Chapter 1

Introduction
1.1 Introduction to sustained release

Drugs are rarely administered as pure chemical substances alone and are always given as formulated preparations or medicines (i.e. drug delivery systems or dosage forms). These can vary from relatively simple solutions to complex drug delivery systems through the use of appropriate additives or excipient in the formulations. It is the formulation additives that, modify solubility, suspend, thicken, preserve, emulsify, modify dissolution, improve the compressibility and flavor drug substances to form various acceptable preparations or dosage forms. Before a drug substance can be successfully formulated into a dosage form, many factors must be considered. These can be broadly grouped into the following three categories.1

- Biopharmaceutical considerations, including factors affecting the absorption of the drug substance from different administration routes;
- Drug factors, such as the physical and chemical properties of the drug substance;
- Therapeutic considerations, including consideration of the clinical indication to be treated and patient factors.

High-quality and efficacious medicines will be formulated and prepared only when all these factors are considered and related to each other. This is the underlying principle of dosage form design.1

The oral route of drug administration is the most important method of administering drugs for systemic effects. The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site(s) in the body to achieve promptly and then maintain the desired drug concentration. The drug delivery system should deliver a drug at a rate dictated by the needs of the body over a specified period of treatment. This idealized objective points to the two aspects most important to drug delivery, namely spatial placement and temporal delivery of a drug. Spatial placement relates to targeting of a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. A bulk of research has been directed at oral dosage forms that satisfy temporal aspect of drug delivery, since many drugs require constant ‘drug blood levels’ within therapeutic range for the required duration of action to be effective.2,3
1.1.1 Conventional drug delivery system
The oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Of the various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules. The gastrointestinal tract provides sufficient fluid to facilitate disintegration of the dosage form and dissolution of the drug. The large surface area of gastric mucosa favors the drug absorption. Therefore, the oral route has continued to be the most appealing route for drug delivery despite the advancements made in the new drug delivery systems. Banker and Anderson stated that at least 90% of drugs used to produce systemic effect are administered orally. The bioavailability of drug is dependent on in vivo disintegration, dissolution, and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluents and superdisintegrant.

Conventional dosage forms of a drug such as tablets, capsules, solution, suspension, suppository etc. releases the active ingredients into the absorption pool immediately. The drug level time profile of such a system is as shown in Fig.1.1.1

![Figure 1.1.1 Typical drug blood level versus time profiles for intravenous injection and an extra vascular route of administration.](image-url)
As seen in the Fig. 1.1.1 administration of drug either by intravenous injection or an extra vascular route, for e.g., orally, intramuscular or rectally administration of the conventional dosage form does not maintain the drug blood levels within the therapeutic range for an extended period of time. Here, the release of drug is much faster than the absorption (Kr>>Ka). The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

One approach to maintain drug blood levels in the therapeutic range for longer periods, for e.g., increasing the initial dose of an i.v. injections, toxic levels may be produced at early times. This approach is undesirable and unsuitable. An alternate approach is to administer the drug repetitively using a constant dosing interval, as in multiple dose therapy. This result are shown in Fig.1.1.2

![Typical blood level versus time profiles following oral multiple dose therapy](image)

**Figure 1.1.2** Typical blood level versus time profiles following oral multiple dose therapy. 

The concentration of a drug in the blood fluctuates over successive doses of most conventional single unit oral dosage forms. The main reason for this is that the drug is released immediately after administration (i.e. burst release effect). This causes the drug blood concentration to rise quickly to a high value (“peak”) followed by a sudden decrease to a very low level (“trough”) as a result of drug elimination.\(^2,6\)
The potential problems associated with multiple dose therapy are:

1. If the dosing interval is not appropriate for the biological half-life of the drug, large ‘peaks’ and ‘valleys’ in the drug blood level may result. For e.g., drugs with short half-lives require frequent dosing to maintain therapeutic levels.

2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.

3. Patient non-compliance with the multiple-dosing regimen can result in failure of this approach.

In many instances, the potential problems associated with conventional drug therapy can be overcome by multiple dosing. However, these problems are significant enough to make drug therapy with conventional dosage forms is less desirable than modified release drug delivery systems.

This fact coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of modified release drug delivery.

1.1.2 Nomenclature to describe modified release dosage forms

A number of terms and phrases have been used to describe the oral dosage forms that portray modified release properties; which include delayed release, repeated action, prolonged release, extended release, controlled release and sustained release. Each drug delivery system is aimed at eliminating the cyclical changes in plasma drug concentration seen after administration of conventional delivery systems. Modified release dosage forms are designed to provide quick achievement of a drug plasma level that remains constant (i.e. controlled release) at a value within the therapeutic range of a drug for a significant temporal period of time or achievement of a plasma concentration of a drug that delivers at a slow rate (i.e. sustained release) that stays within the therapeutic range for a longer period of time. Based on the assumption that a drug, which is to be incorporated into a modified release dosage form, confers upon the body the characteristics of a one-compartment open model, then the basic kinetic design of such a product may be assumed to contain two portions, one that provides the initial priming/loading dose, and one that provides the maintenance or sustained dose. To ensure that the therapeutic concentration of the drug in the body remains constant, two conditions must be fulfilled, namely 1) the zero order rate of drug release must determine the absorption rate of the drug, and 2)
the rate at which the drug is released from the maintenance dose (and subsequently the absorption rate) should be equal to the rate of drug elimination at the required steady-state concentration. A list of important terms that describe different modified release dosage forms are defined below.\textsuperscript{8}

**Modified release dosage forms:** defined by the USP23 (1995) as those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

**Delayed release** indicates that the drug is not being released immediately after administration but at a later time.

**Repeat action** indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

**Prolonged release** indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

**Extended release** slow release of the drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hr).

**Controlled release** The drugs are released at a constant (zero order) rate and provide plasma drug concentration that remains invariant with time.

**Sustained release:** the pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed, and the duration of its therapeutic effect is sustained.

1.1.3 Sustained drug delivery
A new development namely, sustained drug release dosage forms, has evolved from the need for a prolonged drug effect, a better control of drug administration and the reduction of side-effects.\textsuperscript{9,10} In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of drug for an extended period. This is usually accomplished by attempting to obtain zero-order release from dosage form.
Fig. 1.1.3 represents a typical drug kinetic pattern for immediate release, controlled release (zero order) and sustained release dosage forms.

**Figure 1.1.3 Drug level versus time profile showing differences between zero-order release (controlled release), sustained release (slow first-order), and immediate release (from a conventional tablet or capsule) dosage forms.**

In conventional drug delivery systems, the drug concentration in the blood rises when the drug is being administered, then peaks and declines almost to zero. Each individual drug has a maximum safe concentration and a minimum effective concentration. Fluctuations in plasma concentration may mean that drug levels may swing too high leading to toxic side-effects; alternatively drug may fall too low leading to a lack of efficacy. Furthermore, the plasma drug concentration in a patient at a particular time depends on the compliance with the prescribed dosage interval. Sustained drug delivery systems maintain the drug effect in desired therapeutic range with just a single dose, simulating an intravenous infusion of a drug, localizing drug delivery to a particular body compartment, improving tolerability and reducing the need to follow-up pharmaceutical care (i.e. improving patient comfort and compliance). These dosage forms could also preserve medications that are rapidly destroyed by the body.

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**Exploitation of Natural Product In Formulation Design of A Model Drug**
1.1.3.1 Principle of sustained drug delivery

The conventional dosage forms release their active ingredients into an absorption pool immediately. The absorption pool represents a solution of the drug at the site of absorption. The terms $K_r$, $K_a$ and $K_e$ are first order rate constants for drug release, absorption and overall elimination respectively. Immediate release of drug from conventional dosage form implies that $K_r \gg K_a$. Alternatively speaking the absorption of drug across a biological membrane is the rate limiting step. For non-immediate release dosage forms, $K_r \ll K_a$, i.e., the release of drug from the dosage form is the rate-limiting step.

The main objective in designing a sustained release system is to deliver the drug at a rate necessary to achieve and maintain a constant blood level. This rate should be analogous to that achieved by continuous i.v. infusion where the drug is provided to the patient at a constant rate just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. The release of a drug from the dosage form should follow zero order kinetics, as shown by the equation 1,

$$K^0_r = \text{Rate In} = \text{Rate Out} = K_e \times C_d \times V_d$$

(1)

Where, $K^0_r$ = Zero order rate constant for drug release (amount per time), $K_e$ = First order rate constant for overall drug elimination (time$^{-1}$), $C_d$ = Desired drug level in the body (amount per volume), $V_d$ = Volume space in which the drug is distributed (liters).

The values of $K_e$, $C_d$ and $V_d$ needed to calculate $K^0_r$ are obtained from appropriately designed single dose pharmacokinetic study. It is important to recognize that while zero order release may be desired theoretically; non-zero order release may be equivalent clinically to constant release in many cases.

