1.0 INTRODUCTION

1.1 TASTE MASKING TECHNOLOGIES

The drug has to be made palatable in order to enhance patient adherence to reach the at par standard therapeutic efficacy. Hence forth aggressively bitter tasting drugs like the fluoroquinolone antibiotics, penicillins, macrolide antibiotics, and non-steroidal anti-inflammatory drugs are candidates for taste masking. Without changing its safety and efficacy, a drug's taste has to be masked and techniques are being adapted to meet this need, especially for the paediatric and juveniles patients. In present days techniques such as microencapsulation, coating, granulation, ion exchange resins, solid dispersion, complexing agents, suppressants, potentiators, viscosity enhancers, adsorbates, pH modifiers, and have been used in combination with the sweeteners & flavours to mask the bitterness and noxiousness.

Taste masking with sweeteners and flavours:

Sweeteners are commonly used in combination with other taste masking technologies. They can be mixed with bitter taste medicaments to improve the taste of the core material which is prepared for further coating or may be added to the coating liquid. Artificial sweeteners such as sucralose, aspartame and saccharin have been used in combination with sugar alcohols such as lactitol, maltitol and sorbitol to decrease the after-taste perception of artificial sweeteners. Sugar-based excipients have a negative heat of dissolution, dissolve quickly in saliva, and provide a pleasing mouth feel and good taste-masking to the final product. Monosodium glycyrrhizinate together with flavors has been used to mask the bitter taste of guaifenesin.
**Microencapsulation:**

Coating by enteric polymers in combination with water insoluble and gastrosoluble polymers or inorganic or organic pore formers have been used for masking the unpleasant taste of medicaments. Combination of water soluble polymer like gelatin, and water insoluble coating polymer like ethylcellulose was used to prepare taste masked microcapsules by the phase separation method. Microencapsulation processes are commonly based on the principle of solvent extraction or evaporation. However, modifications of other techniques such as phase separation (coacervation) and spray-drying are also utilized for microencapsulation\(^4\). Bitter drugs like caffeine, theophylline and fluoxetine were made into pleasant taste with the help of using ethylcellulose polymer by microencapsulation technique\(^5\).

**Coating:**

Coating is an excellent method of taste masking of bitter drugs. Zelalem Ayenew Vibha Puri, Lokesh Kumar and Arvind K Bansal\(^1\) are classified coating, based on the type of coating material, coating solvent system, and the number of coating layers. Hydrophobic polymers, lipids, sweeteners and hydrophilic polymers can be used as coating materials, either alone or in combination, as a single or multi-layer coat, to achieve the taste masking by aqueous or organic based coating process.
Fig. 1.1.1: Classification of patented taste masking strategies based on coating

Taste masked famotidine was formulated by using a combination of water soluble polymers like polyvinylpyrrolidone and insoluble polymers like cellulose acetate as the coating material. This polymeric solution gave a balance between taste masking and the desired in-vitro release. Kulkarni and Menjoge described the application of reverse enteric coating by using a polymer synthesized from a hydrophobic monomer (cyclohexyl acrylate), a basic monomer (dimethyl aminoethyl methacrylate) and a hydrophilic monomer to mask the unpleasant taste of erythromycin.

Hydrophobic polymers have been popularly used for coating bitter medicaments to achieve taste masking. However, hydrophilic polymers may also provide taste masking. Sweeteners can be included in the coating solution for a better taste masking performance. Kokubo and Nishiyama described a similar approach to prepare the taste masked etoricoxib.
Granulation:

Mixture of bitter medicaments, hydrophobic polymers, and sweeteners can be processed by dry, wet and melt granulation techniques to prepare taste masked oral solid or liquid dosage forms. Polymers, flavors and waxes have been used as granulating agents to achieve the taste masking of bitter medicaments. Liquid and low melting point waxes such as glycerol palmitostearate, glyceryl behenate and hydrogenated castor oil are commonly used ingredients during the granulation to achieve taste masking. Sugar alcohols and flavors are also added in the blend to increase the efficiency of taste masking. Ishikawa et al. developed taste masked pharmaceutical granules of pirenzepine and oxybutynin by the extrusion method using aminoalkyl methacrylate copolymer.\(^\text{11}\)

Ion exchange resins:

Ion exchange resins are high molecular weight polymers with cationic and anionic functional groups. Resins form insoluble resinates through weak ionic bonding with oppositely charged drugs and maintain low concentration of the free drug in a suspension. After ingestion, the resinate exchange the drug with the counter ion in gastrointestinal tract and the drug is eluted to be absorbed. Ion exchange resin like amberlite was used to formulate taste masked fast dissolving orally consumable films of dextromethorphan.\(^\text{12}\)

Solid dispersions:

Hydrophobic polymers and long chain fatty acids have been used to achieve the taste masking by solid dispersion. Natural polymers such as shellac and zein, and enteric polymers like derivatives of acrylic acid polymers and phthalate are good choices to develop the taste masked solid dispersions. Tsau and Damani disclosed a drug-polymer matrix composition to achieve the taste masking of dimenhydrinate. Amine or amido
group of dimenhydrinate can have a physical and chemical interaction with the carboxylic acid and esters groups of copolymers such as shellac, zein and cellulose acetate phthalate\textsuperscript{13}.

**Complex formation:**

The mechanism of taste masking by complex formation has two theoretical possibilities. Either the cyclodextrins wraps the bad tasting molecule to inhibit its interaction with the taste buds, or it interacts with the gatekeeper proteins of the taste buds\textsuperscript{14}. M. Sevukarajan, T. Bachala, and R. Nair are masked the taste of oseltamivir phosphate by making complex with $\beta$ cyclodextrin\textsuperscript{15}. Cyclodextrin was used to achieve taste masking of levosulpiride by complex formation\textsuperscript{16}.

**Taste suppressants and potentiators:**

Most of the Linguagen’s bitter blockers (e.g. adenosine monophosphate) compete with bitter substances to bind with the G-protein coupled (GPCR) receptor sites. In general, the hydrophobic nature of these bitter substances contributes greatly to their binding and inter-action with the receptor sites. Lipoproteins are universal bitter taste blockers. Study on animal model showed that lipoproteins composed of phosphatidic acid and $\beta$ -lactoglobulin inhibit the taste nerve responses to the bitter substances without affecting those due to the sugars, amino acids, salts or acids\textsuperscript{17}. Venkatesh and Palepu (2002) described the application of taste suppressants like phospholipid (BMI-60) in taste making of bitter medicaments\textsuperscript{18}.

