SECTION 1
INTRODUCTION
1. INTRODUCTION

1.1. Diabetes Mellitus

1.1.1. DIABETES: A LOCAL AND GLOBAL EPIDEMIC

The prevalence of diabetes in adults worldwide was estimated to be 4.0% in 1995, and is estimated to rise to 5.4% by the year 2025. This increase is observed across all ages, races, educational levels, weights, and geographic distributions throughout the world. Although diabetes is seen more frequently in developed than in developing countries, the trend is more substantial in the developing world, where the increase in diabetes is projected at 170% by the year 2025 (King et al., 1998). In the last years, diabetes mellitus has reached epidemic proportion and is now becoming cause of premature mortality and morbidity (Zimmet, 2002).

1.1.2. DEFINITION

Diabetes mellitus, a syndrome consisting of interrelated metabolic, vascular, and neuropathic components; and is defined as a group of metabolic diseases that are characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). The lack of effective insulin action leads to alterations in carbohydrate, fat, and protein metabolism (Harmel and Mathur, 2004a). The majority of cases of diabetes fall into two major categories of pathogenesis. Human type I diabetes mellitus (insulin dependent diabetes mellitus, IDDM) is caused by an absolute deficiency of insulin secretion resulted from T cell-mediated, autoimmune destruction of pancreatic β-cells (Rossini et al., 1985) or by a primary defect in β-cell function secondary to another (nonautoimmune) cause. In type II diabetes mellitus (non-insulin dependent diabetes mellitus, NIDDM or ketosis-resistance diabetes or maturity/adult-onset diabetes), the cause of the heterogeneous disease is a combination of factors including insulin resistance at the level of the muscle and liver, and an inadequate insulin secretory response.

People with type II diabetes mellitus are characterized by a pancreatic β-cell dysfunction, resistance to insulin and a relative, as opposed to absolute, insulin deficiency (Bhattacharyya, 2001). The impairment of insulin secretion manifests itself as a reduced or absent first-phase response to intravenous glucose,
delayed and reduced responses to meals and alterations in the normal pulsatile secretion of insulin (Polonsky et al., 1996). As β-cell dysfunction progresses, these defects eventually produce overt hyperglycemia, which may require pharmacological treatment (Sacks and McDonald, 1996). The long-term manifestation of this disease can result in the development of vascular disorders such as; retinopathy, nephropathy, neuropathy, and angiopathy. Figure 1.1 shows the schematic representation of the two-phase insulin release which occurs with constant glucose infusion (or following a meal). First phase is missing in NIDDM and both phases are missing in IDDM as shown in Figure 1.1. The characteristic features and differences in IDDM and NIDDM are depicted in Table 1.1.

Figure 1.1. Schematic diagram of the two-phase release of insulin (Martin).

Individuals with Type II diabetes are treated with diet, exercise, oral hypoglycemic agents, and insulin. It is worth emphasizing that type II diabetes mellitus is a complex metabolic disorder, and good diabetic control should include maintaining a normal body mass index, blood pressure and lipid levels. Dietary regulation (including balanced diet and exercise), with the goal of reducing the total body fat, is the first line therapy for controlling type II diabetes, followed by treatment with insulin or oral anti-diabetic mono-therapy, and lastly different combination therapy (Harmel and Mathur, 2004b). Sulfonylurea drugs or other oral medications are used for patients with Type II diabetes who have failed diet and
Table 1.1. Characteristics of Type 1 and Type 2 Diabetes Mellitus (Martin).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Names</td>
<td>Insulin-Dependent Diabetes Mellitus (IDDM); previously juvenile-onset diabetes mellitus</td>
<td>Non-Insulin Dependent Diabetes Mellitus (NIDDM); previously adult onset diabetes mellitus</td>
</tr>
<tr>
<td>Percent of Diabetic Population</td>
<td>= 8,00,000 in US</td>
<td>= 10 million or more in US</td>
</tr>
<tr>
<td>Age at Onset</td>
<td>Usually &lt;30 years; peaks at 12-14 years; rate before 6 months; some adults develop Type 1 during 5th decade</td>
<td>Usually &gt; 40 years</td>
</tr>
<tr>
<td>Pancreatic Function</td>
<td>Usually complete lack of functional β cell activity; insulin completely absent</td>
<td>Insulin present in low, ‘normal’, or high amounts</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Associated with certain HLA types; presence of islet cell antibodies suggests autoimmune process</td>
<td>Defect in insulin secretion; tissue resistance to insulin; increased hepatic glucose output</td>
</tr>
<tr>
<td>Family History</td>
<td>Generally not strong</td>
<td>Strong (60-90%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>History of Ketoacidosis</td>
<td>Often present</td>
<td>Rare</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>Moderate to severe symptoms which progress relatively rapidly (days-weeks): polyuria, polydipsia, fatigue, weight loss, ketoacidosis</td>
<td>Mild polyuria, fatigue; often diagnosed on physical examination</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin</td>
<td>Diet and Exercise</td>
</tr>
</tbody>
</table>

exercise therapy. Since obese diabetic patients are in a state of insulin resistance, large doses of insulin may be required to control their blood glucose levels. Insulin is lipogenic and may promote further weight gain; therefore, oral hypoglycemics are the preferred agents (Martin). Intensive treatment of diabetes mellitus with subcutaneous insulin is associated with pain and inconvenience from the multiple daily injections. Moreover, subcutaneous administration of insulin has a relatively slow onset (1–3 hr) and a prolonged duration of action (4–6 hr), which does not match with the endogenous insulin secretory profile. In a non-diabetic patient, post-prandial insulin secretion peaks at 30 min and returns to basal levels within 2–4 hr (White et al., 1997). To provide better mealtime glucose control and relatively improved life-style to diabetics, novel and non-invasive ways of glucose control are being preferred.
1.2. Oral Antidiabetic Agents

The maintenance of homeostatic blood glucose concentration is an integrated process predominantly regulated by the antihyperglycemic hormone insulin. When blood glucose rises, uptake of glucose into the pancreatic β-cells leads to an elevation in ATP/ADP ratio and closure of $K_{\text{ATP}}$ channels. The closure of $K_{\text{ATP}}$ channels and the resultant membrane depolarization lead to the increase in $Ca^{2+}$ influx through voltage-gated $Ca^{2+}$ channels, which triggers exocytosis and insulin release (Ashcroft et al., 1984; Cook and Hales, 1984). Many agents that are capable of blocking $K_{\text{ATP}}$ channels in pancreatic β-cells can induce insulin secretion and hence serve as antidiabetic drugs (Shiling et al., 1999). Figure 1.2 classifies the different oral antidiabetic agents based on the functional groups and Figure 1.3 outlines the site of action of these hypoglycemic agents.

![Oral Antidiabetic Agents](image)

Figure 1.2. Classification of oral anti-diabetic agents.

Impaired insulin secretion from pancreatic β-cells in response to glucose, particularly loss of the first phase of insulin secretion, is an important feature in the pathology of non-insulin-dependent diabetes mellitus (NIDDM) (Porte, 1991; Taylor et al., 1994). This defect contributes to the cause of postprandial hyperglycemia in patients with NIDDM (Firth et al., 1986; Kelley et al., 1994). To compensate for this defective insulin release, sulfonylurea derivatives have been the most widely used hypoglycemic agents (Gerich, 1989; Groop, 1992) for many years.
As shown in Figure 1.4, sulfonylurea derivatives induce insulin release by inhibition of the ATP-sensitive K+ channel of the pancreatic β-cells after binding to the sulfonylurea receptor (Rajan et al., 1990; Gromada et al., 1995). However, it cannot ameliorate the impairment of the first phase of insulin secretion in response to high glucose, resulting in failure to improve postprandial hyperglycemia in patients with NIDDM (Groop et al., 1986). Furthermore, there are several disadvantages to sulfonylurea therapy: severe and prolonged
hypoglycemia because of lengthy duration of glucose-independent action (Jackson and Bressler, 1981; Ferner and Neil, 1988; Gerich, 1989; Jennings et al., 1989), and failure of response to sulfonylurea derivatives (secondary failure) and degeneration of pancreatic β-cells after chronic therapy (Groop et al., 1986; Sodoyez et al., 1990; Davalli et al., 1992). Therefore, a new class of hypoglycemic agent that improves insulin secretion in response to high plasma glucose levels by restoring pancreatic β-cells sensitivity to glucose would be beneficial for the treatment of patients with NIDDM.

Glipizide, a representative of the second generation sulfonylureas and appears to be the most effective insulin secretogogue both in first phase insulin secretion and in sustained stimulatory response during long term administration. A decrease in blood glucose concentration level occurs within 30 min of ingestion of glipizide, providing peak plasma level concentrations within 1–3 h after a single oral dose with an elimination half-life ranging from about 2 to 4 h.

Nateglinide, (also known as A-4166) a D-phenylalanine derivative, is a new agent investigated for the treatment of type II diabetes mellitus as mono-therapy or in combination with other oral agents when diet and exercise alone are not successful. It is chemically and pharmacologically distinct from the sulphonylureas and biguanides. This meglitinide derivative share a common mechanism of action by binding to the sulphonylurea receptor to inhibit K_{ATP} channels in pancreatic β-cells (Rajan et al., 1990; Akiyoshi et al., 1995; Fuhlendorff et al., 1995; Gromada et al., 1995; Fujita et al., 1996), which results in calcium influx and subsequent insulin release. As plasma glucose rises, β-cell sensitivity to nateglinide increases and insulin release amplifies. Following ingestion, it is absorbed rapidly (within 30 min) with a maximum plasma concentration occurring within one-half to two hours (t_{max}, 1.5 ± 1.1 h) and has very short half-life of 1-1.25 h.

Such a rapidly absorbed drugs having faster elimination rate with short half-life make them suitable candidates to be formulated for the sustained delivery.

1.3. Pharmaceutical Dosage Form Development

Pharmaceutical dosage form development, NDDS (Novel Drug Delivery Systems) is a science as well as an art. Art - because the final dosage form developed is the work of creative scientists. And Science - the creative idea is implemented using highly developed scientific insights and tools. The result is a dosage form that is efficacious, patient friendly, stable and delivering the drug with minimal adverse effects as closely as possible to the intended target (Chikhalikar and Moorkath, 2002). An active substance can not meet patient's needs without an appropriate formulation. Formulation development activity is not only restricted to
new chemical entities but also improvement of drug delivery of existing drugs. The pharmaceutical companies are increasingly seeking innovative dosage forms by way of pharmaceutical dosage form development as they represent strategic tool for expanding markets and indications, extending product life-cycles and generating newer opportunities (Chikhalikar and Moorkath, 2002). Pharmaceutical dosage form development is no longer a theory. It is a reality and this is illustrated by the fact that around 13% of the current global pharmaceutical market is accounted for by sales of products incorporating Drug Delivery Systems. There are two broad reasons for companies to look at NDDS as a strategy for growth: commercial compulsions and technological advances (Chikhalikar and Moorkath, 2002).