1.1.3.2 Advantages of sustained drug therapy

1. Avoid patient compliance problems.
2. Employ less total drug,
   a) Minimize or eliminate local side effects
   b) Minimize or eliminate systemic side effects
   c) Obtain less potentiation or reduction in drug activity with chronic use
   d) Minimize drug accumulation with chronic dosing
3. Improve efficiency in treatment,
   a) Cure or control condition more promptly
   b) Improve control of condition i.e. reduce fluctuation in drug level
   c) Improve bioavailability of some drugs
   d) Make use of special effects, e.g. sustained release aspirin for relief of arthritis in morning by dosing before bedtime

4. Economy
Although the initial unit cost of most sustained release drug delivery systems is usually greater than that of conventional drug delivery systems, but the average cost of treatment over an extended time period may be less. Economy may result from a decrease in nursing time, reduction in hospitalization, less lost work time, etc. The most important reason for sustained drug therapy is improved efficiency in the treatment i.e., optimized therapy.

1.1.3.3 Disadvantages of sustained drug therapy
1. Administration of sustain release medication does not permit the prompt termination of therapy.
2. The physician has less flexibility in adjusting the dosage regimens. This is fixed by the dosage form design.
3. Sustained release forms are designed for normal population i.e., on the basis of average drug biologic half-life. Problems may be observed in diseased conditions where drugs disposition is altered, if the liver and kidney functions are impaired.
4. Economic factors must also be assessed, since more costly processes and equipments are involved in manufacturing of any sustained release dosage forms.

1.1.4 Release pattern of drug from polymer matrices
Recently, several technical advancements have been made in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and / or targeting the delivery of drug to a tissue. Although these advancements have led to the development of several novels drug delivery systems that could revolutionaries the method of medication and provide a number of therapeutic benefits. It also creates
some confusion in the terminology between ‘controlled release’ and ‘sustained release’. Unfortunately these terms have been often used interchangeably in the scientific literature and technical presentations over the years.

1.1.4.1 Methods for preparing sustained release oral dosage form

The most acceptable technologies used to obtain sustained release oral products are as follows:\textsuperscript{12}

1. Release from slow eroding solid matrices,
2. Release from solid hydrophilic gel matrices,
3. Release from porous inert solid matrices,
4. Release from coated granules disintegrating at a controlled rate,
5. Release from granules coated with diffusion controlling membrane,
6. Release from ion exchange resin complexes, and
7. Release by reducing the solubility of drugs.

1.1.5 Formulation of modified release dosage forms

The basic principle that governs all modified release dosage forms is drug diffusion that occurs from a region of high concentration to a region of low concentration. This concentration difference is the driving force for drug diffusion out of the system. The inside of the system should have lower water content initially than the surrounding medium to control the diffusion of a drug effectively.\textsuperscript{8}

Different methods have been employed to provide modified drug release, which include modifications to the physical and chemical properties of the drug or changes to the dosage form as indicated in Fig. 1.1.4
1.1.5.1 Methods to modify drug release by drug modification

These methods take advantage of the changes in the physicochemical properties of drug moieties caused by complex formation, drug adsorbate preparations and prodrug synthesis. These modifications are possible only with drug moieties containing appropriate functional groups. This approach is independent of the dosage form design.7

Fig. 1.1.5 shows the mechanisms of sustained release based on drug modification. In the case of drug complexes the effective release rate of the drug is a function of two processes, including the rate of dissolution and breakdown of the complex in a solution. If the rate of dissolution is greater than the rate of dissociation, a zero-order release pattern might be achieved. In this case, the concentration of the complex is maintained at its saturation point if the solubility of the complex is sufficiently low so that excess solid complex is present during the onset of the maintenance time. If the rate of dissociation is greater than the rate of dissolution, the dissolution of the complex will be the rate-determining step.7
Another approach for drug modification is through the formulation of a prodrug. This can be achieved through designing a bio-reversible derivative (prodrug) that can afford an increased or selective transport of the drug to the site of action (e.g., levodopa as prodrug for the central nervous system anti-parkinsonism agent dopamine) or by designing a derivative that goes everywhere in the body but undergoes bio-activation only on the target. The solubility, specific absorption rate and elimination rate constant of an effective prodrug should be significantly lower than that of the parent drug. In drug adsorbates, drug availability is determined only by the rate of dissociation and by the access of the adsorbate surface to water as well as the effective surface area of the adsorbate.  

1.1.5.2 Methods to modify drug release by dosage form modification  
The most modified release dosage forms of this class employ either an embedded matrix or a physical barrier principle to provide slow release of the maintenance dose. The techniques used to build this matrix or barrier into the dosage form include the
monolithic or matrix systems, the reservoir or membrane controlled systems, the osmotic pump systems, coated beads and micro encapsulation. 7, 8, 13

1.1.5.2.1 Monolithic or matrix systems

These systems can be divided into two groups: (1) those with drug particles dispersed in a soluble matrix, with drug becoming available as the matrix dissolves or swells and dissolves (hydrophilic colloid matrices); and (2) those with drug particles dispersed in an insoluble matrix, with drug becoming available as a solvent enters the matrix and dissolves the particles (lipid matrices and insoluble polymer matrices).

Drugs dispersed in a soluble matrix rely on slow dissolution of the matrix to provide sustained release. Excipients used to provide a soluble matrix often are those used to make soluble film coatings. Alternatively, slowly dissolving fats and waxes can be used. Synthetic polymers, such as poly orthoesters and poly anhydrides, have also been used. These polymers undergo surface erosion with little or no bulk erosion. If the matrix is presented with conventional tablet geometry, then on contact with dissolution media the surface area of the matrix decreases with time, with a concomitant decrease in drug release.

Drug particles may be incorporated into an insoluble polymer matrix. Drug release from these matrices follows penetration of fluid into the formulation, followed by dissolution of the drug particles and diffusion of the solute through fluid-filled pores. This type of delivery system would not be suitable for the release of compounds that are insoluble or those compounds that have low aqueous solubility. Excipients used in the preparation of insoluble polymers include hydrophobic polymers such as polyvinyl acetate, ethyl cellulose and some waxes. At this point each of the three main types of monolithic/matrix systems will be discussed.

1.1.5.2.1.1 Lipid matrix systems

Wax matrices prepared by direct compression; hot-melt granulation or roller compression; have their active agent contained in a hydrophobic substance that remains intact during drug release. The release of the drug depends on an aqueous medium dissolving the channeling agent, which leaches out of the matrix forming capillary pores. The active ingredient then dissolves in the aqueous medium and diffuses out of the matrix, by way of the water-filled capillaries. A typical formulation consists of an active drug, a wax matrix former (hydrophobic material that are solids at room temperature and do not melt at body temperature, e.g., hydrogenated...
vegetable oils, cottonseed oils, soya oils, microcrystalline wax and carnauba wax), a channeling agent (soluble in the GIT, in water and leaches out of the formulation leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released, e.g., sodium chloride and sugars), solubiliser and pH modifier, an anti-adherent/glidant and a lubricant.

1.1.5.2.1.2 Insoluble polymer matrix systems

Drugs are embedded in an inert polymer, which is not soluble in the gastrointestinal fluid. Drug release has been compared to the leaching from a sponge. The release rate depends on drug molecules in aqueous solution diffusing through a network of capillaries formed between compact polymer particles. The factors influencing drug release rate from insoluble polymer matrix systems are-

- Pore structure – pore forming salts and compression force,
- Excipients – wettability changed by the soluble and insoluble components,
- Particle size of polymer component – influences the surface area exposed to the medium.

There are three primary mechanisms by which active agents can be released from a matrix delivery system, which involve diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given drug release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the modified-release device. The diffusion can occur on a macroscopic scale - as through pores in the polymer matrix - or on a molecular level, by passing between polymer chains. The particle size of the insoluble matrix components influences the release rate, larger particles leading to an increase in release rate. This is attributed to these coarser particles producing matrices with a more open pore structure. An increase in drug loading tends to enhance release rate, but the relationship between the two is not clearly defined. One possible explanation may be a decrease in the tortuosity of the matrix.

An insoluble polymer and an active agent have been mixed to form a homogeneous system, also referred as a matrix diffusion system as shown in Fig. 1.1.6. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to be released.
1.1.5.2.1.3 Hydrophilic colloid matrix systems

A hydrophilic matrix, controlled release system is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling and polymer dissolution. At the same time, other soluble excipients or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away.

The mechanisms by which drug release is controlled in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer which present throughout the tablet, hydrates on the outer tablet surface to form a gel layer (Fig. 1.1.7). Throughout the life of the ingested tablet, the rate of drug release is determined by diffusion (if soluble) through the gel and by the rate of tablet erosion. With soluble drugs, the primary drug release mechanism is by diffusion through the gel layer and with insoluble drugs, the primary drug release mechanism is by surface erosion. A fast rate of hydration followed by quick gelation and polymer/polymer coalescing is necessary for a rate-controlling polymer to form a protective gelatinous layer around the matrix. This prevents the tablet from immediate disintegration,
resulting in premature drug release. Fast polymer hydration and gel layer formation are critical when formulating with water-soluble drugs and water-soluble excipient.