Potentiators increase the perception of the taste of sweeteners and mask the unpleasant after taste. Potentiators such as thaumatine, neohesperidine dihydrochalcone (NHDC) and glycyrrhizin can increase the perception of sodium or calcium
saccharinates, saccharin, aspartyl-phenylalanine, acesulfame, cyclamates, and stevioside. Thaumatine was used with sugar alcohols to achieve the taste masking of bromhexine\textsuperscript{19}.

**Viscosity enhancers:**

Usage of viscosity enhancers in these cases would retard the migration of dissolved medicament from the surface of the solid particle to the suspending medium. Additionally, they can also decrease the contact between the bitter medicament and the taste receptors, thus improving the overall taste masking efficiency. Hypromellose was used as a viscosity modifier in taste masked azelastine suspension consisting of sucralose as the sweetening agent\textsuperscript{20}.

**Adsorbates:**

The drug may be adsorbed or/and entrapped in the matrix of the porous component, which may result in a delayed release of the bitter active during the transit through the oral cavity thereby achieving taste masking. Kashid et al. developed a taste masked loperamide formulation with magnesium aluminum silicate by blending the drug and the adsorbate, and further granulating with hydrophobic polymers to achieve taste masking\textsuperscript{21}.

**pH modifiers:**

pH Modifying agents are capable of generating a specific pH microenvironment in aqueous media that can facilitate \textit{in situ} precipitation of the bitter drug substance in saliva thereby reducing the overall taste sensation for liquid dosage forms like suspension. Wyley described an application of pH modifying agent such as L-arginine for taste masking of bitter medicament. L-arginine maintains alkaline pH of the suspending vehicle to promote \textit{in situ} precipitation of des-quinolone in saliva\textsuperscript{22}.
REFERENCES


1.2 ION EXCHANGE RESIN COMPLEXATION

Ion exchange resins (IER) are insoluble polymers that contain acidic or basic functional group and have the ability to exchange counter-ions within aqueous solutions surrounding them. Synthetic ion exchange resins have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950.\textsuperscript{1,2,3}

Being high molecular weight water insoluble polymers, the ion exchange resins are not absorbed by the body and are therefore inert. The long-term safety of ion exchange resins, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol is an established unique advantage of IER due to the fixed positively or negatively charged functional groups attached to water insoluble polymer backbone. These groups have an affinity for oppositely charged counter ions, thus absorbing the ions into the polymer matrix. Since most drugs possess ionic sites in their molecule, the resin's charge provides a means to loosely bind such drugs and this complex prevents the drug release in the saliva, thus resulting in taste masking. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug. The nature of the drug resin complex formed is such that the average pH of 6.7 and cation concentration of about 40meq/L in the saliva are not able to break the drug resin complex but it is weak enough to break down by hydrochloric acid present in the stomach. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected 3-4.
1.2.1 Ion exchange resins (IER)

IER have since been extensively explored in the field of drug delivery, leading to some important patents. Research over the past few years has revealed that IER are equally suitable for drug-delivery technologies, including controlled release, transdermal, site-specific, fast dissolving, iontophoretically assisted transdermal, nasal, topical, and taste masked systems.

Polymer matrix

The most commonly used polymer backbone for anion exchange and strong cation exchange resin is based on polystyrene. Divinylbenzene (DVB) is included in the copolymerization for crosslinking the polymer chains. The amount of DVB, usually expressed as percentage by weight has a strong effect on the physical properties. The weak cation exchange resins are generally polyacrylic or polymethacrylic acids with DVB as crosslinking agents depending on the presence of ions. Four major types of ion exchange resins are available which are summarized in Table 1.2.1.

**Table 1.2.1: Common ion exchange resins**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Type</th>
<th>Exchange species</th>
<th>Polymer back bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Strong anion</td>
<td>$N^+R^3$</td>
<td>Polystyrene-DVB</td>
</tr>
<tr>
<td>2</td>
<td>Weak anion</td>
<td>$N^+R^2$</td>
<td>Polystyrene-DVB</td>
</tr>
<tr>
<td>3</td>
<td>Strong cation</td>
<td>$-SO_3^-$H, $-SO_3^-$Na</td>
<td>Polystyrene-DVB</td>
</tr>
<tr>
<td>4</td>
<td>Weak cation</td>
<td>$-COOH, -COOK$</td>
<td>Methacrylic acid</td>
</tr>
</tbody>
</table>
Mechanism of binding of ion exchange resin with drugs

The principle property of resins is their capacity to exchange bound or insoluble ions with those in solution. Soluble ions may be removed from solution through exchange with the counter ions adsorbed on the resin as illustrated in equation 1 and 2.

\[
\text{Re-SO}_3\text{Na}^+ + \text{drug}^+ \rightleftharpoons \text{Re-SO}_3^\text{- drug}^+ + \text{Na}^+ \quad (1)
\]

\[
\text{Re-N(CH}_3\text{)}_3^+\text{Cl}^- + \text{drug}^- \rightleftharpoons \text{Re-N(CH}_3\text{)}_3\text{drug}^- + \text{Cl}^- \quad (2)
\]

These exchanges are equilibrium reactions in which the extent of exchange is governed by the relative affinity of the resins for particular ions. Relative affinity between ions may be expressed as a selectivity co-efficient derived from mass action expression\textsuperscript{5,6} given in below equation.

\[
K_{DM} = \frac{[D]_R[M]_S}{[D]_S[M]_R}
\]

Where

[D] R = Drug concentration in resin

[D] S = Drug concentration in the solution

[M] S = Counter ion concentration in the solution

[M] R = Counter ion concentration in the resin

Factors that influence selectivity include valency, hydrated size, pKa and the pH of the solutions\textsuperscript{4,6}.

Properties of Ion exchange resins (IER)

Ion exchange resins contain positively or negatively charged sites and are thus classified as either cationic or anionic exchangers. Within each category, they are classified as strong or weak, depending on their affinity for soluble counter ions. The
strong cation exchangers contain sulfonic acid sites, whereas weak cation exchange resins are based on carboxylic acid moieties. The strong anionic exchange resins have quaternary amine ionic sites attached to the matrix, whereas weak anion exchangers have predominantly tertiary amine substituents.