1.3.1. COMMERCIAL COMPULSIONS

Increasing costs and risks associated with discovery and development of NCEs have prompted companies to look elsewhere for growth in business. NDDS represents a strategic tool for pharmaceutical companies to expand markets and indications, extend product life cycles and generate new opportunities. As a result NDDS are making significant contributions to global pharmaceutical sales. Another important aspect that is driving companies to look at NDDS is the issue of patent expiry of "blockbuster" molecules. Patent expiry is projected to result in a revenue loss to the tune of US$20 billion (Drs Gordon Findlay and Faiz Kermani: Novel drug Delivery Technologies and Drug Development, pp 170, WMRC Business Briefing, Pharmatech 2001). One way to offset this loss is by switching a current formulation to a NDDS for the existing molecules, thereby extending product life cycles and marketing exclusivity.

1.3.2. TECHNOLOGICAL ADVANCES

Advances in pharmacology and pharmacokinetics have resulted in the rational identification for drug-input functions or absorption rates that will lead to improved treatment. The progress in pharmacokinetics was sparked by recognition of the therapeutic need to maximize the efficacy of drugs thus leading to the establishment of mathematical models that permit one to relate concentrations of drugs in various tissues and compartments to overall drug disposition in a biological system. Pharmacokinetic - pharmacological investigations over the past two decades have clearly demonstrated that the rate and the extent of systemic drug availability ultimately determined the therapeutic response and not the dose. Recent technological advances in the development of NDDS, including CR/SR dosage forms and targeted drug delivery systems are the powerful tools...
in the hands of the formulator towards achieving the desired pharmacokinetic profile.

In recent years, controlled/sustained/modified release dosage forms have increasingly gained popularity over other conventional dosage forms in treating diseases as the therapeutic efficacy and safety of drugs, administered by conventional methods, can be improved by more precise spatial and temporal placement within the body. Moreover, they reduce the size and number of doses, reduce total disease management cost, thereby providing economic merit to the society and improve patient compliance (Li et al., 1987; Brabander et al., 2003).

1.3.3. TERMINOLOGY

Before initiating a discussion of sustained and controlled release dosage forms, it is necessary to provide a short explanation of terminology used to avoid the confusion between similar terms. The general consensus is that controlled release denotes systems which can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body. Whereas, prolonged release or sustained release systems, which only prolong therapeutic blood or tissue levels of the drug for an extended period of time, cannot be considered as controlled release systems (Li et al., 1987).

According to USP XXIV, a modified-release dosage form is one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. Delayed-release and extended-release dosage forms are two types of modified-release dosage forms (USP 29 - NF 24, 2006).

- Delayed-release dosage forms is one that releases a drug(s) at a time other than promptly after administration.
- Extended-release dosage form is one that allows at least a twofold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance as compared to that presented as a conventional dosage form.

The terms controlled release, prolonged action, and sustained release are used synonymously with extended release.

1.3.4. RATIONALE OF SUSTAINED/CONTROLLED DRUG DELIVERY

Most sustained release drug delivery systems developed are aimed at slowing the apparent absorption rate by reducing drug release rate from the dosage form. The basic rationale for controlled drug delivery is to alter the pharmacokinetics
and pharmacodynamics of pharmacologically active moieties by using novel drug
delivery systems or by modifying the molecular structure and/or physiological
parameters inherent in a selected route of administration. It is desirable that the
duration of drug action become more a design property of a rate-controlled
dosage form, and less, or not at all, a property of the drug molecule's inherent
kinetic properties (Li et al., 1987).
The controlled drug delivery systems are aimed to ensure safety and to improve
efficacy of drugs as well as patient compliance. This is achieved by better control
of plasma drug levels and less frequent dosing.

- SR formulation reduces fluctuation of drug blood levels about the mean. In
cases where a constant drug level is desirable, (a) it reduces the peak blood
levels ($C_{\text{max}}$) and thus, reducing dose related side effects, and (b) increases
the minimum plasma concentrations ($C_{\text{min}}$), thereby increases efficiency
(Skelly and Barr, 1987).

- SR formulations increase in the time interval required between doses. This
provides a reduction in the total number of doses required per day. The
decrease in frequency of daily doses is more convenient to the patients and
can lead to improved patient compliance. Evaluation of cost-benefit as
opposed to risk-benefit, however, is considerations for the market place rather
than regulatory assessment.

Generally, primary objectives of controlled drug delivery are to ensure safety and
to improve efficacy of drugs as well as patient compliance, which can achieved
by better control of plasma drug levels and less frequent dosing (Li et al., 1987).
Conventional dosage forms are not able to control either the rate of drug delivery
or the target area of drug administration and provide an immediate or rapid drug
release. This necessitates frequent administration in order to maintain a
therapeutic level. As a result, drug concentrations in the blood and tissues
fluctuate widely. The concentration of drugs may be initially high, that can cause
toxic, and/or side effects, then quickly fall down below the minimum therapeutic
level with time elapse. In contrast, sustained release dosage forms are not only
able to maintain therapeutic levels of drug with narrow fluctuations but they also
make it possible to reduce the frequency of drug administration. The serum
concentration of a drug released from controlled release dosage forms fluctuates
within the therapeutic range over a long period of time. The serum concentration
profile depends on the preparation technology, which may generate different
release kinetics, resulting in different pharmacological and pharmacokinetic
responses in the blood or tissues.
In order to maintain a constant drug level in either plasma or target tissue, release rate from the controlled release system should be equal to the elimination rate from plasma or target tissue. The most conventional method to achieve a constant plasma level is the use of intravenous infusion. However, this would be inconvenient for most therapeutic situations so that other noninvasive routes, such as the oral or transdermal routes, are preferred (Li et al., 1987). Historically, the oral route is by far the most popular route of drug administration for both conventional and novel drug delivery systems (Jantzen and Robinson, 2002). In fact, the vast majority of drugs dosage forms are designed for oral ingestion, primarily for ease of administration. There are many obvious reasons for this, not the least of which would include acceptance by the patient and ease of administration. Indeed, for sustained-release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products. The types of sustained and/or controlled release systems employed for oral administration include virtually every currently known theoretical mechanism for such application. This is because there is more flexibility in dosage design for oral route than for the parenteral or other route, since constraints, such as sterility and potential damage at the site of administration, are minimized (Hui et al., 1987; Jantzen and Robinson, 2002).

During the past four decades, the pharmaceutical industry has invested vast amounts of time and money in the study of tablet compaction. The expenditure is quite reasonable when one considers how valuable tablets, as a dosage form, are to the industry. Because oral dosage forms can be self-administered by the patient, they are obviously more profitable to manufacture than parenteral dosage forms that must be administered, in most cases, by trained personnel. This is reflected by the fact that well over 80% of the drugs in the United States that are formulated to produce systemic effects are marketed as oral dosage forms. Compared to other oral dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package, and shipment; increased stability and virtual tamper resistance. The most common solid dosage forms in contemporary use are tablets, which may be defined as unit forms of solid medicaments prepared by compaction (Kottke and Rudnic, 2002).

As mentioned earlier, the constant blood or tissue drug level is achieved when the drug is uniformly released from the controlled release system and then uniformly absorbed. Usually, the rate-limiting step in drug delivery from a controlled release product is release from the dosage form rather than
absorption. Thus, rapid drug absorption, relative to drug release from the dosage form is expected (Li et al., 1987). In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through the biological milieu, and absorption through an epithelial membrane to the blood. Apart from route of drug delivery and target side, there are varieties of both physicochemical and biological factors that come into play in the design of such systems. Thus, optimal design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug.

1.3.6. PHARMACOKINETIC/PHARMACODYNAMIC BASIS OF CONTROLLED/SUSTAINED DRUG DELIVERY

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

1.3.6.1. Biological Factors Influencing Oral SR Dosage Form Design

1.3.6.1.1. Biological Half-life

Since the therapeutic index for most drugs is around 2, it will be necessary to dose the patients at intervals shorter than half-life. Such a inconvenient regimens often result in reduced compliance and inadequate treatment. In general, dosing interval may be increased either by modifying the drug molecule to decrease the rate of elimination ($k_e$) or by modifying the release rate of a dosage form to decrease the rate of absorption ($k_a$). Both approaches seek to decrease fluctuations in plasma levels during multiple dosing, allowing the dosing interval to increase without either overdosing or underdosing (Li et al., 1987). To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life. Drugs with short half-lives require frequent dosing in order to minimize fluctuations in the blood levels accompanying conventional oral dosage regimens. Therefore, controlled/sustained release dosage forms would appear very desirable for such drugs. However, this is limited, in that drugs with very short half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limitingly large. In general, drugs with half-lives shorter than 2 h, such as levodopa or frusemide, are poor candidates for sustained release preparations. On the other side, compounds with long half-lives, more than 8 h are also generally not used in sustaining forms, since their effect is already sustained (Jantzen and Robinson, 2002). As the half-
life increases, formulation factors become less important in the development of
the dosing regimen. The most serious restriction to the use of oral sustained release dosage forms
would be the limited residence time of the dosage form in the small intestine. Generally, 0-12 hr is considered reasonable estimate of average effective absorption time after oral administration of a well-absorbed drug in a dosage form that remains intact in the gastrointestinal tract (Silber et al., 1987). Occasionally, absorption from the colon may allow continued drug delivery for up to 24 h (Jantzen and Robinson, 2002).

1.3.6.1.2. Absorption

The usual aim of drug therapy is to achieve and maintain effective concentrations of drug at the receptor site. However, the body is constantly trying to eliminate the drug, and, therefore, it is necessary to balance absorption against elimination to maintain the desired concentration (Bourne, 2002). The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Since the purpose of forming a sustained release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. Considering the transit time of most drugs and devices in the absorptive areas of the gastrointestinal track is about 8-12 h, the maximum half-life for absorption should be approximately 3-4 h, otherwise, the device will pass out of the potential absorptive regions before drug release is complete. This corresponds to a minimum apparent absorption rate constant of 0.17-0.23 h\(^{-1}\) to give 80-95% over this time period (Jantzen and Robinson, 2002). Compounds that demonstrate too lower absorption rate constants will probably be poor candidates for sustaining systems. Generally, absorption rate of therapeutic agent is assumed to be relatively uniform over the entire length of small intestine. But if a drug is absorbed by active transport or transport is limited to a specific region of the intestine, sustain release preparation with an attempt to formulate low-density pellets, capsules, or tablets that can float on the top of gastric juice, and thereby, delay their transfer out of stomach is desirable. Other alternative is use of bioadhesive polymer which have an affinity for the gastric surface, most probably the mucin coat.

1.3.6.1.3. Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or in the tissue of the intestine, can show decreased bioavailability from sustained release dosage forms. As the drug is released at a slower rate in gastrointestinal
track, less total drug is presented to the enzymatic degradation during a specific period, allowing more complete conversion of the drug to its metabolite (Jantzen and Robinson, 2002).

1.3.6.2. Physicochemical Factors Influencing Oral SR Dosage Form Design

1.3.6.2.1. Dose Size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0 g is considered maximal for a conventional as well as sustained release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of a drug with a narrow therapeutic range (Jantzen and Robinson, 2002). Table 1.2 shows the ratio of sustaining dose $\Omega_m$ to immediate release dose $\Omega_i$ as function of the biological half-life of drug and intended duration of release $T_d$.