**Figure 1.1.7 Drug release from a matrix tablet.**

These swellable-soluble matrices are hydrogels that swell on hydration. The systems are capable of swelling followed by gel formation, erosion and dissolution in aqueous media. Their behavior is in contrast to a true hydrogel, which swells on hydration but does not dissolve. Drug particles are dispersed in an insoluble matrix and the drug becomes available as the solvent enters the matrix and dissolves the drug particles. This is enhanced by the swelling, which is followed by gel formation, erosion of the matrix system and the dissolution of the drug. Hydrophilic polymer matrix systems comprise a mixture of the drug, the hydrophilic colloid, release modifiers and lubricant/glidant. Diffusion of the drug through the hydrated matrix is the rate limiting step in drug release. The tortuosity of the diffusion path and the ‘micro-viscosity’ and interactions within the interstitial continuum govern the diffusion of the drug through the hydrated gel layer and hence, the release of the drug.

Two common types of hydrophilic matrix systems are the true gels which are cross-linked polymeric structures formed Drug diffusion with increasing time of exposure to dissolution media by chemical bonds (covalent) or physical bonds (helix formation based on hydrogen bonds or ionic interactions), for which gelatin is an excellent polymeric example, and the viscous matrices which are simple entanglements of adjacent polymer chains, For e.g., HPMC and alginates.
Table 1.1.1 Comparison of different types of hydrophilic colloid matrix systems.

<table>
<thead>
<tr>
<th>True gel matrices</th>
<th>Viscous matrices</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The diffusion pathway is via the continuous phase in the interstices of the gel</td>
<td>• The diffusion pathway is via the continuous phase trapped between the adjacent polymeric chains</td>
</tr>
<tr>
<td>• The cross-links are more or less 'fixed' after the gel has formed</td>
<td>• There are no 'fixed' cross-links</td>
</tr>
<tr>
<td>• The bulk viscosity of the gel is derived from the structure of the cross-linked polymeric chains with a contribution from the continuous phase</td>
<td>• The bulk viscosity is related to the enlargement of adjacent polymer chains which are free to move within the continuous phase</td>
</tr>
<tr>
<td>• Bulk viscosity generally does not correlate with diffusion</td>
<td>• Bulk viscosity correlates with diffusion</td>
</tr>
<tr>
<td>• Diffusion in the gel correlates with 'microviscosity'</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.1.1 compares the different types of hydrophilic colloid matrix systems, which are the true gel matrix system and the viscous matrix system. The two are more like extreme opposites of each other in terms of their cross-linked chain structure, viscosity and the ways they release drug substances.

1.1.6 Polymers in drug delivery

One of the most remarkable and useful features of a polymer's swelling ability manifests itself when that swelling can be triggered by a change in the environment surrounding the delivery system. Ranges of materials have been employed to control the release of drugs and other active agents. The earliest of these polymers were originally intended for non-biological uses and were selected because of their desirable physical properties. To be successfully used in controlled drug delivery formulations, a material must be chemically inert and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging and be readily processable. However, in recent years additional polymers designed primarily for medical applications have entered the arena of controlled release. Many of these materials are designed to degrade within the body.
Hydrophilic matrices are an interesting option when developing an oral sustained release formulation. They can be used for controlled release of both water soluble and water insoluble drugs. The release behavior of drugs varies with the nature of the matrix and its complex interaction of swelling, diffusion and erosion process.\(^{15-19}\)

1.1.6.1 Classification of hydrophilic polymers

The hydrophilic polymers can be arranged into three broad groups: \(^{20}\)

1. **Non-cellulose Natural or Semisynthetic Polymers:** These are products of vegetable origin and are generally used for pharmaceutical purpose. Agar \(^{21}\), alginates \(^{22-24}\), chitosan \(^{25-28}\), xanthan gum \(^{29}\), guar gum \(^{29-32}\), carrageenan \(^{33,34}\), starches \(^{35-39}\) etc., are commonly used polymers.

2. **Polymer of Acrylic acid:** These are arranged in the carbomer group and commercialized under the brand name of Carbopol \(^{40}\). The major disadvantage of this type of polymers is its pH dependent gelling characteristics. \(^{41-44}\)

3. **Cellulose Ethers:** This group is semi-synthetic cellulose derivatives is the most widely used group of polymers. Non-ionic polymers such as HPMC of different viscosity grades are widely used. \(^{45-47}\) Methylcellulose \(^{48}\), in contrast, has not proved especially useful in this field. In the last few years a number of interesting applications of the ionic sodium CMC have been found. \(^{48-52}\)

1.1.6.2 Advantages of hydrophilic matrix tablets \(^{3,53-59}\)

1. Proper control of the manufacturing process, reproducible release profiles are possible.

2. Though the structure makes the immediate release of a small amount of active principle, there is no risk of 'dose dumping'.

3. Their capacity to incorporate active principle is large, which suits them to delivery of large doses.

4. The manufacturing processes are notably straightforward. The usual route of formulating tablets is done via direct compression or by wet granulation.

5. Large variety of non-expensive gelling agents is approved for oral use by the competent official organizations.

6. Comparatively simple concept.
7. Excipients are generally economic and are usually GRAS (Generally Regarded As Safe).

8. Capable of sustaining high drug loadings.

9. Erodible, so reducing the possibility of 'ghost' matrices.

10. Well established technology.

1.1.6.3 Disadvantages of hydrophilic matrix tablets

1. For a hydrophilic sustained release matrix tablet, in which the release is mainly controlled by erosion of the swollen polymer gel barrier at the tablet surface, the presence of food may shear the hydrated polymer gel layer to cause dose dumping or it may block the pores of the matrix and inhibit the drug release rate.

2. Release of the drug is dependent on two diffusion processes.

[a] penetration of water through the hydrated matrix into the non-hydrated core, and

[b] diffusion of dissolved drug through the hydrated matrix.

3. Required batch-to-batch consistency in the matrix forming materials, other components and process parameters.

4. Need optimal rate-controlling polymers for different actives.

1.1.7 Matrix diffusion-controlled drug delivery systems \(^{60, 61}\)

In this type of sustained release drug delivery systems, the drug reservoir results from the homogeneous dispersion of drug particles in either a lipophilic or a hydrophilic polymer matrix. Fig. 1.1.8 shows the top of a swellable matrix tablet during drug release showing the three fronts.

**The swelling front**, the boundary between the glassy polymer and its rubbery phase.

**The diffusion front**, the boundary between the solid as yet undissolved drug and the dissolved drug in gel layer, and

**The erosion front**, the boundary between the matrix and the dissolution medium.

The mechanisms of drug release from swellable matrix are diffusion of drug though the gel layer and drug transport due to relaxation of the polymer. The rate of diffusion through the gel layer depends on drug dissolution and matrix erosion, both evidently affecting the drug concentration gradient in gel layer. Drug release from swellable matrix tablet is strictly linked to gel layer dynamics, also where the solubility of the
drugs is so low that the possibility exists for it to be released as solid particles from the dissolving layer of gel.

![Figure 1.1.8 Picture of the top of a swellable matrix tablet during drug release showing the three fronts.](image)

The drug dispersion in the polymer matrix is accomplished either by blending a dose of finely ground drug particles with a viscous liquid polymer or a semisolid polymer, followed by cross linking of polymer chains or mixing drug particles with a melted polymer. The resultant drug-polymer dispersion is then extruded to form drug delivery devices of various shapes and sizes designed for specific application. It can also be fabricated by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation in a mold at an elevated temperature and/or under a vacuum.

The rate of drug release from this matrix diffusion controlled drug delivery systems is time dependent and defined in equation 2,

\[
\frac{dq}{dt} = \left( \frac{A \times Cr \times Dp}{2t} \right)^{1/2}
\]

Where, A is the loading dose initially dispersed in the polymer matrix, Cr is the drug solubility in the polymer, which is also the drug reservoir concentration in the
polymer matrix, and Dp is the diffusivity of the drug molecule in the polymer matrix. The following equation is obtained on integration of equation 2,

\[ \frac{Q}{t^{1/2}} = (2A \times Cr \times Dp)^{1/2} \]  

(3)

Where, Q defines the flux of drug release at steady state from matrix diffusion controlled drug delivery system.

Hydrophilic matrix dosage forms essentially consist of a compressed blend of hydrophilic polymer and drug. According to the generally accepted mechanism (Fig.1.1.8), the drug release from hydrophilic matrix dosage forms starts when the tablet comes in contact with GI fluid. The surface of the tablet hydrates to release exposed drug and at the same time form a viscous polymer mucilage or gel. This gel fills the interstices within the tablet retarding further ingress of liquid.
1.2 Introduction to disintegrants
Despite increasing interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the GIT. The proper choice of disintegrant and its consistency of performance are of critical importance to the formulation development of such tablets. In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth.

Bioavailability of a drug depends on absorption of the drug, which is affected by solubility of the drug in GI fluid and permeability of the drug across GI membrane. The drugs solubility mainly depends on physical – chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet.