**Particle size and form:**

The rate of ion exchange reaction depends on the size of the resin particles. Decreasing the size of the resin particles significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium; hence larger particle size affords a slower release pattern.

Ion exchange resins are commercially available in different size ranges, generally expressed in micrometer or mesh ranges. The most commonly used are spherical beads of 297-840μm (20-50 mesh); they are best for column operations. Smaller size ranges (150-300μm or 50-100mesh; 75-150μm or 100-200mesh; 40-75μm or 200-400mesh) provide better chromatographic separations and may be more appropriate for pharmaceutical applications. A series of pharmaceutical-grade resins (Amberlite IRP from Rhom & Haas) have ranges of 40-150 μm (100-400 mesh). Although useful when employed directly in formulations, this size range does not function well in column absorption or filtration operations.

**Porosity and swelling:**

Porosity is defined as the ratio of volume of the material to its mass. The limiting size of the ions, which can penetrate into a resin matrix, depends strongly on the porosity. The porosity depends upon the amount of cross-linking substance used in polymerization method. The amount of swelling is directly proportional to the number of hydrophilic
functional groups attached to the polymer matrix and is inversely proportional to the degree of DVB cross linking present in the resin\textsuperscript{8}.

**Cross-linking:**

The percentage of cross-linking affects the physical structure of the resin particles. Resins with low degree of cross-linking can take up large quantity of water and swell into a structure that is soft and gelatinous. However resins with high DVB content swell very little and are hard and brittle. Cross-linkage has dramatic effect on loading efficiency. It affects porosity and swelling properties of resin. Higher grades have finer pore structure thus reducing loading efficacy with increase in cross linking\textsuperscript{7}. Low cross linkages increase loading efficacy but also increases release rates\textsuperscript{9}.

**Exchange capacity:**

The exchange capacity refers to the number of ionic sites per unit weight or volume (mEq. per gram or meq per ml). The weight basis value (mEq. per gm) is much higher than the volume based exchange capacity since the wet resin is highly hydrated. The exchange may limit the amount of drug that may be adsorbed on a resin, hence affect potency of the complex. Carboxylic acid resins derived from acrylic acid polymers have higher exchange capacities (10meq. /gm) than sulfonic acid (about 4meq. / gm) or amine resins because of bulkier ionic substituents and the polystyrene matrix. Therefore, higher drug percentages may often be achieved with carboxylic acid resins\textsuperscript{7}.

**Stability:**

The ion exchange resins are inert substances at ordinary temperature and excluding the more potent oxidizing agents are resistant to decomposition through
chemical attack. These materials are indestructible. They get degraded and degenerated in presence of gamma rays.

**Purity and toxicity:**

Since drug resin combination contains 60% or more of the resin, it is necessary to establish its toxicity. Commercial product cannot be used as such. Careful purification of resins is required. Resins are not absorbed by body tissue and are safe for human consumption. Test for toxicological tolerance showed that it does not have any pronounced physiological action at recommended dosage and is definitely non-toxic.

**Selectivity of resin for counter ion:**

Since ion exchange resin involves electrostatic forces, selectivity mainly depends on relative charge and ionic radius of hydrated ions competing for an exchange site and to some extent on hydrophobicity of competitor ion.

**Resinate preparation**

Once the selection of a resin is made, the next step involves preparing its complex with drug, before designing a suitable delivery system. The main hurdle is to optimize the conditions of preparation, in order to obtain the desired drug loading in the resinates. Generally, the following steps are involved in the preparation of resonates.

1. Purification of resin by washing with absolute ethanol, ethanol and water mixture. Final washing with water removes all the impurities.

2. Changing the ionic form of IER might occasionally be required to convert a resin from one form to another, if it does not have the desired counter ions. Strongly acidic CER are usually marketed in Na$^+$ form and strongly basic AER in Cl$^-$ form. They are generally converted into hydrogen and hydroxide forms, respectively. The
conversion can be achieved by soaking the resins with acid or alkali solutions, respectively. After changing the ionic form, the resin is subjected to washing with distilled water until elute becomes neutral in reaction, and finally is dried at 50°C.

**Preparation of resinate is normally done by two techniques**

1. Batch technique - after suitable pretreatment, a specific quantity of the granular IER is agitated with the drug solution until the equilibrium is established\(^\text{13}\) and;

2. Column technique - resinate is formed by passing a concentrated solution of drug through the IER-packed column until the effluent concentration is the same as the eluent concentration.

**The process in drug delivery\(^\text{14}\)**

Ion exchange (IE) is the reversible interchange of ions (of like charge) between a liquid and a solid phase, involving no radical change in the structure and properties of the solid\(^\text{15}\). The solid phases in the IE process are referred to as IER, and are usually the polymers with integrated ionic moieties. Based on the nature of the ionic species being interchanged, the IE process is known as either cation exchange (CE) or anion exchange (AE). The IER used in these processes are referred to as cation-exchange resin (CER) or anion-exchange resin (AER), respectively. The IE process is competitive in nature. In practice, drug in an ionic form (usually in solution) is mixed with the appropriate IER to form a complex, known as ‘resinate’. The performance of resinate is governed by several factors, such as:

- The pH and temperature of the drug solution;
- The molecular weight and charge intensity of the drug and IER;
- Geometry;
• Mixing speed;
• Ionic strength of the drug solution;
• Degree of cross linking and particle size of the IER;
• The nature of solvent; and
• Contact time between the drug species and the IER\textsuperscript{16-19}.