Table 1.2. The ratio of sustaining dose $\Omega_m$ to immediate release dose $\Omega_i$ as function of the biological half-life of drug and intended duration of release $T_d$ (Li et al., 1987).

<table>
<thead>
<tr>
<th>$T_B$ (h)</th>
<th>$T_d=6$ h</th>
<th>$T_d=8$ h</th>
<th>$T_d=12$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.6</td>
<td>5.54</td>
<td>8.32</td>
</tr>
<tr>
<td>2</td>
<td>2.08</td>
<td>2.77</td>
<td>4.16</td>
</tr>
<tr>
<td>3</td>
<td>1.39</td>
<td>1.85</td>
<td>2.77</td>
</tr>
<tr>
<td>4</td>
<td>1.04</td>
<td>1.39</td>
<td>2.08</td>
</tr>
<tr>
<td>5</td>
<td>0.83</td>
<td>1.11</td>
<td>1.66</td>
</tr>
<tr>
<td>6</td>
<td>0.69</td>
<td>0.92</td>
<td>1.39</td>
</tr>
<tr>
<td>7</td>
<td>0.59</td>
<td>0.79</td>
<td>1.19</td>
</tr>
<tr>
<td>8</td>
<td>0.52</td>
<td>0.69</td>
<td>1.04</td>
</tr>
<tr>
<td>9</td>
<td>0.46</td>
<td>0.62</td>
<td>0.92</td>
</tr>
<tr>
<td>10</td>
<td>0.42</td>
<td>0.55</td>
<td>0.83</td>
</tr>
</tbody>
</table>

1.3.6.2.2. Aqueous Solubility, Ionization and $pK_a$

Most drugs are weak acids or bases. Since the unchanged (unionized) forms of drug preferentially permeates across lipid membranes, it is important to note the relationship between the $pK_a$ of the compound and the absorptive environment. Unfortunately, the situation becomes more complex by the fact that the drug’s aqueous solubility will generally be decreased in unionized form as compared to ionized form. Considering that the dosage form must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, there should be proper balance between the solubility and $pK_a$ of the compound. Compounds with very low solubility (<0.01 mg/ml) are inherently sustained, since
their release over the time course of a dosage form in the gastrointestinal track will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml (Jantzen and Robinson, 2002). Since drugs must be in solution before they can be absorbed, compounds with very low aqueous solubility usually suffer oral bioavailability problems because of limited gastro-intestinal transit time of the undissolved drug particles and limited solubility at the absorption site. The choice of mechanism for oral sustained/controlled release systems is limited by aqueous solubility of the drug. Diffusional systems will be poor choices for slightly soluble drugs since the driving force for diffusion, the concentration in aqueous solution, will be low. In contrast, such drugs may be effectively incorporated in matrix systems. In selecting polymers for sustained/controlled release systems, the dissolution rate of a drug must be considered. The slow dissolution rate of drug can be utilized to achieve sustained/controlled drug release by incorporation in a matrix system (Li et al., 1987).

1.3.6.2.3. Partition Coefficient

To produce a therapeutic effect in the body, the drug administered in the gastrointestinal track must cross a variety of biological membranes. Hence, partition coefficient of drugs becomes important in determining the effectiveness of membrane barrier penetration. Partition coefficient is defines as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly, drugs with high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. They can localize in the lipid membranes of cells and usually persists in the body for long periods. On the other side, compounds with low partition coefficients will have difficulty in penetrating membranes, and results in poor bioavailability (Jantzen and Robinson, 2002).

1.3.6.2.4. Stability

Orally administered drugs can be subject to both acid and base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in the solid state; therefore, this is the preferred composition of delivery for problem cases. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. Apart from these, route of drug delivery, target sites, acute or chronic therapy, the disease type are the other factors to be considered.
1.3.7. PROS AND CONS OF CONTROLLED RELEASE DOSAGE FORMS

As controlled release dosages are often more expensive than conventional formulations, they cannot be justified unless they offer some clinical or practical advantages. Some advantages are (Kim, 2000):

- Reduction in dosing frequency
- Use of less total drug
- Minimization of drug accumulation
- Improvement in treatment efficiency
- Reduced fluctuations in circulating drug levels
- Increased patient compliance
- Avoidance of night time dosing
- Reduction in GIT irritation
- Reduction of other dose related local or systemic side effects
- Reduction in total cost of therapy

Controlled release dosage forms have several potential limitations. They include cost, unpredictable and often poor in vitro-in vivo correlations, dose dumping, reduced potential for dosage adjustment, delayed onset and increased potential for first-pass clearance and also of poor systemic availability in general. For oral sustained dosage form, effective drug release period is influenced and limited by gastro-intestinal residence time.

1.3.8. CLASSIFICATION OF CONTROLLED RELEASE DOSAGE FORMS

Controlled release dosage forms (CRDFs) may be classified according to their physicochemical, pharmaceutical or clinical aspects. Regardless of the route of drug administration (oral, transdermal, ocular, parenteral, vaginal, etc.), the basic principles involved in fabricating the CRDFs and releasing drugs from them are the same. Based on their release mechanism, they can be classified as follows (Heller, 1987; Kim, 2000; Venkatraman et al., 2000):

A. Physical Systems
   (I) Diffusion-controlled devices
      a. Monolithic systems
         (i) Dissolved drug
         (ii) Dispersed drug
         (iii) Porous systems
         (iv) Biodegradable/Bioerodible systems
b. Reservoir systems/Membrane controlled systems
   (i) Constant activity reservoir
   (ii) Non-constant activity reservoir
   (iii) Unsteady state: time-lag & burst-effect

(II) Solvent-controlled devices
   a. Osmotically controlled devices
      (i) Elementary osmotic pump systems (OROS)
      (ii) Micro-porous osmotic pumps (MPOP)
      (iii) Push-pull systems
   b. Swelling-controlled devices
      (i) Hydrogel systems

(III) Polymer dissolution controlled systems
   a. Acid-catalyzed degradation and erosion systems
   b. Polymer degradation via autocatalysis
   c. Polymer erosion/drug diffusion controlled systems
   d. Swelling/erosion controlled systems

(IV) Gradient matrix systems
   a. Hydrogel beads
   b. Laminated slabs and films
   c. Granules or pellets
   d. Megaloporous matrix
   e. Erodible matrix

(V) Ion-exchange resin systems: Cross-linked and uncross-linked
   a. Swellable polyelectrolyte gels
   b. Erodible polyelectrolyte gels

(VI) Geometrically modified systems
   a. Pie shaped, perforated tablets and multi-hole systems
   b. Cone-shaped and hemisphere systems
   c. Multi-layer tablets and cylinder systems

(VII) Other systems
   a. Hydrodynamically modified systems

B. Chemical systems
   (I) Immobilization of drugs
   (II) Prodrugs

C. Biological systems
   (I) Gene therapy

Among all these techniques, dissolution and diffusion controlled systems have classically been of primary importance in oral delivery of medication because of their relative ease of production and cost compared with other methods of
sustained/controlled delivery (Jantzen and Robinson, 2002). With diffusion-controlled devices, two fundamentally different methodologies can be used: release of active agent from monolithic devices and release of active agent from reservoir devices.

1.3.9. MATRIX SYSTEMS - FIRST CHOICE OF MANUFACTURER

From all above mentioned controlled release dosage forms, the most convenient way to achieve sustained/prolonged release of active agent involves physical blending of drug with polymer matrix, followed by compression molding, injection molding, extrusion, or solvent casting. The potential simplest approaches include (Heller, 1987):

- Monolithic device, a heterogeneous dispersion of drug particles in a solid matrix/rate-controlling polymer which can be either biodegradable or non biodegradable and which controls drug release by diffusion through the matrix, by erosion of the matrix, or by a combination of both diffusion and erosion. It is necessary to consider two types of devices. In one, the active agent is dissolved in the polymer, whereas in the other, the active agent is dispersed in the polymer (Heller, 1987). When the active agent is dispersed in the polymer, release kinetics has been derived by Higuchi. Although active agent released from monolithic systems does not proceed by zero-order kinetics, it is the simplest and most convenient way to achieve prolonged/sustained release of an active agent.

- Swellable hydrogel matrix, a heterogeneous dispersion of drug particles in a water swellable hydrogel polymers, which controls drug release by slow surface-to-center swelling of the matrix by water and subsequent diffusion of the drug from the water-swollen part of the matrix (Hui et al., 1987).

A major limitation of the matrix devices is that drug release rate continuously decreases with time. This is a consequence of increased diffusional distance and decreased surface area at the penetrating solvent front. Consequently, to achieve zero order release from the matrix devices, it will be necessary to select a geometry that compensates the increase in diffusional distances with a corresponding increase in surface area for dissolution (Hui et al., 1987).

Matrix systems can be conveniently prepared by using simple polymer fabrication techniques involving a physical blending of the active agent with a polymer matrix, followed by direct compression into a tablet form, compression molding, extrusion, or solvent casting (Heller, 1987). Here, the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet and particle surface. The
porosity of the tablet, i.e. surface area available, can be altered in a compressed tablet by compression force, adhesion between adjacent particles as well as size and shape of the particles. In addition, hydrophobic fillers can be added to decrease the effective porosity by limiting the number of pores that can be penetrated by the eluting fluid (Hui et al., 1987).

Patients overwhelmingly prefer solid oral dosage over other drug forms. In addition, hydrophilic monolithic swellable matrix systems are among the most widely used means for controlled drug delivery in solid oral dosage forms. Hydrophilic matrix controlled release tablets are relatively simple systems that are more forgiving of variations in ingredients, production method, and end-use conditions than coated controlled-release tablets and other sustained release systems. This results in more uniform release profiles with a high resistance to dose dumping. Matrix systems are relatively easy to formulate with existing, conventional equipments, and processing methods. This is true for almost any size tablet, whether it involves direct compression, dry granulation, or wet granulation. All these help speedy development work and can shorten approval times as well. Ultimately, matrix tablets are economic to the manufacturers as well as to the patients also.

1.3.10. DIRECT COMPRESSION - SCIENTIFIC & ECONOMIC APPEAL

Tablet formulation and design may be described as the process whereby the formulator insures that the correct amount of drug in the right form is delivered at or over the proper time at the proper rate and in the desired location, while having its chemical integrity protected to that point (Peck et al., 1989). Until the late 1950s the vast majority of tablets produced in the world were manufactured by a process requiring granulation of the powdered constituents prior to tableting. The primary purpose of the granulation step is to produce a free-flowing and compressible mixture of active ingredients and excipients. Despite of few advantages of wet granulation (better mechanical handling, improved flow properties, improved uniformity of powdered density, reduce air entrapment, makes hydrophobic surfaces hydrophilic), it is subject to a great many problems. Each unit process gives rise to its own specific complications. The more unit processes, the more chance for problems to occur. Granulation essentially involves the production of a new physical entity, the granule. It is therefore necessary to control and validate all the steps involved in making a new material (granule) and to assure that this final form is in fact reproducible. In addition to blending, problems include (a) type, concentration, rate of addition, distribution, and massing time of the binder solution; (b) effects of temperature, time and rate of drying on drug stability and distribution during the drying process; and (c)
granule size and segregation during the dry screening and subsequent final granulation blending. Each of these factors often involves a considerable effort in regard to both process and equipment validation (Shangraw, 1989). The formulation of solid oral dosage forms, and tablets in particular, has undergone rapid change and development over the last decades with the emergence of precompression, induced die feeding, high-speed and weight controlling by computerized systems, the availability of many new directly compressible materials. The availability of new excipients or new forms of old excipients, particularly fillers and binders has allowed the production of tablets by the much simpler procedure of direct compression. At the same time, major advances were made in tablet compression machinery, such as improved positive die feeding and precompression stages that facilitate direct compression tabletting. By the beginning of 1980s, the excipients and machinery had become available to make possible the direct compression of the vast majority of tablets being manufactured. However, in spite of its many obvious advantages, tabletting by direct compression has not been universally adopted even in those cases where it would seem to be technically feasible and advantageous (Shangraw, 1989).