The drug will dissolve at a slower rate from a nondisintegrating tablet due to exposure of limited surface area to the fluid. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration. 62 - 64

1.2.1 Disintegrants 65, 66

Figure 1.2.1 Schematic representation of tablet disintegration and subsequent drug dissolution.
Disintegrant is a term applied to various agents added to tablet formulation for the purpose of causing the compressed tablet to break apart when placed in an aqueous environment and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants. The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet. Fig. 1.2.1 shows schematic diagram of disintegration. Basically, the major function of disintegrant is to oppose the efficiency of tablet binder and physical force that acts under compression to form the tablet. Disintegrants, act by different mechanisms. Disintegrants that enhance the action of capillary forces in a rapid uptake of aqueous liquids and those that swell in contact with water are considered the more important. These mechanisms include factors like deformation of particles, capillarity, heat of wetting, particle-particle repulsion and hydrogen bond annihilation. Some others, less common mechanisms are: act by melting at body temperature, releasing gases to disrupt the tablet structure and those, which destroy the binder by enzymatic action.

To obtain a rapid disintegration a disintegrant force must develop inside the tablet that is capable of weakening and breaking inter-particle bonds. This is generated by the replacement of solid/air with solid/liquid interfaces. The displacement of air by water or aqueous liquids is a wetting process that may lead to hydration of the involved particles and produce disintegration. Particles with different properties will produce greater disruptive shear forces and smaller disintegration times. This means that disintegration could be a function of a given surface of contact between particles with different hydration properties.

1.2.2 The ideal characteristics of disintegrant

- Poor solubility
- Poor gel formation
- Good hydration capacity
- Good molding & flow property
- No tendency to form complex with drug
1.2.3 Types of disintegrants based on their working mechanisms

1.2.3.1 Disintegrants those propagate capillary effects or wicking or porosity

1.2.3.2 Disintegrants those swell

1.2.3.3 Gas producing disintegrants

1.2.3.4 Enzymes as disintegrants

1.2.3.5 Heat of wetting (air expansion) as disintegrants

1.2.3.6 Due to disintegrating particle/particle repulsive forces act as disintegrant

1.2.3.7 Deformation of particles as a disintegrant

1.2.3.1 Disintegrants those propagate capillary effects or wicking or porosity

Water uptake caused by capillary forces is crucial factor in the disintegration process of many formulations. In such system, the pore structure of the tablet is of prime importance, and any inherent hydrophobicity of the tablets mass will adversely affect it. Therefore, disintegrants in this group must be able to maintain a porous structure in the compressed tablet and show a low interfacial tension toward aqueous fluid. Rapid penetration by water throughout the entire tablet matrix is essential to facilitate its break up. Disintegration by capillary action is always the first step. When we put the tablet into suitable media, the media penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles.

Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. These types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles. Tablet porosity provides pathways for the penetration of fluid into tablet. The disintegrant particles (with low cohesiveness and compressibility) themselves act to enhance porosity and provide these pathways into tablet. Liquid is drawn up into these pathways through capillary action and rupture the interparticle bonds causing the tablet to break apart. Concentrations of disintegrants that ensure a continuous matrix of disintegrant are desirable and level between 5 - 20 % are common. For e.g., starch, MCC, cross-povidone etc.

1.2.3.2 Disintegrants those swell

The most widely accepted general mechanism of action for tablet disintegration is swelling. This class of disintegrants acts by swelling in the presence of aqueous GI
fluids. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

Main problem with this group of disintegrants is that on swelling, many disintegrants produce a sticky or gelatinous mass that resists break up of the tablet, making it particularly important to optimize the concentration in the formulation. Although untreated starches do not swell sufficiently, certain modified forms, such as SSG, do swell in cold water and are better as disintegrant. Alginic acid, agar, karaya and tragacanth etc., are also used as disintegrant. Fig. 1.2.2 shows disintegration mechanism by wicking and swelling.

![Swelling and Wicking Mechanism](image)

(a) Wicking mechanism
(b) Swelling mechanism

Figure 1.2.2 Disintegration mechanism (a) by wicking and (b) by swelling mechanism.

Black particles in both cases are disintegrating agent.

1.2.3.3 Gas producing disintegrants

Gas producing disintegrants are used when rapid/extra rapid disintegration or a readily soluble formulation is required. This group of disintegrants acts by evolution of a gas when tablet is exposed to the aqueous GI fluids. The most common effervescent agents are mixture of citric and tartaric acid plus carbonates or bicarbonates. Carbon dioxide released within tablets on wetting due to interaction...
between bicarbonate and carbonate with citric or tartaric acid. The tablet disintegrates
due to generation of pressure within the tablet.
Their main drawback is the need for more stringent environment control during
manufacturing and storage. In particular, gas-producing disintegrants are quite
sensitive to small changes in humidity level & temperature. So, strict control of
environment is required during manufacturing of the tablets. The effervescent blend is
either added immediately prior to compression or can be added in to two separate
fraction of formulation.

1.2.3.4 **Enzymes as disintegrants**

Such tablets are not naturally very cohesive and thus have been manufactured by a
wet granulation process. There was a requirement to involve the binders; on the same
time addition of small quantities of appropriate enzyme may be sufficient to produce
rapid disintegration. Some times enzymes presents in the body act as disintegrants.
These enzymes destroy the binding action of binder and helps in disintegration.
Table 1.2.1 shows list of enzymes used in tablet formulation.

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>BINDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylase</td>
<td>Starch</td>
</tr>
<tr>
<td>Protease</td>
<td>Gelatin</td>
</tr>
<tr>
<td>Cellulase</td>
<td>Cellulose and it's derivatives</td>
</tr>
<tr>
<td>Invertase</td>
<td>Sucrose</td>
</tr>
</tbody>
</table>

1.2.3.5 **Heat of wetting (air expansion) as disintegrants**

Matsumaru was the first to propose that the heat of wetting of disintegrat particles
could of mechanism of action. When disintegrants with exothermic properties gets
wetted, localized stress is generated due to capillary air expansion, which helps in
disintegration of tablet. It has also been proposed that disintegration action might
result from expansion of the entrapped air owing to generation of 'heat of wetting'.
For e.g., starch. This explanation, however, is limited to only a few types of
disintegrants and can not describe the action of most modern disintegrating agents.
1.2.3.6 Due to disintegrating particle/particle repulsive forces act as disintegrant \(^7^5\)

Researchers found that repulsion is secondary to wicking where disintegration of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory, that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration where water is required to initiate mechanism.

1.2.3.7 Deformation of particles as a disintegrant \(^7^9\)

It had proved that during tablet compression, disintegrant particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. This increase in size of the deformed particles produces a break up of the tablet. For e.g., the swelling capacity of starch was improved when granules were extensively deformed during compression.

![Diagram](image)

Particles swell to precompression size and break up the matrix  
Water is drawn into the pores and particles repel each other because of the resulting electrical force

Figure 1.2.3 Disintegration mechanism by deformation and repulsion.

1.2.4 Methods of addition of disintegrants \(^8^0\)

The method of addition of disintegrants to a tablet is very crucial part. Disintegrating agent can be added either prior to granulation (intragranular) or prior to compression (after granulation i.e. extragranular) or at the both processing steps. Extragranular fraction of disintegrant (usually, 50% of total disintegrant requires) facilitates breakup
of tablets to granules and the intragranular addition of disintegrants produces further erosion of the granules to fine particles.

The extragranular portion ensure rapid disintegration, while the intragranular fraction leads to harder tablets and a finer size distribution on dispersion. There are advantages to be gained in dividing the disintegrant into both extra- and intragranular portions.

1.2.5 Factors affecting disintegration

1.2.5.1 Effect of fillers

The solubility and compression characteristics of fillers affect both the rate and mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents and as they are water soluble, they are likely to dissolve rather than disintegrate. Insoluble diluents produce rapid disintegration with adequate amount of disintegrants. Chebli and cartilier proved that tablets made with spray dried lactose (water soluble filler) disintegrate more slowly due to its amorphous character and has no solid planes on which the disintegrating forces can be exerted than the tablet made with crystalline lactose monohydrate.

1.2.5.2 Effect of binder

The concentration of binder can also affect the disintegration time of tablet. It was observed that as the concentration of binder is increased there was increased in disintegration time. The binding capacity of binder increases, disintegrating time of tablet increases and this counteract the rapid disintegration.

1.2.5.3 Effect of lubricants

Mostly lubricants are hydrophobic in nature (Mg-stearate) and they are usually used in smaller size than any other ingredient in the tablet formulation. When the mixture is mixed, lubricant particles may adhere to the surface of the other particles. This hydrophobic coating inhibits the wetting and consequently tablet disintegration. Lubricant has a strong negative effect on the water uptake if tablet contains no disintegrants or even high concentration of slightly swelling disintegrants.