**Selection of IER**

Selecting the resin for a specific application requires consideration of a number of factors. Generally, the type charge (cation or anion exchange) is obvious, although some amphoteric compounds may allow use of either type. For rapid dissolution in the GI tract, weak cation or anionic resins, low cross-linkage, small particle size, and high drug potency are required. Slow or gradual release or maximum taste protection may be obtained with strong cation or anion resins, high cross linkage, a large size range, and lower drug content If maximum potency or payload (mg drug per gram resinate) is a requirement with a low-molecular-weight drug, a resin with a high exchange capacity (carboxylic acid resins) is chosen. A high molecular weight often limits the drug's ability to be absorbed, and very low cross-linkage may be necessary for meaningful loadings. Drug stability must be of concern when a sulfonic acid or quaternary amine may act as a catalyst for degradation even in the dry state. The hydrodynamics of the absorption process and economics are also of importance. It is often advantageous to begin with the larger commercial particle size range and mill the complex after loading. Obviously the considerations are many, but the options are likewise plentiful. In practice, the best approach is to select several alternative resins, prepare absorbates of different potencies, and rely on *in vitro* and *in vivo* testing for the best decision.
**Mechanism of complexation**

\[
\text{Drug}^+ + \text{RH}^+ \rightleftharpoons \text{RD} + \text{H}^+
\]

\[
\text{Drug}^- + \text{R}^+\text{A}^- \rightleftharpoons \text{RD} + \text{A}^-
\]

**Mechanism of drug release in GIT**

If the drug resin complex is administered orally, a small amount of drug may be released. This would be followed by significant and continuous release in the stomach where the drug is exposed to high acid and chloride concentrations. Anionic exchange resins and the strong cation exchangers release a limited amount of drug in the stomach as shown in Eqs.

\[
\text{Re-SO}_3\text{Drug}^+ + \text{H}^+ \rightleftharpoons \text{Re-SO}_3\text{H}^+ + \text{Drug}^+
\]

\[
\text{Re-N (CH}_3\text{)}_3^+\text{Drug}^- + \text{Cl}^- \rightleftharpoons \text{Re-N (CH}_3\text{)}_3^+\text{Cl}^- + \text{Drug}^-
\]

In contrast, drugs bound to weakly acidic carboxylic acids are released much more rapidly in the stomach as illustrated in Eq.

\[
\text{Re-COO}^+\text{Drug}^+ + \text{H}^+ \rightleftharpoons \text{Re-COOH} + \text{Drug}^+
\]

The high effective pKa of the resin drives the equilibrium toward the formation of undissociated acid in a low pH environment. This may promote rapid drug release.

**Applications of ion exchange resins in pharmaceutical formulations**

In theory, drug release from resinate relies on the ionic environment and should therefore be less susceptible to other conditions, such as enzyme content, at the site of absorption. Therefore the suitability of the IER approach to drug delivery depends on the route and target of the delivery. Peroral controlled- and sustained-release DDSs have been widely studied with this approach, because of the ionic environment in the gastro-intestinal tract (GIT), for the exchange process. The IE process might not be optimally
applicable to the skin, external canals (e.g. nasal and ear), or other areas with limited quantities of eluting ions. By contrast, the subcutaneous and intramuscular routes, where the pool of ions is more controlled, would appear better suited for this approach.

**Taste masked oral DDSs:**

At salivary pH (6.8), resinate remains in intact form, making the drug unavailable for the taste sensation. As the formulation enters the upper segment of the GIT the environment changes to acidic and drug release takes place\(^\text{21}\). Polystyrene matrix CER have been used to mask the bitter taste of chlorpheniramine maleate, ephedrine hydrochloride and diphenhydramine hydrochloride\(^\text{22}\). The ionic binding of the drugs to polymeric materials such as carbopol is emerging as an important mechanism of taste masking. Erythromycin and clarithromycin have been taste masked by binding to carbopol\(^\text{21}\). However, as IER could also retard the release of drugs, a proper and careful selection of IER is essential to yield optimal taste masking without affecting the bioavailability. Generally, less cross-linked IER are helpful in taste masking\(^\text{23}\).

**Controlled or sustained release systems:**

The use of IER has occupied an important place in the development of controlled or sustained release systems because of their better drug retaining properties and prevention of dose dumping. The polymeric (physical) and ionic (chemical) properties of IER will release the drug more uniformly than that of simple matrices (because of physical properties only)\(^\text{24}\). Moreover, IER impart flexibility in designing a variety of delivery systems, such as liquids\(^\text{25-28}\), beads\(^\text{29-31}\), and microparticles\(^\text{32-34}\) and simple matrices\(^\text{35}\).
Simple resonates:

Resinates alone are the simplest forms of controlled or sustained release delivery systems. Resinates can be filled directly in a capsule, suspended in liquids, suspended in matrices or compressed into tablets. Drug from the resinate will be slowly released and absorbed as compared to the drug particles, but will also be significantly faster than the modified resinates (coated or microencapsulated). The release of diclofenac at the desired rate to avoid gastric irritation was achieved for arthritic patients\textsuperscript{36}.

Microencapsulated or coated resinates:

Several scientists have succeeded in using microencapsulated or coated resinates\textsuperscript{17,25,26,30}, and most of the patented and marketed formulations belong to this category. Microencapsulation of resinates provides better control over the drug release because of the presence of a rate controlling membrane. Often, water insoluble coating materials are used, such as ethyl cellulose or waxes. The release rate at the desired level can be tuned by optimization of coating thickness\textsuperscript{37}. Microencapsulation of resinates can be achieved by air-suspension coating (Wurster process), interfacial polymerization, solvent evaporation or pan coating.

Pennkinetic systems:

Further modification of the coating of resinates for improved monitoring of the drug-release pattern has been the concept of Pennkinetic systems (Fisons BV, Rochester, NY, USA, originally patented by Pennwalt Corporation)\textsuperscript{38}. In this system, resinate is pretreated with polyethylene glycol 400 to maintain the geometry and improve the coating process. The pretreated resinates are then coated with ethyl cellulose or any other water insoluble polymer. Polyethylene glycol helps in controlling the rate of swelling of
the resinate matrix in water, while an outer ethyl cellulose coating modifies the diffusion pattern of ions in and out of the system.

**Hollow fiber systems:**

Hollow fiber systems have advantages of high surface area to volume ratio, loading flexibility, membrane permeability, and potentially slower GIT transit time. These characteristics could provide a method to obtain controlled release for drugs in the small intestine and/or in the colon. Hollow fibers made from suitable polymeric materials are filled with resinate to obtain a controlled or sustained-release profile. *In vitro* and *in vivo* release of phenylpropanolamine (PPA) from polyurethane fibers filled with PPA-Dowex 50 W complex (resinate) have shown sustained effect\(^{39}\). However, the miniaturization of the system and the optimization of the release were necessary for the delivery of drugs. Such systems can be used for oral drug delivery.

**Site specific DDSs**

Delivering drugs at the desired biological location or site could have several advantages in therapeutics, such as:

• Localizing the required drug concentration to maintain a minimum effective concentration throughout the treatment;

• Reducing the systemic toxicity, especially with cytotoxic anticancer drugs; and

• Bifurcating the hostile environment of the drugs to prevent the drug degradation.

