transit to the target area and its fate in the biophase.

1.4.6 Physicochemical properties of a drug influencing drug product design and performance

The performance of a drug in its release pattern from the dosage form as well as in the body proper is a function of its properties. These properties can at times prohibit / restrict placement of the drug in a sustained / controlled release form, restrict the route of drug administration and significantly modify performance for one reason or another.
1.4.6.1. Aqueous solubility

Since drugs must be in solution before they can be absorbed, compounds with very low aqueous solubility usually suffer oral bioavailability problems because of limited gastrointestinal transit time of the undissolved drug particles and limited solubility at the absorption site.

The choice of mechanism for oral sustained or controlled release systems is limited by aqueous solubility of the drug. Diffusional systems will be poor choices for slightly soluble drugs since the driving force for diffusion, the concentration in aqueous solution will be low. Such drugs may be effectively incorporated in matrix system. Aqueous solubility limits the loading efficiency of drugs into a variety of carriers such as liposomes, erythrocytes and other micro particles. Most water soluble drugs tend to leak out from such carriers readily.

1.4.6.2. Partition coefficient and molecular size

Partition coefficient and molecular size influence not only the permeation of a drug across biological membranes but also diffusion across or through a rate controlled membrane or matrix. The ability of a drug to diffuse through the membranes, its so called diffusivity, is related to its molecular size by the following equation.

\[ \log D = S_V \log V + K_V = -S_M \log M + K_M \]

Where D is diffusivity, M is molecular weight, V is molecular volume and \( S_V \), \( S_M \), \( K_V \) and \( K_M \) are constants in a particular system. In general the denser the medium, the smaller the diffusivity.

1.4.6.3. Drug stability

The stability of a drug in the environment to which it is exposed is another physicochemical factor to be considered in the design of controlled release systems. Drugs that are unstable in the stomach can be placed in a slowly soluble form or have their release delayed until they reach the small intestine.

1.4.6.4. Protein binding

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most part recirculated and not eliminated, drug protein binding can serve as a depot for drug producing a prolonged release
profile, especially if a high degree of drug binding occurs. Quaternary ammonium compounds bind to mucin in the G.I. tract. Drugs bound to mucin may increase absorption, if the bound drug acts as a depot.

1.4.7 Biological factors influencing the design and performance of controlled release products

The design of controlled release product should be based on a comprehensive picture of drug disposition. This would entail a complete examination of the ADME characteristics of a drug following multiple dosing. In the following discussion, it is assumed that the level of drug in blood or body tissue parallels biological activity of the drug.

1.4.7.1. Absorption

To maintain constant blood or tissue level of drug, it must be uniformly released from the controlled release system and then uniformly absorbed. The fraction of the drug absorbed from a single non-controlled dose or drug can sometimes be quite low for a variety of reasons such as drug degradation due to solvolysis or metabolism, binding of drugs to proteins, physical loss or perhaps site or dose dependent absorption. If the drug was eratically absorbed, as might occur in a route of administration with variable absorptive surface, such as the G.I. tract, design of a controlled release product would be more difficult or prohibitive with respect to the oral route, it is well known that the absorptive character of the different segments of the G.I. tract varies which in turn can influence the amount and rate of absorption of certain drugs. The oral anticoagulant dicumarol, the quaternary ammonium compounds and the amino glycosides such as gentamycin are examples of such drugs.

1.4.7.2. Distribution

The distribution of drugs into tissues can be an important factor in the overall drug elimination kinetics since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extra cellular fluids. In general, the bound portion of the drug can be considered inactive and unable to cross membranes. At high binding one sees prolonged drug action. The apparent volume of distribution of a drug is frequently used to describe the magnitude of distribution, including binding, within the body. The total apparent volume of distribution for a drug at steady state can be calculated from the following equation.
\[ V_{dss} = \left( \frac{\left(k_{21} + k_{12}\right)}{k_{21}} \right) V_p \]

Where \( V_{dss} \) is the apparent volume of distribution at steady state \( k_{12} \) is the constant for the distribution of drug from the central to peripheral compartment. \( k_{21} \) is from the peripheral to the central compartment. \( V_p \) is the volume of central compartment.