On the contrary, the disintegration time is hardly affected if there is some strongly swelling disintegrants are present in the tablet. For e.g., SSG whose effect remains unaffected in the presence of hydrophobic lubricant.
1.2.5.4 Effect of compression force or hardness of tablet\textsuperscript{88, 89}

An unusual occurrence of decreasing tablet disintegration time with increasing tablet hardness was explored. For e.g., tablets were made with varying ratios of starch disintegrant to starch paste and compressed with eight different forces. There was an unusual disintegration pattern was observed.

1.2.6 Classification of disintegrating agents according to its chemical nature\textsuperscript{90}

1. **Starches**: Natural starch (corn, potato), pregelatinized starch, modified corn starch, SSG etc.
2. **Clays**: Veegum HV
3. **Cellulose**: Purified cellulose, methyl cellulose, sodium CMC, MCC
4. **Algins**: Alginic acid
5. **Gums**: Agar, guar gum, locust bean gum, karaya gum, pectin, tragacanth etc.
6. **Miscellaneous**: Surfactants, natural sponge, resins, effervescent mixtures, hydrous aluminum silicate etc.
1.3 Introduction to gums and mucilages

1.3.1 Introduction

Robbins has stated, "in spite of the problems which have beset the gums market in recent years, the fact remains that in many cases the gums provide a valuable source of income for many poor smallholders or itinerant labourers, either in very poor countries or in the poorest regions of rather more developed countries. As such they are important commodities ...". This remains true today. Tens of thousands of people worldwide, living in regions ranging from semi-arid lands to moist rainforest, depend on the collection of gums, resins and latexes as a means of cash income. Equally, many millions of people in consuming countries make use of these products in their everyday life.

Mother Nature has gifted India with great variety of flora and fauna. Since centuries man has made an effective use of materials from natural origins in the medical and pharmaceutical field. Now a day, the whole world is turning towards natural drugs and excipient. The natural materials do hold advantages over the synthetic materials because they are non toxic, less expensive and freely available. Further, it can be modified to obtain tailor made materials for drug delivery system and then can compete with the synthetic products available in the market. Various kind of natural gums are used in the food industry and are regarded as safe for human consumption. It should be noted that many 'old' materials compete successfully today after almost a century of efforts to replace them. It is usual balance of economics and performance that determines the commercial realities.

Gums are considered to be pathological products formed upon injury of the plant or owing to unfavorable conditions, such as drought, by a breakdown of cell walls (extra cellular formation; gummosis). Conversely, mucilages are generally normal products of metabolism, formed within the cell (intracellular formation) and/or are produced without injury to the plant. An effort has made to distinguish between mucilage and gums on the basis that gums readily dissolve in water, whereas, mucilage form slimy masses. Other investigators have tried to distinguish them on the basis that mucilages are physiological products and gums are pathological products. Acacia, tragacanth, guar gum etc, are examples of gums while mucilages are often found in different parts.
Introduction

of plants. For e.g., in epidermal cells of leaves (senna), in seed coats (linseed, psyllium), roots (marshmallow), barks (slippery elm) and middle lamella (aloe). Gums and mucilage are plant hydrocolloids. They are translucent amorphous substances. They are polymers of monosaccharide or mixed monosaccharide and many of them are combined with uronic acids. Gums and mucilage have similar constituents and on hydrolysis yield a mixture of sugars and uronic acids. Mucilages are neutral or acidic or mixtures of both.

Gums and mucilages have hydrophilic molecules, which can combine with water to form viscous solutions or gels. The nature of the molecules influences the properties of the various gums. Linear polysaccharide molecules occupy more space and are more viscous than highly branched molecules of the same molecular weight. The branched compounds form gels more easily and are more stable because extensive interaction along the chains is not possible.

Mucilage is a thick gluey substance produced by many plants and some microorganisms. Mucilage is an exopolysaccharide—a polymer composed of sugar residues and secreted by a microorganism into the surrounding environment. Mucilage in plants act as water storage, protection for seed germination, as a membrane thickener and food reserve. Mucilage has a unique purpose in some carnivorous plants. The plant genera Drosera (Sundews), Pinguicula, and others have leaves studded with mucilage-secreting glands, and use a "flypaper trap" to capture insects. Exopolysaccharides are the most stabilising factor for micro aggregates and are widely distributed in soils. Therefore exopolysaccharide-producing "soil algae" play a vital role in the ecology of the world's soils.

1.3.2 Reasons for developing new excipients
Due to certain reasons there was an increase in interest for the development of new excipient/diluents.

1. Some drugs show incompatibilities with many of the current range of excipients. For e.g., Atenolol-PVP, Atenolol-Mg-stearate. One of the more common drug-excipient incompatibilities is the reaction between aldehydic sugars, such as lactose and primary and secondary amines, leading to the formation of Schiff's bases. These complex series of reactions lead to browning and discoloration of the dosage form. Despite being a carrier of choice for dry powder aerosol
formulations, lactose may need to be replaced with a different carrier, such as mannitol or sucrose, when formulating primary and secondary amines.\(^4\) Mg-stearate is incompatible with aspirin, some vitamins and most alkaloidal salt.\(^99\)

2. There is a need for excipients that will allow faster manufacturing of formulations. For e.g., in tablet dosage form, new excipients having better compressibility at very high compression speeds are need of today. Today, it is not unheard of to have tableting equipment compressing 8,000 to 10,000 tablets per min. It is critical under these conditions to have an excellent flowing granulation/powder blend. Many sugar-based excipients, such as maltose, mannitol, and sorbitol are not compressible in their natural state and need to be modified for use in direct compression tableting.

3. Some future developments may require new delivery systems. For e.g., new drug delivery systems for oral administration of biotechnology products need new excipient, which will avoid the inconvenience of multiple daily injections. Progress in the development of peptides as useful drugs has been impeded in part by their rapid excretion, resulting in short circulating lifetimes. This generated considerable interest in improving the duration of action of drugs through conjugation with the water-soluble, biocompatible excipient, poly (ethylene glycol). Such conjugates have reduced enzymatic degradation rates and lengthened circulating lifetimes compared to the native compounds. There are six FDA-approved PEGylated products on the market, vouching for the safety and commercial viability of this technology. Other novel lipophilic carbohydrate excipients, termed oligosaccharide ester derivatives (OEDs), have been used to modify pharmacokinetic profiles of drugs. This technology is quite flexible, offering the ability to formulate drug molecules with modified-release characteristics and improved bioavailability. In other technology, use of selected carbohydrate excipient, such as trehalose and sucrose to stabilize molecules in the dry state, there by preventing their physical and chemical degradation at ambient temperatures and above. These patent-protected drug delivery technologies are suited to the delivery of macromolecules, such as proteins and peptides by the pulmonary, oral, and injectable routes.

4. Drug targeting systems like liposome delivery systems need newer excipient, because the existing excipients for liposome are too costly.
1.3.3 Disadvantages of synthetic polymers

The synthetic polymers have certain disadvantages such as high cost, toxicity, environmental pollution during synthesis, non-renewable sources, side effects, less patient compliance.

1. Acute and chronic adverse effects (skin and eye irritation) have been observed in workers handling the related substances methyl methacrylate and poly-(methyl methacrylate) (PMMA).\(^{100}\)

2. Reports on adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site formulated with povidone. Evidence also exist that povidone may accumulate in organs following intramuscular injections.\(^{101}\)

3. Acute oral toxicity studies in animals indicated that carbomer-934P had a low oral toxicity at a dose up to 8 g/kg when administered without fatalities occurring. Carbomer dust is irritating to the eyes, mucous membranes and respiratory tract. So, gloves, eye protection and dust respirator are recommended during handling.\(^{102}\)

4. Studies in rats have shown that 5% polyvinyl alcohol aqueous solution injected subcutaneously can cause anemia and can infiltrate into various organs and tissues.\(^{103}\)

5. Some disadvantages of biodegradable polymers in tissue engineering application are their poor biocompatibility, release of acidic degradation products, poor process ability and loss of mechanical property very early during degradation. It was studied that poly glycolides, polylactides and their co-polymers have an acceptable biocompatibility but shown systemic or local reactions due to acidic degradation products. An initial mild inflammatory response has been reported by using poly-(propylene fumarate) on rat implant studies.\(^{104}\)

1.3.4 Advantages of natural gums & mucilages\(^{93, 95}\)

The advantages of natural plant based materials includes:

1. Biodegradable
2. Biocompatible and non toxic
3. Low cost
4. Renewable source
5. Environmental-friendly processing
6. Local availability (especially in developing countries)
7. Better patient tolerance as well as public acceptance
8. From edible sources

1.3.5 Disadvantages of natural gums & mucilages

1. Microbial contamination
2. Batch to batch variation
3. Uncontrolled rate of hydration
4. Thickening nature
5. Drop in viscosity on storage

1.3.6 Classification of mucilages

Polysaccharides are widely distributed in nature. The polysaccharides are complex carbohydrates containing one or more monosaccharide or their derivatives linked in a bewildering linkages and structures. Polysaccharides are abundantly present in plants, animals, seaweeds, fungi and other microbial sources, where they perform diversified structural and metabolic functions, with the plant sources being the largest. The polysaccharides can be classified according to their sources, nature etc.