Several studies have reported the use of IER for drug delivery at the desired site of action\(^{40-50}\).
Gastric retentive systems:

Floating dosage forms are one of the alternatives designed to prolong gastric residence of drugs. A novel floating extended release system consisting of bicarbonate charged resin coated with a semipermeable membrane was studied for improving gastric-residence time.40

Site-specific delivery of drugs for cancer treatment:

Entrapment of anticancer drugs within the particulate carriers (microspheres, microcapsules) is a popular approach for the development of delivery systems for cancer treatment. Several anticancer drugs (e.g. doxorubicin) are ionic in nature and can be complexed with IER. Attempts have been made to deliver some of these drugs in a controlled release fashion to the anticancer cells with the help of IER47, 48. These studies revealed that the drug loading is at its maximum level with the IER complex approach.

Sigmoidal-release systems:

The drug release should be controlled in accordance with the therapeutic purpose and the pharmacological properties of the active substance51. Accordingly, the maintenance of a constant drug blood level is not always required, as in the case of nitrates, antibiotics and contraceptive steroids. To avoid the development of tolerance, the rhythmic variations of blood concentration must be maintained for such medicaments. ‘Time controlled’, instead of ‘rate controlled’, dosage forms have been designed to meet the requirement of pulsatile release.

A sigmoidal-release system rapidly releases the drug from a multiple-unit device after a predetermined lag time, and can achieve both time-controlled and rhythmic release. IER were studied in the development of sigmoidal-release systems. Eudragit RS
(Rohm, Darmstadt, Germany), an AER with limited quaternary ammonium groups, is coated over beads with a sugar core surrounded by organic acid and drug mixture. The ionic environment, induced by the addition of an organic acid to the system, was found to be responsible for pulsatile release\textsuperscript{49,50}.

**Nasal or ophthalmic DDSs:**

Attempts have been made to deliver therapeutic peptides or synthetic drugs via nasal mucosa with the IER complexation approach. A composition was developed to deliver nicotine in a pulsatile fashion to the systemic circulation via the nasal route\textsuperscript{52}. An excess amount of nicotine, as an immediate dose, was either dispersed in a non-IE material or overloaded in IER. The excess uncomplexed nicotine was thus available for immediate absorption, while the complexed portion served as the depot for prolonging the absorption. The prerequisite for nasal delivery by the IER approach is a high ion-exchange capacity of the resin. Generally, IE capacity should be 0.2 to 10 meq g\textsuperscript{-1}.

A sustained drug delivery composition, comprising an aqueous carrier and microspheres containing a pharmaceutically active material complexed with IER was developed for the treatment of glaucoma\textsuperscript{53,54}. These ophthalmic systems contained carbopol, which provided appropriate bioadhesion to the formulation. Betaxolol hydrochloride was delivered in a controlled manner by this approach.

**Iontophoretically assisted transdermal DDSs:**

IER could be considered as concentrated electrolytes with one immobile ionic species (the fixed ionic group). The addition of IER to gels or other composite vehicles complicates the process of passive drug release\textsuperscript{55}. However, transdermal systems can be developed, in which the drug release can be controlled by electric current. Another
advantage of such a system is exposure to a relatively constant pH during iontophoretic delivery, thus alleviating the problem of skin irritation. *In vitro* studies with nicotine, tacrine, propranolol, nadolol and sodium salicylate revealed that IER are more suitable as delivery vehicles in iontophoretic drug delivery\textsuperscript{55,56}. However, the *in vivo* suitability of these systems needs to be established.

**Clinical applications of IER**

Sulfonated and carboxylic resins with a polystyrene backbone are most widely used in clinical medicine. The pharmacological activity of these resins is attributed to their ability to adsorb ions, which are more selective to the resin than the counter ion of the resin. Resins are mostly used in conditions of sodium- and water-retention, such as cardiac failure, renal disease (nephrotic syndrome), toxemia of pregnancy and cirrhosis of the liver\textsuperscript{57}. In hypertension and edema, dietary restriction of sodium to less than 0.5 g per day is difficult.

IER have been used as reinforcement of a low sodium diet or to enable high salt intake in the diet. IER have also been used for hemoperfusion and management of drug overdoses (poisoning). At present, cholestyramine and cholestipol (AER) are used in the treatment of type II hyperlipoproteinemia and familial hyperlipoproteinemia in children and young adults\textsuperscript{58}. Both resins are mixed with fluids and administered as slurry.
1.2.2 INDION 414

Description:

Indion 414 is a high pure pharmaceutical grade weak acid cation exchange resin supplied as a dry powder in potassium form. It is suitable for use in tablet disintegration and taste masking of bitter drugs. It is based on cross linked polyacrylic acid.

Characteristics:

Appearance: White to pale cream powder
Matrix: Crosslinked acrylic co-polymer
Functional group: Carboxylic acid
Ionic form as supplied: Potassium
Solubility: Insoluble in water and in common solvents

Specifications:

Particle size distribution: 150µ (1% maximum)

75 µ (70% minimum)
Moisture content: 10% minimum
Exchangeable potassium: 5.25 meq/dry g, minimum
Potassium content: 20.6-25.1 %
Sodium content: 0.2%, maximum
pH of 10% slurry: 7.0-9.0
Iron content as Fe: 100ppm, maximum
Heavy metal content as Pb: 20 ppm, maximum
Arsenic content as As: 3ppm, maximum
Retained on 200 BSS mesh (75 microns): 1%w/w, maximum
Applications:

Indion 414 is an extremely effective tablet disintegrant which provides necessary hardness and chemical stability to the tablet. The product swells up to a very great extent (about 700%) when in contact with water or gastro-intestinal fluids, causing rapid disintegration without formation of lumps. Depending on the formulation, the use of 0.5% to 2% of Indion 414 is recommended for effective disintegration of tablet. Some of the advantages of using Indion 414 as a tablet disintegrant are:

- Remarkable swelling tendency on wetting, causing rapid disintegration.
- No lump formation on disintegration.
- Compatible with commonly used therapeutic agents and excipients.
- Works equally efficiently in hydrophilic and hydrophobic formulations.
- Gives good mechanical strength to the tablet, facilitating easy packing and transportation.
- Does not dissolve or have an adhesive tendency as in case of gums.
- Does not stick to punches and dyes.