Though the simplicity of the direct compression process is obvious, it should not be conceived as a simplified modification of the granulation process for making tablets. It requires a new and critical approach to the selection of raw materials, flow properties of powder blends, and effects of formulation variables on compressibility. The properties of each and every raw material and the process by which these materials are blended become extremely critical to the compression stage of tabletting (Shangraw, 1989). The increasing need for suitable polymers to achieve a desired drug release has facilitated screening of a large variety of both synthetic and natural polymers for their ability to retard the release of specific drug substances. Since the cost of synthesizing a new polymeric substance and testing for its safety is enormous (Ebube and Jones, 2004), a new focus has been directed towards investigating the use of polymer blends of pharmaceutically approved polymeric materials as matrix excipients to retard drug release.

The term direct compression is defined as the process by which tablets are compressed directly from powder blends of the active ingredient and suitable excipients (including fillers, disintegrants, and lubricants), which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation procedures is necessary. The advent of direct compression was made possible by the commercial availability of directly compressible tablet vehicles that possess both fluidity and compressibility. Few of directly compressible excipients includes, spray-dried lactose, Avicel
(microcrystalline cellulose), starch 1500 (partially pregelatinized starch, possess higher degree of flowability and compressibility than plain starch while maintaining its disintegrant properties), Emcompress, a free-flowing compressible dicalcium phosphate.

When taken as an aggregate, these problems can be imposing, and it is easy to see why direct compression has both a scientific and economic appeal.

1.3.10.1. Advantages of Direct Compression

- The direct-compression process assumes that all materials can be purchased or manufactured to specifications that allow for simple blending and tableting.
- The most obvious advantage of direct compression is economy. Saving can occur in number of areas, including reduced processing time and thus reduce labor costs, fewer manufacturing steps and pieces of equipment, less process validation, and a lower consumption of power.
- The only two unit processes are common in wet granulation and direct compression re-blending and tableting.
- The most significant advantage in terms of tablet quality is that of processing without the need for moisture and heat, which is inherent in most wet granulation procedures, and the avoidance of high compaction pressures involved in producing tablets by slugging or roll compaction. The unnecessary exposure of any drug to moisture and heat can question about the active ingredient's stability in the formulation.
- The viscosity and temperature of the granulating solution can affect the properties of granules. The type of length of mixing, and the method and rate of wet and dry screening can change the density and particle size of granules. There is no question that, when more unit processes are incorporated in production, the chances of batch-to-batch variation are compounded.
- Probably one of the least recognized advantage of direct compression is the optimization of tablet disintegration. In direct compression, all of the disintegrant is able to perform optimally, and when properly formulated, tablets made by direct compression should disintegrate rapidly to the particles.
- As compared to tablets prepared by wet granulation, the direct compression tablets are less likely prone to stability problems (because of lack of moisture) as well as less changes in dissolution profiles.
- Most directly compressible excipients do contain apparently high levels of moisture; this moisture in most cases is tightly bound either as water of
hydration (e.g. lactose monohydrate) or by hydrogen bonding (e.g. starch, microcrystalline cellulose) and is not available for chemical reaction.

1.3.10.2. Limitations of Direct Compression

- The technological limitations revolve mainly about the flow and bonding of particles to form a strong compact, and the speed at which this must be accomplished in an era of ever-increasing production rates.
- With an increased emphasis on dissolution and bioavailability, many drugs are commonly micronized. Micronization invariably leads to increased interparticulate friction and decreased powder fluidity, and may result in poor compressibility.
- The choice of excipients is extremely critical in formulating direct compression tablets. This is most true of the filler-binder, which often serves as the matrix around which revolves the success or failure of the formulation, hence excipient must possess compressibility and fluidity.
- The cost of specialty raw materials is higher than the comparable fillers.
- The lack of moisture in the blends may give rise to static charges that can lead to unblending.
- Differences in particle size or density between drug and excipient particles may also lead to unblending in the hopper or feed frame of the tablet press. This problem can be solved by selecting nearly similar particle size of drug and excipients as well as ordered blending.
- Direct compression is more likely to be used by noninnovator companies because by the time patents have expired, the physical properties of the drug substance are more clearly defined.

For any CR/SR dosage form, in order to reduce the tablet-to-tablet and batch-to-batch variations, it is very important to use minimum number of excipients with minimum processing steps. Direct compression is therefore, the most suitable technique for CR/SR tablets as this not only reduces the processing steps but is also easily upscalable (Chikhalikar and Moorkath, 2002).
1.4. Aims and Objectives

Diabetes mellitus, a syndrome consisting of interrelated metabolic, vascular, and neuropathic components; and is defined as a group of metabolic diseases that are characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. In type II diabetes mellitus (NIDDM), the cause of the heterogeneous disease is a combination of factors including insulin resistance at the level of the muscle and liver, and an inadequate insulin secretory response. Glipizide, a representative of the second generation sulfonylureas and appears to be the most effective insulin secretogogue both in first phase insulin secretion and in sustained stimulatory response during long term administration. A decrease in blood glucose concentration level occurs within 30 min of ingestion of glipizide, providing peak plasma level concentrations within 1–3 h after a single oral dose with an elimination half-life ranging from about 2 to 4 h. Nateglinide is a D-phenylalanine derivative and belongs to meglitinide class. As plasma glucose rises, β-cell sensitivity to nateglinide increases and insulin release amplifies. Following ingestion, it is absorbed rapidly (within 30 min) with a maximum plasma concentration occurring within one-half to two hours (t\text{max}, 1.5 ± 1.1 h) and has very short half-life of 1-1.25 h. Such a rapidly absorbed drugs having faster elimination rate with short half-life make them suitable candidates to be formulated for the sustained delivery.

An active substance cannot meet patient's needs without an appropriate formulation. Pharmaceutical dosage form development results in a dosage form that is efficacious, patient friendly, stable and delivering the drug with minimal adverse effects as closely as possible to the intended target. In recent years, controlled/sustained/modified release dosage forms have increasingly gained popularity over other conventional dosage forms in treating diseases as the therapeutic efficacy and safety of drugs, administered by conventional methods, can be improved by more precise spatial and temporal placement within the body. Moreover, they reduce the size and number of doses, reduce total disease management cost, thereby providing economic merit to the society and improve patient compliance.

Most sustained release drug delivery systems developed are aimed at slowing the apparent absorption rate by reducing drug release rate from the dosage form. The basic rationale for sustained drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel approaches or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. The oral route is by far the most popular route of drug administration for both conventional and novel drug delivery systems. Compared to other oral dosage forms, tablets are the
manufacturer's dosage form of choice because of their relatively low cost of manufacture, package, and shipment; increased stability and virtual tamper resistance. Patients overwhelmingly prefer solid oral dosage over other drug forms due to simple, easy, convenient, and safe self-administration. In addition, hydrophilic monolithic swellable matrix systems are among the most widely used means for sustained drug delivery in solid oral dosage forms, as they are more forgiving of variations in ingredients, production method and relatively easy to formulate with existing, conventional equipments, and processing methods. Moreover, it results in more uniform release profiles with a high resistance to dose dumping. Matrix systems can be conveniently prepared by using simple polymer fabrication techniques involving a physical blending of the active agent with a polymer matrix, followed by direct compression into a tablet form. Ultimately, matrix systems are economic to the manufacturers as well as to the patients also. Hence, it was the objective of the research work to design and evaluate the sustained release oral dosage forms (matrix tablet) of glipizide and nateglinide by direct compression method.

1.5. References


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2. POLYMERS & EXCIPIENTS

2.1. General Considerations for Direct Compression Excipients-Fillers-Binders

Direct compression excipients, particularly filler-binders, are specialty excipients, modified in the chemical manufacturing process to impart them greater fluidity and compressibility. Many factors influence the choice of the optimum direct compression filler to be used in a tablet formulation. These factors vary from primary properties of powders (particle size, shape, bulk density, solubility) to characteristics needed for making compacts (flowability and compressibility) to factors affecting stability (moisture), to cost, availability, and governmental acceptability. The key to making any excipient or drug directly compressible thus becomes obvious and the possibility of making all tablets by direct compression appears to be within the scope of present technology.

2.2. Spray-Dried Lactose

2.2.1. INTRODUCTION

Nonproprietary Names: None adopted.
Chemical Name: Spray-dried lactose is a mixture of amorphous lactose, which is a 1:1 mixture of α-and-β-lactose, and O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate

![Figure 2.1. Structure of spray-dried lactose.](image_url)
Spray-dried lactose, see Figure 2.1, occurs as white to off-white crystalline particles or powder. It is odorless and slightly sweet-tasting. Spray-dried direct-compression grades of lactose are generally composed of 80–90% specially prepared pure α-lactose monohydrate along with 10–20% of amorphous lactose.

2.2.2. MANUFACTURING

A suspension of α-lactose monohydrate crystals in a lactose solution is atomized and dried in a spray drier (Hutton et al., 1972; Vromans et al., 1989). Approximately 10–20% of the total amount of lactose is in solution and the remaining 80–90% is present in the crystalline form. The spray-drying process predominantly produces spherical particles. The compactibility of the material and its flow characteristics are a function of the primary particle size of the lactose monohydrate and the amount of amorphous lactose (Vromans et al., 1987).

2.2.3. FUNCTIONAL PROPERTIES

Spray-dried lactose is the earliest and still one of the most widely used direct compression fillers. Coarse and regular grade sieved crystalline fractions of α-lactose monohydrate have very good flow properties but lack compressibility. However, spray drying produces an agglomerated product that is more fluid and compressible than regular lactose. The fluidity of spray-dried lactose results from the large particle size and intermixing of spherical aggregates. The compressibility is due to the nature of the aggregates and the percentage of amorphous material present and the resulting plastic flow, which occurs under compaction pressure (Shangraw, 1989). Spray-dried lactose is effective direct-compression filler when it makes up the major portion of the tablet (more than 80%), but it is not effective in diluting high dose drugs whose crystalline nature is, in and of itself, not compressible. Furthermore, spray-dried lactose does not lend itself to reworking because it loses compressibility upon initial compaction (Shangraw, 1989). Spray-dried lactose has excellent fluidity, among the best for all direct-compression fillers. It contains approximately 5% moisture, but most of this consists of water of hydration. The free surface moisture is less than 0.5% and does not cause significant formulation problems. It is relatively non-hygroscopic.
2.2.4. PHARMACEUTICAL APPLICATION

Spray-dried lactose is widely used as a diluent, filler, binder, filler-binder, and flow aid in capsules and direct compression tableting (Bernabe et al., 1997; Hwang and Peck, 2001). Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation. Lactose is also used as a diluent in dry-powder inhalation (Larhrib et al., 1999; Steckel et al., 2004). Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

2.3. Pregelatinized Starch

2.3.1. INTRODUCTION

Nonproprietary Names: BP: Pregelatinised starch, PhEur: Amylum pregelificatum, USPNF: Pregelatinized starch
Chemical Name: Pregelatinized starch
CAS Registry Number: 9005-25-8
Empirical Formula and Molecular Weight: \((C_6H_{10}O_5)_n\), where \(n = 300–1000\).