1.3.6.1 According to Sources-

[a] Algal (seaweed) polysaccharides: Agar, Carrageenan, Alginic acid, Laminarin

[b] Plant polysaccharides: Exudates - Gum Arabica, Gum ghatti, Gum karaya, Gum tragacanth

Seed polysaccharides: Guar gum, Locust bean gum

Extracts: Pectin, Larch gum

[c] Animal polysaccharides: Chitin and Chitosan


[e] Cellulose derivatives: CMC, Hydroxy ethyl cellulose, HPMC, MC, MCC
1.3.6.2 According to Source-

[a] Starch Polysaccharides: Starch, Amylose, Cellulose.

[b] Polysaccharides from plant source: Pectins, Inulin, Guar gum, Locust Bean gum, Glucomannan, Khaya and Albizia gums,

c] Polysaccharides from animal source: Chondroitin sulfate, Hyaluronic acid, Chitosan

d] Polysaccharides from bacterial source: Dextran, Curdlan

e] Polysaccharides from Algal source: Alginates

[f] Polysaccharides from fungal source: Scleroglucan

1.3.6.3 According to nature-

1. Natural:

[a] Seed gum: Guar, Locust, Psyllium

[b] Shrubs OR Tree exudates: Acacia, Karaya, Tragacanth

[c] Plant extract: Pectin

d] Marine gums: Agar, Alginates, Carragennans

e] Microbial gums: Dextran, Xanthan, Gellan, Emulsan, Pullulan

2. Semi-synthetic:

Starch and other cellulose derivatives – Hetastarch, CMC, Ethyl Cellulose, HPMC

1.3.6.4 Other ways of classification of polysaccharides

1.3.6.4.1 By Shape

[a] Linear: Algins, Amylose, Cellulose, Pectins.


ii. Branch-on-branch – Amylopectin, gum Arabic, Tragacanth.

1.3.6.4.2 By Manomeric Units

[a] Homoglycans: Amylose, Arabinanas, Cellulose.

[b] Di-heteroglycans: Algins, Carragennans, Galactomannans.


d] Tetra-heteroglycans: Gum arabic, Psyllium seed gum.

e] Penta-heteroglycans: Ghatti gum, Tragacanth.
1.3.6.4.3 By Charge

[a] **Neutral**: Amylose, Arabinans, Cellulose, Galactomannans.
[b] **Anionic**: Algin, Carrageenans, Gellan, Arabic, Pectic acid, Xanthan.

1.3.6.4.4 Polysaccharides

[a] **Starch**: Amylose, Amylopectin, Modified food starch.
[b] **Non-starch**: Pectins, Hemicellulose, Cellulose, β-glucan, Fructans, Gums, Mucilages, Algal polysaccharides.

1.3.6.4.5 Polysaccharide by Source

[a] **Seaweed extract**: Agar, Algin, Carragennans.
[b] **Higher plants**:  
   i. Insoluble – Cellulose  
   ii. Extract – Pectins  
   iii. Seeds – Starch, Guar  
   iv. Tuber and Roots – Potato starch  
   v. Exudates – Gum Arabic, Tragacanth  
   vi. Microorganism (Fermenting Gums) – Xanthan, Gellan  
   vii. Derived –  
      [A] Cellulose – CMC, Methyl Cellulose  
      [B] Starch, - Starch acetate, Starch Phosphates  
      [C] Synthetic - Polydextrose

1.3.7 Applications of gums and mucilages 111-114

There are growing concerns for the safety on pharmaceutical excipients derived from natural sources. Plant gums and exudates are getting screened for their use as pharmaceutical adjutants. Mucilages are used for their binding, thickening, stabilizing and humidifying properties in medicine. Newer uses in cosmetics and textiles had hiked up demand and screening of gums had become a vital pharmaceutical interest. However pharmaceutical adjutants have stringent specifications, which few natural agents can fulfill. Gums and mucilages have following various applications;

1. **Applications in food industry**: In confectionery food, flavoring and soft drinks, as gelling, stabilizing, and suspending agents.

2. **Pharmaceutical applications**: Gums and mucilages find diverse applications in pharmacy. It is used in medicine for its demulcent properties for cough suppression. They are ingredients in dental and other adhesives and as bulk laxatives. These hydrophilic polymers are useful as tablet binders, disintegrants, emulsifiers, suspending agents, gelling agents, stabilizing
agents, thickening agents, film forming agents in transdermal and periodontal films, buccal tablets, sustaining agents in matrix tablets and coating agents in microcapsules including protein delivery has been demonstrated. Various natural materials with their common name, biological sources, family and applications are listed in Table 1.3.1.

3. Industrial uses- are for cosmetics, textiles, adhesives, lithography, paints, papers and inks.

1.3.8 Precautions
They deteriorate when kept, especially in warm weather. So, preservatives are added, such as solution of formaldehyde (10 minims to each pint) or benzoic acid (10 grains to each pint).

1.3.9 Identification of gums and mucilage
1. The powder samples are mounted on glass slide with ruthenium red. After few seconds, it gives pink color.
2. Molisch’s test is carried out on the sample solutions gives purple color at junction.

1.3.10 Characterization
1. To determine the purity of the selected gum and mucilage, tests for alkaloids, glycosides, carbohydrates, flavanoids, steroids, amino acids, terpenes, saponins, oils and fats, and tannins and phenols were carried out.
2. The gum and mucilage are characterized by various organoleptic and physicochemical properties such as color, odor, shape, taste, touch, texture, solubility, pH, swelling index, loss on drying, hygroscopic nature, angle of repose, bulk and true densities, porosity and surface tension. Different ash values are also estimated. The microbial load and presence of specific pathogens are also determined. In vitro cytotoxicity is also determined.
3. Rheological properties of excipients are important criteria in deciding their commercial use. The flow behavior of the samples is determined using Brookfield RVDV II+ viscometer.
4. The compatibility studies of gum/mucilage/drugs are performed by using spectrophotometer/FTIR/DSC.
Table 1.3.1 Pharmaceutical applications or uses of natural gums and mucilages.