Toxicity:

It is a high molecular weight polymer. It is not absorbed by body tissue and is totally safe for human consumption.

Storage:

Indion 414 is hygroscopic in nature. It is therefore essential to store it in a tightly packed container to prevent absorption of atmospheric moisture. If moisture is absorbed, the Indion 414 can be dried at 90°C to 100°C for 6 hours to reduce the moisture content below 10%.
1.2.3 INDION-254

Description:

Indion 254 is a high pure pharmaceutical grade strong acid cation exchange resin supplied as a dry powder. It is suitable for taste masking of bitter drugs. It is derived from a sulphonated co-polymer of styrene and divinyl benzene.

Characteristics:

- Appearance: Light cream to buff coloured powder
- Matrix: Cross linked polystyrene
- Functional group: sulphonic acid
- Ionic form as supplied: sodium
- Solubility: In soluble in water and in common solvents

Specifications:

- Particle size distribution: 150µ (1% maximum)
- Moisture content: 10% minimum
- Exchangeable potassium: 110 to 135 mg/dry g
- Sodium content: 9.4 to 11.5 %
- Iron content as Fe: 100ppm, maximum
- Heavy metal content as Pb: 20 ppm, maximum
- Arsenic content as As: 3ppm, maximum

Applications:

When used as a drug carrier indion 254 provides a means for binding the active drug. This can afford an effective means for minimising the problem of taste and odour which may be associated with the drug. The principal behind the technique of making a
tasteless formulation with the help of indion 254 is very simple and does not involve major capital investment. The complex is made from the drug and indion 254. The nature of the complex is such that the average cation concentration of about 40 meq/L and pH of 6.7 in saliva is not able to break the complex. The complex is weak enough to be broken down by the hydrochloric acid present in the stomach. Thus, the complex is absolutely tasteless and stable with no after taste, but at the same time, its bio-availability is not affected.

Sustained release properties can also be imparted to oral dosage formulations through the formulations through the formulation of a complex using indion 254. The drug is released from resinate in vivo as it reaches equilibrium with the high electrolyte concentration which is typical of the gastro intestinal tract.

Toxicity:

Indion 254 is a high molecular weight polymer. It is not absorbed by body tissue and is totally safe for human consumption.

Storage:

Indion 254 is hygroscopic in nature. It is therefore essential to store it in a tightly packed container to prevent absorption of atmospheric moisture. If moisture is absorbed, the indion 254 can be dried at 90°C to 100°C for 6 hours to reduce the moisture content below 10%.
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1.3 SOLID DISPERSIONS

Definition of solid dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

Advantages of solid dispersion:

1. Particles with reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.

2. Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co solvent effects.

3. Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance,
solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate\textsuperscript{8}. The increased porosity of solid dispersion particles also hastens the drug release profile.

4. Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility\textsuperscript{9, 10}. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process\textsuperscript{11}. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form\textsuperscript{2, 4}. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them\textsuperscript{12}.

Preparation of solid dispersions:

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, de-mixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. It was already recognized in one
of the first studies on solid dispersions that the extent of phase separation can be minimized by a rapid cooling procedure \(^5,\text{13}\). Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. On the other hand, phase separation is prevented by maintaining the driving force for phase separation low for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

**A. Fusion method**

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix\(^5\) which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. This procedure resulted in solid dispersions of type I. Poly (ethylene glycol) (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. This often results in solid dispersions of type III since many drugs are incorporated as separate molecules in the helical structure present in a crystalline PEG. The helices are aligned in orderly fashion, illustrating that PEG easily crystallizes. Another polymer frequently applied as a matrix in the fusion method is poly (vinyl pyrrolidone) PVP. PVP, supplied in the amorphous state, is heated to above its Tg (glass transition temperature). The drug has to fuse with or dissolve in the rubbery matrix, which is subsequently cooled to vitrify the solid dispersion. When PVP is used as matrix, solid dispersions of type V or VI are obtained. The mode of incorporation
of the drug depends on the PVP-drug miscibility and the preparation procedure. Grinding is required to obtain the solid dispersion as powder that is easy to handle.

Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture\textsuperscript{14,15}, which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants\textsuperscript{16,17}.

Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions\textsuperscript{18,19}. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug. For example, to melt a sugar matrix of galactose a temperature of 169°C was required\textsuperscript{20} and in order to get the glassy PVP in the rubbery state a temperature of about 170°C is required. Poly ethylene glycols melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method.

**B. Hot melt extrusion**

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar\textsuperscript{21-23}, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms\textsuperscript{24}. Just like in the traditional fusion process, miscibility of drug and
matrix can be a problem. Solubility parameters are investigated to predict the solid state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder be a problem for heat sensitive materials\textsuperscript{21-23,25}. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.

**C. Solvent method**

The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces two challenges.

The first challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible\textsuperscript{26}, preferably drug and matrix material are in the dissolved state in one solution.

Various strategies have been applied to dissolve the lipophilic drug and hydrophilic matrix material together in one solution. Low drug concentrations are used to dissolve both drug and matrix material in water\textsuperscript{27}, but this requires evaporation of tremendous amounts of solvent, making the process expensive and impractical. Solubilisers like cyclodextrins or surfactants like Tween80® increase the aqueous solubility of the drug substantially. However, the amount of solubilisers or surfactants in
the final product is often eminent. This results in solid dispersions that, to a significant extent, consist of solubilisers or surfactants, materials that significantly change the physical properties of the matrix (e.g., decrease of Tg). Moreover, only dosage forms with low drug loads are possible. In addition, they are not always tolerated well in the body or may even be toxic.

Chloroform$^{28}$ or dichloromethane$^{16}$ have been used to dissolve both drug and PVP as matrix simultaneously. These solvents are used also in other preparation methods. However, according to the ICH guidelines, these solvents belong to class I, comprising the most toxic solvents. Therefore, the use of these solvents is unacceptable and impractical because the amount of residual solvent present in the solid dispersion after drying has to be below the detection limits. The last strategy for the dissolution of both drug and matrix is the use of solvent mixtures. Water and ethanol$^{29}$, or dichloromethane and ethanol$^{30}$ have been used for this purpose. However, dissolution of drug and matrix in these mixtures is not always possible in the required concentration or ratio.