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amyllose, 15% of free amylopectin, and 80% unmodified starch. Cornstarch has long been used as a disintegrant in oral solid dosage forms. Physical modifications of cornstarch, through partial pregelatinization, have added functional benefits in terms of flowability and partial solubility, while retaining its disintegrant capability and moisture stability.
One of the most widely used tablet excipients starch, in its natural state does not possess the two properties necessary for making good compacts: compressibility and fluidity. There have been many attempts to modify starch to improve its binding and flow properties. The only modification of starch that has received widespread acceptance in direct compression is Starch 1500. Starch 1500 is more fluid than regular starch and meets the specifications for pregelatinized starch N.F. Starch 1500 consists of intact starch grains and ruptured starch grains that have been partially hydrolyzed and subsequently agglomerated (Shangraw, 1989).

### 2.3.2. MANUFACTURING

Starch 1500 is a unique pharmaceutical excipient combining several properties in a single product. It is extremely versatile, being effective in a variety of processing methods for solid oral dosage forms. Starch 1500 also exhibits synergy, enhancing the functionality of other commonly used excipients in formulations. Starch 1500, a partially pregelatinized maize starch brings benefits through binding capability, improved disintegration/dissolution properties, and enhanced flow and lubricity. The manufacturing process involves a physical modification of the starch (no chemical additives or surfactants are used), resulting in the combined benefits of the soluble and insoluble functionality of Starch 1500.

Maize starch is composed of two polymers, amylose and amylopectin, which are tightly bound in a specific spherocystalline structure. Through partial pregelatinization, the bond between a portion of the two polymers is broken, providing Starch 1500 with its unique properties. The process results in partial solubility, increased particle size, improved flow properties, and compactability.

![Figure 2.2. Structural unit of starch (a) Amylopectin and (b) Amylose.](image-url)
As shown in Figure 2.2, amylopectin has a branched chain molecular structure, which makes it readily soluble in cold water. Amylopectin functions as a binder in wet granulation processes. Whereas amylose has a straight chain molecular structure, which exhibits a very strong intermolecular bonding capacity. It swells significantly when wetted, giving it excellent disintegrating characteristics.

2.3.3. MULTI-FUNCTIONALITY

Starch 1500 has good cold water binding and granulation properties, yet retaining effective tablet disintegrant properties. The physical structure of Starch 1500 also imparts good compactability, flow and lubrication capabilities. These multifunctional properties can be utilized in a variety of applications, including direct compaction, wet granulation, fluid bed granulation and capsule plug formation. The distinct benefits of Starch 1500 can bring significant process flexibility to solid dosage forms.

2.3.3.1. Flow-Aid

Starch 1500 provides excellent flow properties, demanded by today’s high-speed tableting and capsule filling equipment; ensuring that manufacturers can produce tablets and capsules with consistent uniform weight and drug content.

2.3.3.2. Self-Lubricant

The high inherent lubricity of Starch 1500 enables the formulator to lower the levels of traditional lubricants, such as magnesium stearate. For example, magnesium stearate added in high levels, or when over-blended, can slow dissolution and cause problems with compaction (soft tablets) and film coating (poor film adhesion). Therefore, Starch 1500 enables lubricant levels and their potential problems to be reduced or eliminated.

2.3.3.3. Wet Granulation

- In wet granulation applications, Starch 1500 exhibits dual functionality as both binder and disintegrant as a result of partial cold water solubility. Starch 1500 allows process flexibility:
- It can be dry-blended with other ingredients before adding water, or a portion can be dispersed in cold water. A slurry of Starch 1500 in cold water provides
effective binding properties at higher solids and lower viscosity than traditional starch pastes, which must be heated and prepared at lower concentrations.

- Processing costs are reduced by eliminating the time and expense of preparing traditional binder solutions. In addition, granulations using Starch 1500 as a binder give excellent tablet hardness and fast disintegration.
- In fluid bed granulations, Starch 1500 alone can be used as both binder and disintegrant. The low viscosity of Starch 1500 in cold water allowed higher binder content solutions and faster spray times, resulting in reduced process times.

2.3.3.4. Direct Compaction

Starch 1500 performs key functions in direct compaction formulations as a binder, disintegrant, flow-aid and self-lubricant. It also promotes formulation flexibility by complementing and enhancing the functionality of other excipients, e.g.

- Binder - As a dry binder, it compresses well, predominately deforming plastically. Starch 1500 can be used with other excipients, such as microcrystalline cellulose, lactose, and dicalcium phosphate, to produce tablets with excellent hardness and low friability at compaction forces typically used in tableting operations.
- Disintegrant - Starch 1500 performs the actions of two disintegrants; maize starch and free amylose in dry processes. In some applications, 2% to 10% of Starch 1500 provides disintegrant action as effective as super disintegrants, greatly reducing costs. The combination of maize starch and free amylose has a positive impact on drug dissolution.

2.3.3.5. HPMC Matrices with Starch

As compared to MCC and lactose, Starch 1500 significantly decreases the drug release from HPMC containing matrices. An important factor for the modified release of these matrix formulations is the ability of the hydrophilic polymer to readily hydrate and form a gel. Starch 1500, due to its partial pregelatinized nature, may contribute to the gel formation and aids in controlling the release rate of the active by changing the tensile strength of the gel layer. Hence, it is not an inert filler in HPMC matrices, but it actively contributes to the mechanism of drug release causing a decrease in drug release rate. Matrix tablets produced by combining Starch 1500 and HPMC are resistant to dose dumping, robust, and are unaffected by variations in ingredients and provide reproducible release profiles. Thus, Starch 1500 aids in controlling the release rate of the active as
well as brings the benefits of enhanced flow and lubricity, along with binding capability. In addition, replacing a portion of the HPMC with Starch 1500 can lower the overall cost of the formulation.

2.3.3.6. Low Dose Medicines

Low dose medicines can be very difficult to formulate due to content uniformity and physical stability issues. Many of these medicines are manufactured by a wet granulation method to assure each tablet contains the proper amount of the active material. Direct compression methods can offer a simplified and more economical process if drug uniformity can be assured. Switching from a wet granulation process to a direct compression process often results in substantial savings in total process time and cost. Capacity issues can also be alleviated. Starch 1500 in these formulations can provide consistent drug uniformity, allowing the product to be manufactured by a direct compression process. The spherogranular morphology and partially pregelatinized nature of Starch 1500 produces an ordered adhesive mixture of drug and excipient in the premix and hence, enhanced particle to particle homogeneity. This superior adhesive characteristic can also be contributed to the inherent moisture content of Starch 1500 of approximately 10%. The highly polar water molecules allow for the formation of hydrogen bonds between the drug and excipient molecules. It is speculated that during the premixing of the active and Starch 1500, a form of granulation takes place as a result of the change in free energy (Ahmed and Shah).

2.3.3.7. Moisture of Sensitive Actives

Moisture sensitive drugs can be a challenge to formulators because of their tendency to hydrolyze when exposed to humidity and/or high temperatures. In moisture sensitive applications it is important that the core formulation be made up of excipients that will help to protect the drug from decomposing. Starch 1500 has been shown to provide moisture stability. The amount of water that penetrates into the core during film coating can be directly linked to the type and amount of hydrophilic components used in the formulation (Faroongsang and Peck, 1991). Starch 1500 has a lower propensity for moisture uptake than many of the other commonly used binders and fillers. Therefore, it will draw less moisture into the tablet under high humidity conditions and may actually inhibit the moisture from interacting with the drug.
2.3.3.8. Super-Disintegrants

Super-disintegrants can also adversely affect moisture sensitive drugs because they function primarily by drawing large amount of water into the tablet and simultaneously swelling. This can have severe consequences on tablet quality attributes, particularly when the tablet requires film coating. In comparison, Starch 1500 has a very low propensity for moisture uptake. Because Starch 1500 is partially pregelatinized, there are two agents working as disintegrants. The unmodified corn starch with its deformation-recovery mechanism causes the starch to expand on contact with water pushing the tablet apart. And the free amylase fraction with its tendency to swell when wetted causes further disruption of the tablet. This double action eliminates the need for additional disintegrants resulting in meaningful saving in process time and expense. And, unlike superdisintegrants, Starch 1500 also imparts other benefits to the formulation as a flow-aid, self-lubricant and binder.

2.3.4. APPLICATIONS

It has extremely high moisture content (12-13%), but there is little indication that this moisture is readily available to accelerate the decomposition of moisture sensitive drugs. Although Starch 1500 will readily compress by itself, it does not form hard compacts. Its dilution potential is minimal, and generally it is not used as the filler-binder in direct compression, but as direct-compression filler disintegrant.

The major advantage of Starch 1500 is that it retains the disintegrant properties of starch without increasing the fluidity and compressibility of the total formulation, which is not the case with the plain starch. Because Starch 1500, like other all starches, deforms elastically when a compression force is applied, it imparts little strength to compacts.

- The other potential advantages of partially pregelatinized Starch 1500 includes-Multifunctional for formulation versatility (Binder, disintegrant, flow-aid, lubricant)
- Cost-effective, i.e. it cuts process and material costs by reducing or eliminating excess binders, superdisintegrants and additional lubricants-glidants
- Manufactured exclusively for the pharmaceutical industry
- Meets global regulatory requirements.
2.4. Microcrystalline cellulose (MCC)

2.4.1. INTRODUCTION

Nonproprietary Names: BP: Microcrystalline cellulose, JP: Microcrystalline cellulose, PhEur: Cellulosum microcristallinum, USPNF: Microcrystalline cellulose
Synonyms: Avicel PH, Cellex, Celphere, Crystalline cellulose, Emcocel, Fibrocel, Pharmacel, Tabulose, Vivapur.
Chemical Name: Cellulose
CAS Registry Number: 9004-34-6
Empirical Formula and Molecular Weight: \((C_6H_{10}O_5)_n \approx 36,000\), where \(n = 220\)

The most important modification of the cellulose for tableting was the isolation of the crystalline portions of the cellulose fiber chain. This product, microcrystalline cellulose (Avicel, Figure 2.3), was introduced as a direct-compression tableting agent in the early 1960s and stands today as the single most important tablet excipient developed in modern times (Shangraw, 1989).

![Figure 2.3. Structure of microcrystalline cellulose (MCC) showing \(\beta-1,4\) glycosidic linkage between anhydro glucose unit in the cellulose molecular chain.]