1.4.7.3. Metabolism

Metabolism of a drug can either inactivate an active drug or convert an inactive drug to an active metabolite. Metabolic alteration of a drug can occur in a variety of tissues, some of which are richer in enzymes than others. For example, the organ most responsible for metabolism is the liver and thus the greatest metabolic conversion occurs after a drug has been absorbed into the general circulation. Clearly for optimal bioavailability, the route of drug administration may be dictated by the drug's metabolic pattern. Metabolism of a drug will be reflected in the elimination constant of a drug or by the appearance of a metabolite. It is possible to incorporate this pharmacokinetic property into the design of controlled release product, provided that the rate and extent of metabolism are predictable and that the rate constant (\( S \)) for the process are not too large. Undoubtedly, complex metabolic patterns would make the design much more difficult, particularly when biological activity is wholly or partly due to a metabolite, as is the case in isosorbide 2,5-dinitrate\(^7\).

1.4.7.4. Duration of action

The biological half-life and hence duration of action of a drug obviously play a major role in the process of considering a drug for controlled release. Factors influencing the biological half-life of a drug include its elimination, metabolism and distribution patterns. Drugs with short half lives require frequent dosing in order to minimize fluctuations in blood levels accompanying conventional oral dosage regimens\(^7\). Therefore, controlled release dosage forms would appear very desirable for such drugs. Basic pharmacokinetic principles suggest that for a given steady state drug concentration, the zero order rate of release of a drug from its dosage form is directly proportional to its rate of elimination. Thus, for a drug with a very short half-life, the desired rate of release will be quite large. This large rate of release in turn will lead to a prohibitively large dose, so that the upper limit imposed on the size of the tablet, capsule or other dosage forms may be
exceeded. The numerical value of biological half (four hours) was quoted to make a drug a good candidate for controlled release.

1.4.7.5. Side effects

It is believed that for some drugs, the incidence of side effects is a function of plasma concentration. Theoretically, the incidence of side effects can be minimized by controlling the concentration at which the drug exists in plasma at any given time, and hence controlled release formulations appear to offer a solution to this problem. The technique of controlled release has been more widely used to lower the incidence of GI side effects than that of systemic side effects and appears to produce more satisfactory results. It is postulated that by slowing the rate at which the drugs are released, the likelihood of GI irritation would be reduced due to a smaller amount of drug exposed to the GI mucosa at any given time.

1.4.7.6. Margin of safety

Decisions on margin of safety of a drug perhaps can be better made on the basis of its therapeutic index in combination with the range of plasma combination within which the drug is considered to be therapeutically safe and effective. This approach has been very valuable as a therapeutic guide in monitoring drug therapy. Especially for drugs with narrow therapeutic indices and a narrow range of therapeutic concentration, such as cardiac glycosides and antiarrhythmics.

In designing controlled release systems for drugs with narrow therapeutic indices, it is imperative that the drug release pattern be precise so that the plasma concentration achieved is within the therapeutically safe and effective range.

1.4.7.7. Total clearance (CL)

The CL is that the hypothetical volume of distribution of unmetabolised drug that is cleared per unit of time by any pathway of drug removal. The value of CL can be determined from the dose administered D, and absolute bioavailability and AUC.

\[ CL = \frac{D \cdot F}{AUC} \]

The CL is the key to estimate the dose rate \( R^2 \) for controlled release dosage forms and is related to the mean steady state concentration.
1.4.7.8. Mean residence time (MRT)

The MRT is the mean time a drug molecule resides in the body. It is the time corresponding to 63.2% elimination from the body. It is calculated from AUC and AUMC, i.e., the area under the first-movement curve.

1.4.7.9. Dosage form index (DI)

DI is the ratio between the peak (C \text{ss max}) and trough (C \text{ss min}) values within dosing intervals.

1.5 Oral controlled release drug delivery systems

Oral ingestion is the traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of the drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub- or supratherapeutic plasma concentrations leading to marked side effects. An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provide a uniform amount of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimises side effects and also reduces the frequency of administration. CR products are formulations that release active drug compounds into the body gradually and predictably over a 12 to 24 hr period and that can be taken once or twice a day. Typically these products provide numerous benefits compared with immediate release drugs, including greater effectiveness in the treatment of chronic conditions, reduced side effects, greater convenience and higher levels of patient compliance due to a simplified dosing schedule. Because of the above advantages, such systems form the major segment of the drug delivery market.