<table>
<thead>
<tr>
<th>Common name</th>
<th>Botanical name</th>
<th>Family</th>
<th>Pharmaceutical Applications</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abelmoschus mucilage</td>
<td><em>Abelmoschus esculentus</em></td>
<td>Malvaceae</td>
<td>Binder in tablets, sustained release</td>
<td>115, 116</td>
</tr>
<tr>
<td>Agar</td>
<td><em>Gelidium amansii</em></td>
<td>Gelidaceae</td>
<td>Suspending agent, emulsifying agent, gelling agent in suppositories, surgical lubricant, tablet disintegrants, medium for bacterial culture, laxative</td>
<td>117</td>
</tr>
<tr>
<td>Albizia gum</td>
<td><em>Albizia zygia</em></td>
<td>Leguminoseae</td>
<td>Tablet binder</td>
<td>118</td>
</tr>
<tr>
<td>Aloe mucilage</td>
<td><em>Aloe species</em></td>
<td>Liliaceae</td>
<td>Gelling agent, sustained release agent</td>
<td>119</td>
</tr>
<tr>
<td>Asario mucilage</td>
<td><em>Lepidum sativum</em></td>
<td>Cruciferae</td>
<td>Suspending agent, emulsifying agent, controlled release tablet</td>
<td>120, 121</td>
</tr>
<tr>
<td>Bavchi mucilage</td>
<td><em>Ocimum canum</em></td>
<td>Labiatae</td>
<td>Suspending agent, emulsifying agent</td>
<td>120</td>
</tr>
<tr>
<td>Carrageenan</td>
<td><em>Chondrus cryspus</em></td>
<td>Gigarginaceae</td>
<td>Gelling agent, stabilizer in emulsions and suspensions, in tooth paste, demulcent and laxative</td>
<td>122, 123, 124</td>
</tr>
<tr>
<td>Cashew gum</td>
<td><em>Anacardium occidentale</em></td>
<td>Anacardiaceae</td>
<td>Suspending agent</td>
<td>125, 126</td>
</tr>
<tr>
<td>Cassia tora</td>
<td><em>Cassia tora Linn</em></td>
<td>Leguminosae</td>
<td>Binding agent</td>
<td>127</td>
</tr>
<tr>
<td>Fenugreek</td>
<td><em>Trigonella</em></td>
<td>Leguminosae</td>
<td>Gelling agent, tablet</td>
<td>128, 129,</td>
</tr>
<tr>
<td>mucilage</td>
<td><em>foenum graecum</em></td>
<td>binder, sustaining agent, emollient and demulcent</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>------------------</td>
<td>-------------------------------------------------</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>Guar gum</td>
<td><em>Cyamomopsis tetraragonolobus</em></td>
<td>Leguminoseae</td>
<td>Binder, disintegrant, thickening agent, emulsifier, laxative, sustained release agent</td>
<td>131, 132, 133, 134</td>
</tr>
<tr>
<td>Gum acacia</td>
<td><em>Acacia arabica</em></td>
<td>Leguminoseae</td>
<td>Suspending agent, emulsifying agent, binder in tablets, demulcent and emollient in cosmetics</td>
<td>129, 135</td>
</tr>
<tr>
<td>Gum ghatti</td>
<td><em>Anogeissus latifolia</em></td>
<td>Combretaceae</td>
<td>Binder, emulsifier, suspending agent</td>
<td>129, 136</td>
</tr>
<tr>
<td>Gum tragacanth</td>
<td><em>Astragalus gummifer</em></td>
<td>Leguminoseae</td>
<td>Suspending agent, emulsifying agent, demulcent, emollient in cosmetics and sustained release agent</td>
<td>129, 137</td>
</tr>
<tr>
<td>Hibiscus mucilage</td>
<td><em>Hibiscus esculentus Linn</em></td>
<td>Malvaceae</td>
<td>Emulsifying agent, sustained release agent, suspending agent</td>
<td>129, 138, 139</td>
</tr>
<tr>
<td>Hibiscus mucilage</td>
<td><em>Hibiscus rosasinensis Linn</em></td>
<td>Malvaceae</td>
<td>Suspending agent</td>
<td>140</td>
</tr>
<tr>
<td>Ispagol mucilage</td>
<td><em>Plantago psyllium, Plantago</em></td>
<td>Plantaginaceae</td>
<td>Cathartic, lubricant, demulcent, laxative, sustaining agent</td>
<td>130, 141, 142, 143, 144, 145</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Scientific Name</td>
<td>Family</td>
<td>Function</td>
<td>Page Numbers</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>---------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Karaya gum</td>
<td><em>Sterculia urens</em></td>
<td>Sterculiaceae</td>
<td>Suspending agent, emulsifying agent, dental adhesive, sustaining agent in tablets, bulk laxative</td>
<td>146, 147</td>
</tr>
<tr>
<td>Khaya gum</td>
<td><em>Khaya grandifolia</em></td>
<td>Meliaceae</td>
<td>Binding agent</td>
<td>148</td>
</tr>
<tr>
<td>Leucaena seed gum</td>
<td><em>Leucaena leucocephata</em></td>
<td></td>
<td>Emulsifying agent, suspending agent, binder in tablets, disintegrating agent in tablet</td>
<td>149, 150, 151, 152, 153</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td><em>Ceratania siliqua</em></td>
<td>Leguminoseae</td>
<td>Thickener, stabilizer, controlled release agent</td>
<td>154, 155</td>
</tr>
<tr>
<td>Ocimum seed mucilage</td>
<td><em>Ocimum gratissimum</em></td>
<td>Labiatae</td>
<td>Suspending agent, binding agent</td>
<td>156, 157</td>
</tr>
<tr>
<td>Pectin</td>
<td><em>Citrus aurantium</em></td>
<td>Rutaceae</td>
<td>Thickening agent, suspending agent, protective agent, carrier in microspheres</td>
<td>158, 159, 160, 161, 162</td>
</tr>
<tr>
<td>Satavari mucilage</td>
<td><em>Asparagus racemosus</em></td>
<td>Aapocynaceae</td>
<td>Binding agent and sustaining agent in tablets</td>
<td>163</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td><em>Macrocystis pyrifera</em></td>
<td>Lessoniaceae</td>
<td>Suspending agent, gelation for dental films, stabilizer, sustained release agent, tablet coating</td>
<td>155, 164, 165, 166, 167</td>
</tr>
<tr>
<td>Tamarind seed polysaccharide</td>
<td><em>Tamarindus indica</em></td>
<td>Leguminoseae</td>
<td>Binding agent, emulsifier, suspending agent, sustaining agent</td>
<td>17, 168, 169</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------</td>
<td>--------------</td>
<td>-----------------------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td><em>Xanthomonas lempestris</em></td>
<td></td>
<td>Suspending agent, emulsifier, stabilizer in tooth paste and ointments, sustained release agent</td>
<td>147, 170</td>
</tr>
</tbody>
</table>
1.4 Introduction to Drug - Diclofenac sodium

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The number of new drugs and the marketing of NSAIDs have dynamically increased in the past decades. Today more than 100 preparations are on the market or under clinical investigation.

1.4.1 Description

1.4.1.1 Generic Name: Diclofenac sodium

1.4.1.2 Synonyms: Voltran, Voltarol, Voldal, Voveran, Orthophen, Diclon, Dicloflex Difen, Difene.

1.4.1.3 Chemical Name: 2-[(2, 6-dichlorophenyl) amino] benzene acetic acid monosodium salt, Sodium-[[2,6-dichlorophenyl]-amino]-phenyl-acetate,[o- (2,6-dichloroaniline)phenyl] amino-phenyl acetate.

1.4.1.4 CAS Registry No.: 15307-79-6.

1.4.1.5 Empirical Formula: $\text{C}_{14}\text{H}_{10}\text{Cl}_{2}\text{NO}_{2}\text{Na}$ (salt)

$\text{C}_{14}\text{H}_{10}\text{Cl}_{2}\text{NO}_{2}$ (free acid)

1.4.1.6 Structural Formula

1.4.1.7 Molecular Weight: 318.14 (salt)

1.4.2 Physical Properties

1.4.2.1 Appearance, Color, Odor and Taste

It is white to off-white in color, odourless, crystalline, salty bitter taste and slightly hygroscopic powder.

1.4.2.2 Melting Point: 283-285°C (salt) and 156-158°C (free acid)

1.4.2.3 Solubility: The equilibrium solubility performed in various solvents at the room temperature is shown in Table 1.4.1.
### Table 1.4.1 Solubility of Diclofenac sodium in various solvent.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deionized water (pH 5.2)</td>
<td>&gt; 9</td>
</tr>
<tr>
<td>Methanol</td>
<td>&gt;24</td>
</tr>
<tr>
<td>Acetone</td>
<td>6</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>&lt;1</td>
</tr>
<tr>
<td>HCl (pH 1.1)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Phosphate Buffer (pH 7.2)</td>
<td>6</td>
</tr>
</tbody>
</table>

#### 1.4.2.4 Stability:
It can be frozen for at least two weeks without degradation in biological fluid (serum). DS is stable at 130°C for 8 hr. DS tablets film coated with Acrylate Hydroxypropyl Cellulose were reported to be stable after storage for one week at 30°C at 80% RH.

#### 1.4.2.5 Dissociation Constant:
The pKa is 4.2 in aqueous solution at 30°C.

#### 1.4.2.6 Partition Co-efficient:
The octanol-water partition co-efficient at 25°C is reported as 4 to 4.17. 173

### 1.4.3 Pharmacology

#### 1.4.3.1 Properties
DS is potent non-steroidal, anti-inflammatory drug with pronounced analgesic and antipyretic properties. Its potency is much greater than that of indomethacin, naproxen, phenylbutazone. DS appears to reduce intra-cellular concentration of free arachidonate in leukocytes.

#### 1.4.3.2 Mechanism of actions
DS inhibits cyclooxygenase enzyme. It inhibits the conversion of arachidonic acid to unstable endoperoxide intermediate, PGG₂, a reaction catalyzed by cyclooxygenase. Thus, it inhibits production of prostaglandin content of human serum, urine and synovial fluid of arthritic knee joint and it acts as a potent anti-inflammatory agent. The primary mechanism responsible for its anti-inflammatory, antipyretic and
analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX).

Diclofenac has a low to moderate preference to block the COX-2-isoenzyme (approximately 10-fold) and therefore a somewhat lower incidence of gastrointestinal complaints than noted with indomethacin and aspirin.

Diclofenac inhibits the lipoxygenase pathways, thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). There is also speculation that diclofenac may inhibit phospholipase A₂ as part of its mechanism of action. These additional actions may explain the high potency of diclofenac.

1.4.3.3 Therapeutic uses

Diclofenac sodium is potent non-steroidal, anti-inflammatory drug with pronounced analgesic and antipyretic properties. It is used for musculoskeletal complaints, especially arthritis (rheumatoid arthritis, osteoarthritis, spondylarthritis, ankylosing spondylitis), gout attacks, and pain management in case of kidney stones and gallstones. An additional indication is the treatment of acute migraines. Diclofenac is used commonly to treat mild to moderate post-operative or post-traumatic pain, particular when inflammation is also present, and is effective against menstrual pain.

1.4.3.4 Adverse effects

Adverse reactions reported in clinical trials and spontaneous reports are summarized in Table 1.4.2. Table shows adverse reactions reported in clinical trails.