The family of MCC products began to evolve in the late 1980s and early 1990s. Microcrystalline cellulose (MCC) is a unique ingredient. In water, with shear, it forms a three-dimensional matrix comprised of millions of insoluble microcrystals that form an extremely stable, thixotropic gel. MCC functions at any temperature and provides superior freeze/thaw and heat stability to finished products. It is derived from naturally occurring special grade of purified \(\alpha\) - wood cellulose, similar to that found in fruits and vegetables by severe acid hydrolysis to remove the amorphous cellulose portions, yielding particles consisting of bundles of needlelike microcrystals. Different grades of MCC are developed through various unique co-processing techniques to meet specific viscosity, gelling, suspension, and stabilizing properties.
2.4.2. MANUFACTURING

The raw material for MCC is purified plant fiber, or α-cellulose, and it is composed of millions of microfibrils. Each microfibril is composed of two areas as shown in Figure 2.4. (A) The paracrystalline region, an amorphous flexible mass of cellulose chains, and (B) The crystalline region, which is composed of tight bundles of microfibrils in a rigid linear arrangement. During processing, the fibrous material is hydrolyzed (depolymerized) to remove the amorphous regions, leaving only the crystalline bundles. The resulting cellulose gel can be processed by two methods, to produce either powdered or colloidal MCC (depicted in Figure 2.5).

![Diagram of MCC manufacturing process](image)

**Figure 2.4.** (A) The paracrystalline region, an amorphous flexible mass of cellulose chains, and (B) The crystalline region, which is composed of tight bundles of microfibrils in a rigid linear arrangement (2005).

2.4.3. PROPERTIES AND FUNCTIONALITY

Properly dispersed colloidal MCC sets up into a 3-dimensional network of these colloidal particles, which imparts stability in the finished product; the system is held together by weak hydrogen bonding. The MCC dispersion chemically binds water to a much lesser extent than soluble hydrocolloids (although some water is
bound to the soluble hydrocolloid associated with MCC, e.g. CMC). The formation of this insoluble 3-dimensional matrix creates a physical network that affects the movement of moisture and gives the colloidal grades of MCC their functional properties.

The gel network formed with colloidal MCC offers the following properties:

- **Thixotropy**— gels made with colloidal MCC readily break down with shear; when the shear is removed, the gel will reform over time with minimal loss to viscosity.
- **Foam Stability**—MCC is a premier foam stabilizer. The microcrystalline network thickens the water phase between air cells and acts as a physical barrier to maintain the air cells in suspension. Although MCC does not have significant film forming properties, it does work to increase the film strength.
- **Stabilize Emulsions**—MCC forms a colloidal network of particles when properly dispersed in water. This colloidal network sets up at the oil-water interface to physically prevent the oil globules from coalescing. Hence, the MCC acts to stabilize the emulsion as well as thicken the water phase to improve cling properties.
- **Heat Stability**—temperature changes have little or no effect on the functionality and viscosity of MCC dispersions. This property is extremely important in the preparation of heat stable products, particularly when acids are present. MCC will hold up during heat processing, including baking, retorting, and microwave heating with minimal loss in viscosity.
- **Shorten Textures**—MCC can be used to modify textures— it can shorten textures or add body without creating a gummy or pasty texture. In food systems, this quality results in a cleaner mouthfeel and excellent flavor release.
- **Suspend Particles**—the stability and thixotropic rheology of MCC makes it a useful suspension aid. In an aqueous system, the 3-dimensional matrix sets-up at low use levels to effectively suspend particulates.
- **Replace Fats and Oils**—MCC can be used to replace some or all of the oil in emulsion type products. The MCC mimics many of the rheological properties associated with full oil emulsions.
- **Control Ice Crystal Growth**—the 3-dimensional matrix created with dispersed colloidal MCC and the surface area of the microcrystals create a stabilizing system that maintains a homogeneous state during freeze/thaw cycles. MCC helps prevent moisture migration and inhibits the aggregation of protein and other solids. The 3-dimensional network formed with MCC is extremely effective in maintaining the three-phase system of water/fat/air.
• Extend Starches – using a ratio of 4 parts starch/1 part MCC allows processors to reduce the amount of starch thickener required by as much as 25%. The MCC will also improve heat and shear stability over prolonged process cycles.

• Opacity – insoluble cellulose crystallites act as opacifiers and can add whiteness to products.

• Melting point - chars at 260–270°C.

2.4.4. APPLICATIONS

Apart from food systems, cross-linked or colloidal MCC is used in granulation and tablets preparations. It is excellent binder for tablets/granules or any compacted material, accelerates disintegration and dispersion, has superior stability, provide consistent and reproducible flow rate, and has good water uptake capacity. Avicel PH is a product designed primarily for pharmaceutical solid dosage formulations. Its suitability for tableting operations is shown by the number and variety of functions it can perform. Table 2.1 represents different grades of MCC commercially available with their characteristics and applications.

• Direct Compression : Binder, disintegrant, flow aid, filler

• Wet Granulation : Binder, permits rapid addition of granulation fluid

• Spheronization : Low friability, up to 70% drug loading, good aspect ratio

Table 2.1. Different grades of MCC with characteristics and applications.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristics</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH - 101</td>
<td>Standard Fine Grade</td>
<td>Wet granulation and roller compaction</td>
</tr>
<tr>
<td>PH - 102</td>
<td>Larger particle size grade</td>
<td>Better flow in direct compression, the dry phase of wet granulation and dry granulation</td>
</tr>
<tr>
<td>PH - 103</td>
<td>Medium particle size, low moisture grade</td>
<td>Suitable for moisture-sensitive drugs</td>
</tr>
<tr>
<td>PH - 105</td>
<td>Very fine particle</td>
<td>Suitable for direct compression of coarse and hard to compress materials</td>
</tr>
<tr>
<td>PH - 112</td>
<td>Low moisture with large particle size grade</td>
<td>Used for uniform direct compression with moisture-sensitive ingredients</td>
</tr>
<tr>
<td>PH - 113</td>
<td>Speciality low moisture grade</td>
<td>Helps extend shelf and improve final product stability</td>
</tr>
<tr>
<td>PH - 200</td>
<td>Largest particle size grade</td>
<td>Producing the greatest flow rate in direct compression and dry granulation</td>
</tr>
<tr>
<td>PH - 301</td>
<td>High bulk density grade</td>
<td>Facilitates mixing of fine actives enabling production of small tablets</td>
</tr>
<tr>
<td>PH - 302</td>
<td>High bulk density &amp; large particle size grade</td>
<td>Achieves greater flow rates in production of high dose thin tablets</td>
</tr>
</tbody>
</table>

38 Section I Introduction: Polymers & Excipients
Although Avicel PH can be used in all methods of tableting, it is most effectively used in direct compression. When using Avicel PH, only a simple three-step procedure of weighing, mixing, and compressing is required to prepare a wide variety of tablets. Because of its high chemical purity and low moisture content, improved chemical and color stability of the tablets can result with the use of Avicel. The most widely used grade is PH 101, which was the original product, and PH 102, which is more agglomerated and possesses a larger particle size, resulting in slightly better fluidity but with no significant decrease in compressibility.

Microcrystalline cellulose is the most compressible of all the direct-compression fillers and has the highest dilution potential. This can be explained by the nature of the microcrystalline particles themselves, which are held together by hydrogen bonds in the same way that a paper sheet or an ice cube is bonded. Hydrogen bonds between hydrogen groups on adjacent cellulose molecules account almost exclusively for the strength and cohesiveness of compacts. When compressed, the microcrystalline cellulose particles are deformed plastically due to the extremely large number of clean surfaces brought in contact during the plastic deformation and the strength of the hydrogen bonds formed (Shangraw, 1989).

An excipient with a low bulk density will exhibit a high dilution potential on a weight basis, and the broad particle size range provides optimum packing density and coverage of other excipient materials. It has extremely low coefficient of friction (both static and dynamic) and therefore has no lubricant requirements itself. Because the cost and the density considerations, it is generally not used as the only filler in a direct compression tablet but is more often found in concentrations of 10 to 25% a filler-disintegrant. Hard compacts of microcrystalline cellulose disintegrate rapidly due to the rapid passage of water into the compact and the instantaneous rupture of hydrogen bonds (Shangraw, 1989). Its fluidity is poor compared to that of most other direct-compression fillers because of its relatively small particle size. Tablets made from higher concentrations of microcrystalline cellulose soften on exposure to high humidity due to moisture pick up and loosening of interparticulate hydrogen bonds. Because microcrystalline cellulose is highly compressible, self-lubricating, and a disintegrant, an attempts have been made to use it as the only filler-binder in tablets containing drugs with low doses. At higher concentrations, apparently, the small particles get physically trapped between the deformed microcrystalline cellulose particles, which delays wetting and dissolution, which can be easily overcome by adding portions of water-soluble direct-compression excipients. It is the most effective dry binder which can add significant hardness to compacts at levels as low as 3 to 5% (Shangraw, 1989).
2.5. Sodium Alginate

2.5.1. INTRODUCTION

Nonproprietary Names: BP: Sodium alginate, PhEur: Natrii aiginas, USPNF: Sodium alginate
Synonyms: Algin, alginic acid, sodium salt, Kelcosol, Keltone, Protanal, sodium polymannuronate.
Chemical Name: Sodium alginate
CAS Registry Number: 9005-38-3
Empirical Formula and Molecular Weight: Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid.

Alginate is classified as a hydrocolloid (a water-soluble biopolymer of colloidal nature when hydrated). The British chemist E.C. Stanford made the first scientific studies on the extraction of alginates from brown seaweed at the end of the 19th century, and the large-scale production of alginate was introduced 50 years later. The primary brown seaweed utilized for the extraction of alginates is Laminaria hyperborea. This type of seaweed is harvested along the West Coast of Norway, where large "forests" grow naturally in the clean Arctic waters. Alginate is one of the most versatile biopolymers and is used in a wide range of food, pharmaceutical and specialty applications for: thickening, stabilizing, gelling and film forming.

2.5.2. MANUFACTURING / PROCESSING

Alginate occurs in the seaweed as a mixture of calcium, magnesium, sodium and potassium salts. More than 20 stages of processing are required in order to obtain high quality alginates that offer the exceptional functionality of alginates. More than 200 grades of alginates are available such as – alginic acid and its sodium, sodium triethanolamine, potassium, ammonium, magnesium and calcium salts as well as different grades of esterified alginate in the form of propylene glycol alginate (PGA). Figure 2.6 schematically represents the production of alginic acid followed by its treatment with different chemicals to obtain respective alginate salts.
2.5.3. CHEMISTRY

Alginate is a polysaccharide, composed of several building units (typically 100–3000) linked together in a flexible chain. Polymers of natural origin are commonly called biopolymers. Alginate is built upon the basis of two sugars, which are both uronates, the salts of D-mannuronic and L-guluronic acid. When producing alginates, uronic acid is converted into the salt-forms mannuronate (M) and guluronate (G). See Figure 2.7. As shown in figure above, the G- and M- units are joined together in one of three blocks: GG, MM, and MG. The proportion, distribution, and length of these blocks determine the chemical and physical properties of the alginate molecules. The chemical composition of alginate varies according to seaweed species and even within different parts of the same plant. As with all products produced from natural resource, alginate properties are subject to seasonal variations. By selecting raw materials with varying but known properties, it is possible to manufacture alginates with consistent properties in a wide range of grades.
2.5.4. FUNCTIONALITY AND RHEOLOGY

- Viscosity—Through selection of grade and formulation, the flow characteristics of alginates can be controlled; from free-flowing (low viscosity) to drip-free (high viscosity). The viscosity of an alginate solution depends on the concentration of alginate and the length of the alginate molecules, i.e. the number of monomer units in the chains. The longer the chains, the higher the viscosity at similar concentrations. On dissolving alginates in water, the molecules hydrate and the solution gains viscosity. The dissolved molecules are not completely flexible; rotation around the glycosidic linkages in the G-block regions is somewhat hindered, resulting in a stiffening of the chain. Solutions of stiff macromolecules are highly viscous. Temperature influences the response of alginates to shear forces. As a rule, temperature increases of 1°C lead to a viscosity drop of approximately 2.5%.