The second challenge in the solvent method is to prevent phase separation, e.g. crystallization of either drug or matrix, during removal of the solvent(s). Drying at high temperatures speeds up the process and reduces the time available for phase separation. On the other hand, at high temperatures the molecular mobility of drug and matrix remains high, favoring phase separation (e.g., crystallization).

To dry the solutions, vacuum drying is often used$^{25}$. The solution is dried by the application of vacuum and moderate heating. Sometimes, the solvent evaporation is accelerated by using a rotary evaporator. Afterwards the formed solid dispersion is often stored in a vacuum desiccator to remove the residual solvent. Vacuum drying at
elevated temperature bears the risk of phase separation because the mobility of drug and matrix decreases slowly. Another drying technique is spray drying. The solution is dispersed as fine particles in hot air. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. Moreover, the solid dispersions prepared by spray drying consist of particles of which the size may be customized by changing the droplet size to meet the requirements for further processing or application (e.g., free flowing particles or particles for inhalation). Spray drying usually yields drug in the amorphous state\textsuperscript{31}, however sometimes the drug may have (partially) crystallized during processing\textsuperscript{32}.

An alternative to these drying techniques is freeze drying. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices\textsuperscript{33}, the technique is poorly exploited for the preparation of solid dispersions\textsuperscript{34,35}. One of the reasons might be the low freezing temperature of most organic solvents. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase separation to a minimum\textsuperscript{36,37,38}. Moreover, spray freeze
drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary \textsuperscript{39}, or nasal administration\textsuperscript{40}.

In an electrostatic spinning process a drug-matrix solution is pumped through an orifice and then subjected to an electrical field to form fibres with a diameter of micro or nano scale. This process is restricted to a limited amount of matrices, because only a few high molecular weight materials are fibre forming materials. The fibre diameter can be adjusted by surface tension, electrical field and dielectric constant\textsuperscript{41}. After rapid evaporation of the solvent, the fibres can be directly used or milled and further processed\textsuperscript{42,43}.

Evaporative precipitation into aqueous solutions (EPAS) was used to coat a colloidal suspension of carbamazepine with block copolymers as stabilizing surfactants. A solution of drug in dichloromethane was sprayed in an aqueous solution containing polymeric surfactants as stabilizers. The obtained colloidal suspension was spray dried, freeze dried or spray freeze dried, resulting in solid dispersions of type IV/V. It was concluded that the amorphous state of the drug was best preserved with the spray freeze drying process\textsuperscript{44}.

D. Supercritical fluid methods

Supercritical fluid methods are mostly applied with carbon dioxide (CO\textsubscript{2}), which is used as either a solvent for drug and matrix or as an anti-solvent\textsuperscript{45,46}. When supercritical CO\textsubscript{2} is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO\textsubscript{2} is considered environmentally
friendly, this technique is referred to as ‘solvent free’. The technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility in CO₂ of most pharmaceutical compounds is very low (<0.01wt-%)⁴⁷ and decreases with increasing polarity. Therefore, scaling up this process to kilogram scale will be impractical.

All other supercritical techniques are precipitation methods. Although generally labelled as solvent-free, all these supercritical fluid methods use organic solvents to dissolve drug and matrix and exploit the low solubility techniques represent alternative methods to remove solvents from a solution containing typically a drug and a polymer. Moneghini and co-workers⁴⁸ reported their method as solvent-free, but they dissolved PEG and carbamazepine in acetone. They used a technique that is called the Gas-Anti Solvent technique (GAS) or Precipitation from Gas Saturated Solutions (PGSS). The solution is brought into contact with compressed CO₂. The conditions are chosen so that CO₂ is completely miscible with the solution under supercritical conditions, whereas drug and matrix will precipitate upon expansion of the solution. When the volume of the solution expands the solvent strength (i.e. the ability to dissolve the drug) decreases. This results in precipitation of matrix and drug. Since this technique is often applied with PEG as matrix, this technique results in formation of a solid dispersion with a crystalline matrix⁴¹.

The second type of precipitation technique involves the spraying of a solution containing drug and matrix through a nozzle into a vessel that contains a liquid or supercritical anti-solvent. The supercritical anti-solvent rapidly penetrates into the droplets, in which drug and matrix become supersaturated, crystallize and form particles.
The general term for this process is Precipitation with Compressed Anti-Solvent (PCA)\textsuperscript{47}. More specific examples of PCA are Supercritical AntiSolvent (SAS) when supercritical CO\textsubscript{2} is used, or Aerosol Solvent Extraction System (ASES), and Solution Enhanced Dispersion by Supercritical fluids (SEDS)\textsuperscript{45,47}. However, as with the other solvent techniques described in the previous section, the critical step in these precipitation techniques might be the dissolution of drug and matrix in one solution. The use of water is limited, because the water solubility in compressed CO\textsubscript{2} is limited\textsuperscript{44}. Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix\textsuperscript{41}.

In another process called supercritical fluid impregnation the drug is dissolved in a supercritical fluid and exposed to solid matrix material that swells and absorbs the supercritical solution. By varying the pressure and the time of exposure, the diffusion process can be controlled. The absorption stops when the pressure is reduced. This process is investigated for poly (methyl methacrylate)\textsuperscript{49} but can be applied for other polymers as well.

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1.4 POLYMER USED IN THIS STUDY & STEARIC ACID

Recent years have seen an ever-increasing interest in the application of novel materials in the medical and pharmaceutical fields. Of these materials, polymers are by far the most diverse class and they have considerable benefits upon the patient health care and treatment available today.

**Polymers can be classified on the basis of their interaction with water, into**:  

a) Non-biodegradable hydrophobic polymers  
   Polyethylene vinylacetate (EVA), Polydimethylsiloxane (PDS), Polyethylene urethane (PEU), Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene (PE), Polyvinyl chloride (PVC), etc.

b) Hydrogels  
   Poly hydroxylethyl methacrylate (P-HEMA), Cross linked polyvinyl alcohol (PVA), Cross linked PVP, Poly acrylamide, Dextran etc.

c) Soluble Polymers  
   Polyethylene glycol (PEG), uncross-linked PVA, PVP, HPMC, Copolymers of Methacrylic acid and Acrylic acid methyl ester (Eudragit L), etc.

d) Biodegradable polymers  
   Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), several generic classes such as poly anhydrides and polyortho esters.

**Applications of Polymers**

The applications of polymers are far ranging. These arise from the distinct advantages of polymers, their versatility, relatively easily processing, possession of
biological functions, biocompatibility, inert nature towards host tissues and reasonable costs.