A number of techniques are used to achieve controlled release of drugs via the oral cavity.
The majority of oral controlled release systems rely on dissolution, diffusion, or a combination of both mechanisms to generate slow release of drug to the gastrointestinal milieu.

1.5.1. Dissolution controlled release

Sustained release oral products employing dissolution as the rate-limiting step are in principle the simplest to prepare.

1.5.1.1. Encapsulation dissolution control

These methods generally involve coating individual particles or granules of drug with a slowly dissolving material. The coated particles can be compressed directly into tablets as in Spacetabs or placed in capsules as in the Spansule Products. Since the time required for dissolution of the coat is a function of its thickness and aqueous solubility, one can obtain repeat or sustained action by employing a narrow or a wide spectrum of coated particles of varying thicknesses respectively.

1.5.1.2. Matrix dissolution control

An alternative approach is to compress the drug with a slowly dissolving carrier of some sort into a tablet form. Here, the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This, in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet and particles surface.

1.5.2. Diffusion controlled release

There are basically two types of diffusion controlled systems which have been developed over the past two decades, reservoir devices and matrix devices.

1.5.2.1. Reservoir devices

In this system, a water-insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the membrane, diffuse to the periphery, and exchange with the surrounding media.

1.5.2.2. Matrix devices

In this system, a solid drug is dispersed in an insoluble matrix. The rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution.
1.5.3. Diffusion and Dissolution Controlled Systems

The main feature of this system is that the drug core is enclosed with a partially soluble membrane. Dissolution of part of the membrane allows for diffusion of the contained drug through pores in the polymer coat.

1.5.4. Ion-Exchange Resins

Resins are water-insoluble materials containing anionic or cationic groups in repeating positions on the resin chain. The drug-charged resin is prepared by mixing the resin with drug solution either by repeated exposure of the resin to the drug in a chromatographic column or by keeping the resin in contact with the drug solution for extended periods of time. The drug-resin is then washed to remove contaminant ions and dried to form particles or beads. When a high concentration of an appropriately charged ion is in contact with the ion-exchange group, the drug molecule is exchanged and diffuses out of the resin to the bulk solution.

1.5.5 pH – Independent Formulations

The granules are designed for the oral controlled release of basic or acidic drugs at a rate that is independent of the pH in the GI tract. They are prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients, and finally, coating with a gastrointestinal fluid permeable film-forming polymer. When the GI fluid permeates through the membrane, the buffering agents adjust the fluid inside to a suitable constant pH, thereby rendering a constant rate of drug release.

1.5.6. Osmotically Controlled Release

In this type of drug delivery systems, osmotic pressure is the driving force that generates constant drug release. This system is fabricated by applying a semipermeable membrane around a core of an osmotically active drug or a core of an osmotically inactive drug in combination with an osmotically active salt. A delivery orifice is drilled in each system by laser or by a high-speed mechanical drill.

1.5.7. Altered Density Formulations

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released, it would have little utility. To
this end, several approaches have been developed to prolong the residence time of drug delivery systems in the GI tract. One such approach is the bioadhesion approach, which is based on the adherence of bioadhesive polymers to the mucin / epithelial surface of the GI tract. The other approach is to alter the formulation's density by using either high or low density pellets.

1.5.7.1. High-density approach

In this approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1.4. In preparing such formulations, drug can be coated on a heavy core or mixed with heavy inert materials such as barium sulfate, titanium dioxide, iron powder, and zinc oxide. The weighed pellet can then be covered with a diffusion controlled membrane.

1.5.7.2. Low-density approach

Globular shells which have an apparent density lower than that of gastric fluid can be used as carrier of drug for sustained release purposes. Polystyrol, poprice, and even popcorn are all candidates as carriers. The surface of these empty shells is undercoated with sugar or with a polymeric material such as methacrylic polymer and cellulose acetate phthalate. The undercoated shell is then coated by a mixture of drug with polymers such as ethylcellulose and hydroxypropy cellulose. The final product floats on the gastric fluid for a prolonged period, while slowly releasing drug.
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