- Acid Conditions—Standard grades of alginate will precipitate or form gels in acid conditions. The pKa values for mannuronic and guluronic acid are 3.38 and 3.65, respectively. To increase the stability of an alginate to acid, the alginate may be converted to propylene glycol alginate (PGA).

- Gelation - As previously mentioned, alginates contain various proportions of mannuronate and guluronate monomers. To form a gel, alginates must contain a sufficient level of guluronate monomers in a block to react with...
calcium. The reactivity with calcium and the consequent gelling capacity is a direct function of the average length of the G-blocks. The alginate containing the highest level of GG fractions (i.e. the stem grade alginate from Laminaria hyperborea) possess the highest ability to form strong gels. Regions of guluronate monomers in one alginate molecule can be linked to a similar region in another alginate molecule by means of calcium ions or other multivalent cations (see Figure 2.8). The divalent calcium cation, Ca$^{2+}$, fits into the guluronate block structure like eggs in an egg box. This binds the alginate polymers together by forming junction zones, resulting in gelation of the solution. An alginate gel may be considered part solid and part solution. After gelation, the water molecules are physically entrapped by the alginate matrix, but are still free to migrate. The water holding capacity of the gel is due to capillary forces.

Figure 2.8. Schematic representation of calcium induced gelation of alginate in accordance with the "egg-box" structure.

- Forming a gel - Several gelling systems based on alginates can be formulated, but the most frequently used are diffusion setting or internal setting.
- Diffusion setting, neutral pH - In this system, alginate, or an alginate-containing mix, is gelled by being dipped in to, or sprayed with, a calcium salt solution. Calcium chloride is used most often. The calcium ions diffuse into the mixture containing alginate, forming a calcium alginate gel when the calcium ions react with the alginate. This process is especially suitable for relatively thin or small dimension materials, such as to provide a thin coating on a product surface. The diffusion process can be increased by raising the concentration of calcium in the setting bath or spray and by using a strongly calcium-reactive alginate, i.e. an alginate with a high proportion of G-blocks.
- Diffusion setting, acid pH - In this system, a calcium salt, which is insoluble at neutral pH, is mixed with the alginate. When an acid comes in to contact with
the surface of the mass, the calcium salt is solubilized. The soluble calcium will then react with the alginate and start the gelation process.

- Internal setting, neutral and acid pH - In this process, calcium is released within the product under controlled conditions. It employs the combination of alginate, a slowly soluble calcium salt and a suitable calcium sequestrant, such as a phosphate or citrate. The sequestrant is needed to bind free calcium and prevent pregelation of the alginate during the time the product is mixed, and before it is cast into desired shape. The shorter the mixing time, the lower the level of sequestrant needed. The process may be performed at neutral or acid pH. The acidity may be obtained by the addition of an acidifier, which will accelerate the solubility of calcium salts.

2.6. Carrageenans

2.6.1. INTRODUCTION

Nonproprietary Names: USPNF: Carrageenan
Synonyms: Chondrus extract, Gelcarin, Genu, Hygum TP-1, Irish moss extract, Marine Colloids, SeaSpen PF, Viscarin.
Chemical Name and CAS Registry Number:
Carrageenan [9000-07-1]
κ-Carrageenan [11114-20-8]
λ-Carrageenan [9064-57-7]

Carrageenan is a naturally occurring family of carbohydrates (polysaccharides) extracted from red seaweed. From this natural source, different blends of carrageenans for specific gelling, thickening, and stabilizing properties can be produced. Depending on the algae from which they are extracted and the preparative technique, three main types of carrageenans (Figure 2.9) available; kappa (κ), lambda (λ), and iota (ι). The solubility characteristics (Table 2.2) of carrageenan in water are influenced by a number of factors most important of which are (a) the type of carrageenan, (b) counter ions present, (c) other solutes, (d) temperature, and (e) pH. Acid and oxidizing agents may hydrolyze carrageenan in solution leading to loss of physical properties through cleavage of glycosidic bonds. Acid hydrolysis depends on pH, temperature and time (Table 2.2).
2.6.2. MANUFACTURING

Quality control of carrageenan extract begins at the harvest. The seaweed is systematically gathered, quickly dried, and then baled to maintain its quality. At the manufacturing site, the dried seaweed is mechanically ground and sieved to eliminate impurities such as sand and salt. Following extensive washing to ensure additional quality, the seaweed undergoes a hot extraction process to separate the carrageenan from the extraneous plant fiber. Removal of the cellulosic material requires a two-step clarification process. First, we centrifuge the dissolved carrageenan mixture to eliminate the dense cellulosic particles. Then, filtration is used to remove the smaller particles. The solution is then

Figure 2.9. Different types of carrageenans.
concentrated by evaporation to accommodate the removal of water. The carrageenan is then recovered by one of two processing methods:

- In one method, the concentrated carrageenan solution is deposited into a solution of potassium chloride. This raises the gelling temperature so that the filtrate will gel immediately. The gel is then frozen and compressed while thawing to remove excess water.
- In the second method, the concentrated carrageenan solution is precipitated in isopropyl alcohol. As carrageenan is insoluble in alcohol, the filtrate turns into a coagulum of carrageenan, alcohol and water. The coagulum is compressed to remove the liquids and vacuum dried to completely remove the alcohol. Drying is completed on a belt drier and the dried coagulum is then ground to specification. Finally, the carrageenan is blended to meet the finished product's exact specifications.

Table 2.2. Solubility, stability and gelling mechanism of different types of carrageenans.

<table>
<thead>
<tr>
<th>Medium</th>
<th>Kappa</th>
<th>Iota</th>
<th>Lambda</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>Soluble above 60°C (140°F)</td>
<td>Soluble above 60°C (140°F)</td>
<td>Soluble</td>
</tr>
<tr>
<td></td>
<td>K⁺, Ca²⁺ &amp; NH₄⁺ salt swells</td>
<td>Ca²⁺ salt swells &amp; gives thixotropic dispersions</td>
<td></td>
</tr>
<tr>
<td>Cold water</td>
<td>Soluble</td>
<td>Insoluble but swells markedly</td>
<td>Soluble</td>
</tr>
<tr>
<td>Hot milk</td>
<td>Soluble</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Cold milk</td>
<td>Na⁺, K⁺, &amp; Ca²⁺ salt</td>
<td>Insoluble</td>
<td>Soluble</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stability</th>
<th>At the neutral and alkaline pH</th>
<th>At acid pH</th>
<th>Gelling Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stable</td>
<td>Hydrolyzed in solution when heated.</td>
<td>Gels most strongly with K⁺ ions</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>Stable in gelled form.</td>
<td>Gels most strongly with Ca²⁺ ions</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>Stable in gelled form.</td>
<td>Non-gelling</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>Hydrolyzed in solution.</td>
<td>Elastic, clear, and cohesive without syneresis</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>Stable in gelled form.</td>
<td>Non-gelling</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>Hydrolyzed in solution.</td>
<td>Non-gelling</td>
</tr>
</tbody>
</table>

| Chemistry    | 25% ester sulfate and 34% 3,6-anhydroglucose | 32% ester sulfate and 30% 3,6-anhydroglucose | 35% ester sulfate and little or no 3,6-anhydroglucose |
| Freeze/thaw stability | None | Stable | Stable | Stable |
| Synergistic effect with locust bean gum | High | High | None |
2.6.3. FUNCTIONALITY AND RHEOLOGY

- **Binds Moisture** – Carrageenan has excellent moisture binding capabilities. This allows formulators to manage water and other aqueous fluids in their systems.
- **Stabilizes Emulsions** – Although carrageenan is not a surfactant, it stabilizes existing emulsions. Its thickening and thixotropic properties give integrity to the system and inhibit the oil from coalescing and separating into an oil phase and water phase.
- **Suspends Particles** – The 3-dimensional network which helps stabilize emulsions also functions to suspend particulates. Insolubles will remain uniformly distributed in the bottle for extended periods without remixing or shaking.
- **Controls Flow Properties** – Controlling flow properties of food systems is essential from processing to the final product consistency. Carrageenan is thermally-reversible, so at high temperatures it will impart minimal viscosity, allowing for easier processing conditions and improved heat transfer. Upon cooling, the carrageenan will thicken. With most gelling carrageenans, solutions will begin to solidify and form gels when cooled below 49°C (120°F).
- **Produces Stable Gels at Room Temperature** – Most kappa and iota carrageenan solutions will set into a gel structure at ambient temperatures. The gels require heat to melt into a fluid state for reprocessing.

Generally, carrageenan should be dispersed in cold water and then heated above the solubility temperature of the carrageenan to obtain maximum functionality. There are several other methods of incorporating carrageenan into complex systems or processes that allows it to offer optimum functionality. Upon cooling and in the presence of appropriate cations, kappa and iota carrageenan polymers align themselves to form individual helices. These helices can further associate with divalent cations that are present, e.g. calcium, to form a gel matrix. Figure 2.10 and Figure 2.11 is a schematic representation of the gelling mechanism for carrageenan by heating and in presence of cation, respectively.
Figure 2.11. Schematic presentation of gelling mechanism of different types of carrageenans in presence of cations (FMC Biopolymers, 2005).

Figure 2.10. Schematic representation of gelling mechanism for carrageenan by heat.

Figure 2.11. Schematic presentation of gelling mechanism of different types of carrageenans in presence of cations (FMC Biopolymers, 2005).
2.6.3.1. Factors influencing gelling

- Cations – As the absolute concentration of cations increases, dispersion improves, temperature at which carrageenan goes into solution increases, gelling temperature increases, and remelt temperature increases. Potassium and calcium ions are essential for effective carrageenan gelation. Increasing the level of potassium ions increases the strength of the resulting gel. As the level of potassium (% KCl) is increased, relative increase in gel strength is observed.

Temperature – As discussed earlier, carrageenan water gels are thermally reversible. The gels can be subjected to repeated heat/cool cycles with very little effect on the resulting gel structure (at neutral pH).

- Sugars – High levels of sugars, a common component in many food gels, reduce the solubility of carrageenan. Carrageenan should be dissolved in available water if the sugar concentration of the food system is higher than 50% of the finished product.

- Synergism with Other Gums – Kappa carrageenan is synergistic with locust bean gum and konjac flour. The interaction significantly increases gel strength, improves moisture-binding capabilities, and modifies gel texture to be more elastic and resilient.