- Use in formulation

  As binders in tableting; as coating materials to enhance the release rate, to protect the drug and to target; as carriers for enhancing solubility, for controlled release, as thickening agents and protective colloids to stabilize emulsions and suspensions; to form water soluble jellies and ointment bases and as suppository bases, major constituent of hard and soft capsules, in the preparation of bioactive medical devices such as microcapsules and microspheres, transdermal drug delivery patches; intrauterine device, intravaginal devices.

- Use in Therapeutics

  Polymers are used as drugs. Examples: heparin and its antagonist, protamine sulphate, plasma expanders dextran and normal human serum albumin, bulk laxatives methylcellulose and carboxy methylcellulose.

- Use in Diagnostics

  Biosensors, clinical assays, tissue labeling and image compositions.

- Use as Implants or other support materials

  Vascular grafts; intraocular lenses, heart valves, ventricular shunts, pacemakers, retinal surgery implants, artificial joints, hips and knees, chin and nose prostheses.

- Use in other devices

  Heamodialysis, heamoperfusion, oxygenators, catheters, blood tubings, bags and dispensers; wound and burn covering material, suture material, splints, contact lenses and ocular inserts.
Water Soluble Polymers:

Water soluble polymers have attracted considerable interest as means of improving the dissolution rate and hence possibly bioavailability, of a range of hydrophobic drugs. Water soluble polymers are used to good effect as carriers in solid dispersions and solvent deposited systems of a number of poorly soluble drugs. They are used in controlled release drug delivery systems either alone or in combination with hydrophobic polymers to produce devices that release the drug at a desired rate.

1.4.1 POLYETHYLENE GLYCOL

Polyoxyethylene glycols (PEGs) are polymers of ethylene oxide with a molecular weight usually falling in the range 200-300000. Liquid grades (PEG 200–600) are clear, colorless or slightly yellow-colored, viscous liquids. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. PEG is chemically, α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl). They are represented with a general formula HOCH₂(CH₂OCH₂)ₘCH₂OH, where m represents the average number of oxyethylene groups. All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycols can be used to enhance the aqueous solubility or dissolution
characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. They can be used as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, PEGs can act as emulsion stabilizers. In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms. Mixtures of PEGs can be used as suppository bases. In film coatings, solid grades of PEG can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. They are also useful as plasticizers in conjunction with film-forming polymers.

Increased drug release rate was observed from solid dispersions of following drug-PEG combinations; ibuprofen – PEG 6000², naproxen – PEG 4000/6000³, nimesulide – PEG6000⁴, nimodipine – PEG 6000⁵, trimethoprim – PEG 4000/6000⁶, griseofulvin – 4000/6000/20000⁷, oxazepam – PEG 4000⁸, piroxicam – PEG 4000⁹, zolpidem – PEG 4000¹⁰ and glyburide – PEG 4000¹¹. Improved bioavailability was observed in the case of carbamazepine- PEG 4000/6000¹² and norfloxacin – PEG 6000¹³ combinations. Further, drugs which exhibited elevated release rates when formulated as PEG solid dispersions include ketoprofen¹⁴, nifedipine¹⁵, phenytoin¹⁶ and fenofibrate¹⁷. Liu et al¹⁸ studied the characteristics of rofecoxib - PEG4000 solid dispersions and tablets based on solid dispersions. They observed an improved dissolution rate and quick anti-inflammatory activity of rofecoxib from its solid dispersion based oral tablets.
1.4.2 STEARIC ACID

Description:

Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor (with an odor threshold of 20 ppm) and taste suggesting tallow.

Characteristics:

- Acid value: 195–212
- Boiling point: 383°C
- Density (bulk): 0.537 g/cm³
- Density (tapped): 0.571 g/cm³
- Density (true): 0.980 g/cm³
- Flash point: 113°C (closed cup)
- Melting point: 69-70°C
- Moisture content: Contains practically no water.
- Refractive index: 1.43 at 80°C
- Saponification value: 200-220
- Solubility: Freely soluble in benzene, carbon tetrachloride, chloroform, and ether; soluble in ethanol (95%), hexane, and propylene glycol; practically insoluble in water.

Applications in pharmaceutical formulation or technology:

Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant. Although it may also be used as a binder or in combination with shellac as a tablet coating. It has also
been suggested that stearic acid may be used in enteric tablet coatings and as a sustained-release drug carrier\textsuperscript{23}.

In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams\textsuperscript{24,25}. The partially neutralized stearic acid forms a creamy base when mixed with 5-15 times its own weight of aqueous liquid, the appearance and plasticity of the cream being determined by the proportion of alkali used. Stearic acid is used as the hardening agent in glycerin suppositories. Stearic acid is also widely used in cosmetics and food products.

Belem Lara-Hernandez \textit{et al}\textsuperscript{26} studied the properties of metronidazole/Methocel K4M sustained release floating tablets with varying proportion of the stearic acid, lubricant, on formulations with and without sodium bicarbonate. The presence of stearic acid and sodium bicarbonate improves the floating behaviour for more than 8 hours. Kamlesh Jayantilal Wadher \textit{et al}\textsuperscript{27} demonstrated that tablet formulated with hydrogenated castor oil sustain the release of metformin hydrochloride more than that of stearic acid and glycercyl monostearate. Combination of hydrogenated castor oil and stearic acid provide more sustained effect than the combination of hydrogennated castor oil with glycercyl monostearate and stearic acid with glycercyl monostearate. Hugo Almeida \textit{et al}\textsuperscript{28} prepared solid dispersions of ibuprofen in cethyl alcohol (SD CA), stearic acid (SD SA) and hydrogenated castor oil (SD HCO) were prepared in order to improve physical and mechanical characteristics of this drug. Solid dispersions of ibuprofen with stearic acid and hydrogenated castor oil showed better flow characteristics than pure ibuprofen and the respective physical mixtures. Xin Li \textit{et al}\textsuperscript{29} prepared stearic acid grafted chitosan
oligosaccharide (CSOS-SA) micelle loading 10-hydroxycamptothecin (HCPT), and investigate the physicochemical properties and *in vitro* anti-tumor activity of the drug delivery system. The saturated solubility and stability of HCPT in distilled water were enhanced markedly when HCPT was encapsulated into micelles

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