<table>
<thead>
<tr>
<th>Systems</th>
<th>Type of reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal System</td>
<td>Occasional</td>
</tr>
<tr>
<td></td>
<td>Gastric or abdominal pain, abdominal cramps, nausea, dyspepsia, anorexia, diarrhea, vomiting,</td>
</tr>
<tr>
<td></td>
<td>flatulence.</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Central Nervous System</strong></td>
<td>Dizziness, headache, vertigo.</td>
</tr>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td>**********</td>
</tr>
<tr>
<td><strong>Special senses</strong></td>
<td>**********</td>
</tr>
<tr>
<td><strong>Dermatologic</strong></td>
<td>Rash, pruritus.</td>
</tr>
<tr>
<td>Renal System</td>
<td>Edema (facial, general, peripheral)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Thrombocytopenia, leukopenia, agranulocytosis, hemolytic anemia, aplastic anemia, anemia secondary to gastrointestinal bleeding.</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Elevations of serum aminotransferase enzymes (SGOT or AST, SGPT or ALT). Liver function disorders including hepatitis with or without jaundice.</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Hypersensitivity reactions such as asthma in patients sensitive to ASA e.g. bronchospasm, anaphylactic, anaphylactoid systemic reactions including hypotension.</td>
</tr>
</tbody>
</table>
1.4.3.5 Contradiction

Diclofenac is contraindicated in patients with known or suspected hypersensitivity to diclofenac. Since cross-sensitivity has been demonstrated, Diclofenac should not be given to patients in whom acetylsalicylic acid or other non-steroidal anti-inflammatory agents have induced asthma, rhinitis, urticaria or other allergic manifestations.

Diclofenac sodium is contraindicated in active stomach and/or duodenal ulceration or gastrointestinal bleeding, third-trimester pregnancy, inflammatory intestinal disorders such as Crohn's disease or ulcerative colitis, severe liver insufficiency (Child-Pugh Class C), caution in patients with preexisting hepatic porphyria, as diclofenac sodium may trigger attacks.

Recently, a warning has been issued by FDA not to treat patients recovering from heart surgery.

1.4.3.6 Dosage and Administration

The maximum recommended daily dose is 150 mg. Diclofenac should be taken with food and the tablets should be swallowed whole.

1.4.3.7 Container and Closures

DS was kept in an airtight container, should be protected from light.

1.4.4 Pharmacokinetics

1.4.4.1 Absorption: In humans, orally-administered DS is rapidly and almost completely absorbed and distributed to blood, liver, and kidneys. The plasma concentrations show a linear relationship to the amount of drug administered.

1.4.4.2 Protein Binding and Distribution: At therapeutic concentration, the drug is extensively bound to plasma protein (albumin 99.7%). Apart from liver, bile, and kidney, highest levels of diclofenac are found in blood, heart, and lung. The apparent volume of distribution is $0.17 \pm 0.11$ L/kg.

1.4.4.3 Biotransformation: DS is metabolised in the liver. The principal metabolite is 4'-hydroxyl Diclofenac. Diclofenac undergoes single and multiple hydroxylation and methoxylation, producing 3'-, 4', 5-hydroxy, 4'- 5-hydroxy and 3'-hydroxy-4'-methoxy derivatives of diclofenac. These phenolic metabolites are largely inactive, and (along with the parent compound) are mostly converted to glucuronide conjugates.


1.4.4.4 **Elimination**: DS and its metabolites are excreted through bile (33%) and urine (67%). Unchanged drug is about 0.7% in urine. The clearance rate is reported as $4.2 \pm 0.9$ mL/min/kg, and elimination rate as 1.2 to 1.8 hr. The mean terminal drug half-life in plasma is 1.8 hr after oral doses.

**1.4.5 Drug-Drug & Drug-Food interaction** 186-190

Diclofenac, like other NSAIDs, may increase the toxicity of some drugs. Serum level of digoxin and methotrexate are increased. Though studies have not revealed any interactions with warfarin type of anticoaulants, but close monitoring may be desirable during concurrent therapy. Lithium renal clearance is reduced by diclofenac and side effects of lithium salts may occur during concurrent treatment. Efficacy of diuretics may be reduced by NSAIDs including diclofenac. Concomitant use of potassium sparing diuretics may result in increased serum potassium levels. Aspirin displaces diclofenac from its binding sites.

Foods delays but does not reduce absorption from enteric coated tablets. This is of no clinical significance in long term therapy with DS.

**1.4.6 Method of analysis**

DS has been quantitatively analysed by UV Spectrophotometry, visible spectrophotometry, thin layer chromatography, gas liquid chromatography, HPLC, NMR, Gas and Mass Chromatography.

**1.4.6.1 Visible Spectrophotometry (colorimetric determination)**

1.4.6.1.1 This is a sensitive method based on the reaction of DS with potassium ferrocyanide (1% w/v) in basic medium. The yellow color developed after addition of sodium hydroxide (6% w/v) shows maximum absorbance at 450 nm. The beer’s curve shows linear relation in the concentration range of 2 to 10 µg/mL of DS.191

1.4.6.1.2 DS gives yellow color when treated with sodium nitrite in the presence of HCl with a maximum absorbance at 390 nm. The Beer’s law is governed in the range of 0.05 - 0.60 mg/mL of DS.192

1.4.6.1.3 DS when reacted with p-dimethyl aminobenzaldehyde and ammonium ceric sulphate in acidic medium gives an orange color, which exhibits maximum absorbance at 440 nm. It governs Beer’s law in concentration range of 2 to 16 µg/mL. The color is reported to be stable for 50 min.193
1.4.6.1.4 DS may be reacted with 3-methyl-2-benzothiazolinone hydrazone hydrochloride and cerium ammonium sulfate to form a colored complex which exhibited maximum absorbance at 600 nm.

1.4.6.2 Spectrofluorimetry method

A spectrofluorometric method for the micro determination of DS has been developed through its reaction with cerium (IV) in an acidic solution and measurement of the fluorescence of the Ce (III) ions produced. Under the optimum experimental conditions for the oxidation reaction, 1.0 M H₂SO₄ with 90 min of heating time (100°C), the range of application is 124.3 – 600 ng/mL and the limit of detection is 72.7 ng/mL. The proposed method was applied to the determination of DS in pharmaceutical tablets.

1.4.6.3 UV spectrophotometric determination

This method is based on the measurement of appropriate diluted DS drug solution in UV light in a 1 cm matched quartz tube. The wavelength of maximum absorption is 276 nm.

1.4.6.4 Gas Liquid Chromatography

This method was used to analyze DS or its metabolized using electron capture detector, before injecting into the column.

1.4.6.5 High Performance Liquid Chromatography

1.4.6.5.1 Determination of DS in biological fluids is done by HPLC technique.

1.4.6.5.2 A HPLC method for determination of paracetamol, chlorzoxazone and DS has been developed. The chromatography system used a reversed phase C8 column with UV-Vis detection at 280 nm. Mobile phase consisted of acetonitrile – 0.05 M ammonium dihydrogen ortho phosphate (60:40 v/v) (pH adjusted to 4.06 using 10% ortho phosphoric acid) at a flow rate of 1.5 mL/min. The calibration curve was linear in the concentration range of 4-20 µg/mL for DS.

1.4.6.5.3 A reverse phase HPLC method has been developed for the simultaneous estimation of DS and rabeprazole sodium from pharmaceutical formulations. The method was developed using a HiQ SiL C18 (250 mm × 4.6 mm i.d.) column with a mobile phase consisting of methanol: water, (80:20 v/v), at a flow rate of 1.25 mL/min. Detection was carried out at 284 nm.
1.4.6.6 Nuclear Magnetic Resonance

Proton magnetic method to quantify Diclofenac sodium in pure tablet form has been described. Diclofenac has a well defined sharp peak at 3.62 ppm, which is chosen for quantitative measurement. Internal standard used is anhydrous sodium acetate (1.85 ppm). The amount of DS can be calculated by comparing the peak ratio of Diclofenac to that of the internal standard.

1.4.6.7 HPTLC method

1.4.6.7.1 A HPLC method for the determination of DS in pharmaceutical formulations was developed. The sample were spotted automatically by means of Camag Linomat IV (Switzerland) on a silica gel 60 F254 aluminium plate, using a mixture of toluene : ethyl acetate : glacial acetic acid (60:40:1, v/v/v) as mobile phase. The spot areas were quantified by densitometry at 282 nm. Linear calibration curve was obtained over the range 5-80 µg/mL ($r^2 = 0.9993$). The proposed method is simple, rapid, sensitive, reproducible and accurate.

1.4.6.7.2 DS from serum was determined by a novel HPTLC method. Standard DS was spotted on Silica Gel 60 F254 precoated plates, which were developed using the mobile phase toluene:acetone:glacial acetic acid (80:30:1,v/v/v). Densitometric analysis of DS was carried out at 280 nm with diclofenac being detected at an $R_f$ of 0.58. The method was subsequently developed to estimate DS from serum. The calibration curve of DS in serum was found to be linear in the range of 200–800 ng.
1.5 References


34. Bonferoni MC, Rossi S, Ferrari F, Stavik E, Pena-Romero A, Caramella C. Factorial analysis of the influence of dissolution medium on drug release from...


Chapter 1

Introduction


158. www.cpkelco.com/pectin/applications.html