- Synergism with Starch – Iota carrageenan increases the viscosity of starch systems by as much as 10 times the viscosity of the starch alone. When kappa carrageenan is added to starch systems, no increase is noted.

- Acidulants or pH – Solutions and gels that are formed with carrageenan are stable at room and refrigerated temperatures. At high temperatures, carrageenan solutions that contain acidulants exhibit some loss in viscosity and potential gel strength. In low pH systems, it is recommended that the acidulant be added at the last step of processing, or just prior to filling into containers.

2.6.4. PHARMACEUTICAL APPLICATIONS

Current marketed products containing carrageenan include cough/cold liquids, antibiotic suspensions, topical lotions and creams, and medicated shampoos. New applications for carrageenan continue to be developed and commercialized due to its unique high performance rheology features. Examples of emerging functionality and applications include: bio adhesion in oral liquid products, shape retention in vaulted cavity delivery systems such as otic and vaginal, suppository formulation, and controlled release delivery.
2.7. Carbopol

2.7.1. INTRODUCTION

Nonproprietary Names: BP: Carbomers, PhEur: Carbomera, USPNF: Carbomer
Synonyms: Acritamer; acrylic acid polymer; Carbopol; carboxy polymethylene, polyacrylic acid; carboxyvinyl polymer; Pemulen; Ultrez.
Chemical Name: Carbomer
CAS Registry Number: 9003-01-4. Note that carbomer 910, 934, 934P, 940, 941, 971P and 974P resins share the common CAS registry number 9003-01-4.
Empirical Formula and Molecular Weight: Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol. They contain between 56% and 68% of carboxylic acid (-COOH) groups calculated on the dry basis. The molecular weight of carbomer resins is theoretically estimated at $7 \times 10^5$ to $4 \times 10^9$.

2.7.1.1. Nomenclature:

The USP-NF, European Pharmacopoeia, British Pharmacopoeia, United States Adopted Names Council (USAN), and International Nomenclature for Cosmetic Ingredients (INCI) have adopted the generic (i.e., non-proprietary) name "carbomer" for various Carbopol® homopolymer polymers. The Japanese Pharmaceutical Excipients list Carbopol homopolymers as "carboxyvinyl polymer" and "carboxy polymethylene." The Italian Pharmacopoeia also identifies Carbopol 934P as "carboxy polymethylene" and the Deutschen Arzneibuch calls Carbopol 980NF "polyacrylic acid." Carbopol copolymers, such as Carbopol 1342 NF and 1382, and the Pemulen® polymeric emulsifiers, have also been named "carbomer" by the USP-NF, but are considered "Acrylates/C10-C30 Alkyl Acrylates Crosspolymer" by the INCI. The Noveon® series of products is generically known as "polycarbophil."

2.7.1.2. Chemistry

Carbopol polymers were first described in scientific literature in 1955, first prepared and patented in 1957 (Brown, 1957). Since then, a number of extended release tablet formulations, which involve carbomer matrices, have been patented (B F Goodrich Bulletin, 1987). The carboxyl groups provided by the acrylic acid backbone of the polymer are responsible for many of the product benefits. Carbopol polymers have an average equivalent weight of 76 per
carboxyl (B F Goodrich Company Technical Literature, 1991). They are chemically similar to each other, differing only in ascending molecular weights (which range from carbomer-910 to carbomer-962). They contain between 98.7% and 99.9% acrylic acid. When dried at 80°C for one hour, they contain not less than 56.0% and not more than 68.0% carboxylic acid (—COOH) groups. They are produced from primary polymer particles of about 0.2 to 6.0 micron average diameter. The flocculated agglomerates can not be broken into the ultimate particles when produced. Each particle can be viewed as a network structure of polymer chains interconnected via cross-linking. The general structure can be illustrated as given in Figure 2.12.

![Figure 2.12. Chemical structure of carbopol polymer.](attachment:carbopol.png)

Products within the carbopol® polymer family are chemically similar in that they are all readily water-swellable, high molecular weight, crosslinked homopolymers and copolymers based on acrylic acid, which form hydrogels in aqueous solution. By modifying crosslinker types and levels, as well as amounts and characteristics of the hydrophobic comonomers, a wide range of performance properties can be achieved. However, the polymers differ by crosslink density and can be grouped in to the following categories.

- **Carbopol® homopolymers** (homopolymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythritol)
- **Carbopol® copolymers** (copolymers of acrylic acid and long chain (C10-C30) alkyl acrylate crosslinked with allyl pentaerythritol)
- **Polycarbophils** (calcium salt and acid form) are polymers of acrylic acid crosslinked with divinyl glycol.

Different grades of carbopol polymers differ in performance, but their general properties are alike (Handbook of Pharmaceutical Excipients, 1986; 2002).

**Appearance:** Fluffy, white, dry powder, slight characteristic odor, mildly acidic polymer

**Bulk Density:** Approximately 208 kg/m³ (13 lbs. ft³)
Specific gravity: 1.41
Moisture content as shipped: 2.0% maximum
Equilibrium moisture content: 8-10% (at 50% relative humidity)
pKa: 6.0 + 0.5
pH of 1.0% water dispersion: 2.5 - 3.0
pH of 0.5% water dispersion: 2.7 - 3.5
Equivalent weight: 76 + 4
Ash content: 0.009 ppm (average)
Melting point: Decomposition within 30 min at 260°C.

- Solubility: They are highly ionic and slightly acidic; they are largely insoluble in water and in the majority of common solvents. When neutralized with alkaline hydroxides or with amines, they dissolve in water, alcohol, and glycerin.
- Glass transition temperature: The glass transition temperature of Carbopol polymer is 105°C (221°F) in powder form. However, it drops dramatically as the polymer is exposed to water. The polymer chains start gyrating and the radius of gyration becomes bigger and bigger. Macroscopically, this phenomenon manifests itself as swelling.
- Particle size: The polymers are flocculated powders averaging 2 to 7 microns in diameter, as determined by Coulter Counter. They are produced from primary polymer particles of about 0.2-micron average diameter. The flocculated agglomerates cannot be broken down into the ultimate particle once produced.
- Rheological Properties and Molecular Weights: Different grades of carbopol polymers exhibit different rheological properties, a reflection of the particle size, molecular weight between crosslinks (M_c), distributions of the M_c, and the fraction of the total units which occur as terminal, i.e. free chain ends.
- In simple terms, low viscosity, low rigidity polymer, such as carbopol 941 and carbopol 971P, have a higher M_c. Conversely, they have lower crosslinker densities. The higher the crosslinker level, the lower the equilibrium swelling ratio. Molecular weights for carbomers range from approximately 500,000 to 4,000,000.

2.7.2. MANUFACTURING:

The carbomer polymers are manufactured by reflux polymerization of acrylic acid in an inert solvent in the presence of a catalyst; in doing this, a closed system, free of oxygen and water, is used (CIR, 1979). The chemical composition and the chemical and physical properties of carbomer polymers suggest that they possess similar toxicological properties. All of these polymers have the same
acrylic acid backbone. The main differences are related to the presence of a comonomer and the crosslink density. With very minor adjustments in the crosslink density and comonomer level, a large number of polymers have been engineered to provide specific application properties without substantially changing the gross molecular structure.

The molecular weight range of these polymers is estimated to be from 740,000 to 4-5 million. There are no methods available to measure the actual molecular weight of a cross-linked (i.e., 3-dimensional) polymer of this type. The backbone of the homopolymer carbopol is the same (see Figure 2.12). The main difference is related to cross-link density and molecular weight, rather than the cross-linker used. With very minor adjustments in the cross-linker density, one can produce a large number of Carbopol type products similar in gross molecular structure but varying in application properties, for example, viscosity. Cross-link density can be varied by minor shifts in position of the cross-linker on the acrylic backbone. The three-dimensional nature of these polymers confers some unique characteristics, such as biological inertness, not found in similar linear polymers. The Carbopol resins are hydrophilic substances that are not soluble in water. Rather, these so-called "water soluble" resins swell when dispersed in water forming a colloidal, mucilage-like dispersion (B F Goodrich Bulletin, 2001).

2.7.3. APPLICATIONS

Different types of carbopols are ingredients in pharmaceutical dosage systems of almost every form — from controlled release tablets to oral suspensions to novel delivery systems, as well as a variety of topical products. Due to their physical properties, inertness and low toxicity, the carbopol resins have been used in such preparations as suspending, flow control, thickening and emulsion stabilizing agents. They have a diverse range of applications in the cosmetic, detergent, and pharmaceutical industries to provide:

- Controlled release in tablets (Choulis et al., 1976; Perez-Marcos et al., 1991b; Perez-Marcos et al., 1991a; Durrani, 1992). Carbopol polymers offer consistent performance over a wide range of desired parameters — from pH-derived semi-enteric release to near zero-order drug dissolution kinetics — at lower concentrations than competitive systems. It can be used as a matrix ingredient in tablets and capsules at general use levels of 5 - 30% wt. to achieve controlled release of actives.
- Tablet formulations using Carbopol polymers have demonstrated zero-order and near zero-order release kinetics. These polymers are effective at low concentrations (less than 10%). Still they show extremely rapid and efficient swelling characteristics in both simulated gastric fluid (SGF) and simulated...
intestinal fluid (SIF). The Carbopol polymers produce tablets of excellent hardness and low friability. These polymers can be successfully formulated into a variety of different tablet forms, including the traditional swallowable tablets, chewable tablets, buccal tablets, sublingual tablets, effervescent tablets, and suppositories; providing controlled-release properties as well as good binding characteristics. Carbopols show larger dissolution times at lower concentrations than other excipients. Because of these factors, carbopol polymers have greater extent in formulating dosage forms (Durrani, 1992; Durrani et al., 1994).

- Bioadhesion in buccal (Guo, 1994a; b), ophthalmic (Davies et al., 1991; 1992), intestinal (Akiyama et al., 1995), nasal (Micheal et al., 1999) , vaginal (Claudia et al., 2001) and rectal (ElHady et al., 2003) applications.
- Thickening at very low concentrations (less than 1%) to produce a wide range of viscosities and flow properties in topical lotions, creams and gels, oral suspensions, and in transdermal gel reservoirs (Briede, 1983; Al-Khamis et al., 1986).
- Permanent suspensions of insoluble ingredients in oral suspensions and topicals (Berney and Deasy, 1979).
- Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially n need for irritating surfactants.

Carbopol polymers readily absorb water, get hydrated and swell. In addition to its hydrophilic nature, its cross-linked structure, and it's essentially insolubility in water makes them a potential candidate for use in sustained/controlled release drug delivery system (Carnali and Naser, 1992; Garcia-Gonzalez et al., 1994).

2.7.4. POLYMER SWELLING & PERFORMANCE MECHANISM

Each primary particle can be viewed as a network structure of polymer chains interconnected by crosslinks. Without the crosslinks, the primary particle would be a collection of linear polymer chains intertwined but not chemically bonded. These linear polymers are soluble in a polar solvent, such as water. Carbopol polymers are crosslinked and do not dissolve in water but hygroscopic in nature. Because of their ability to absorb and retain water, these polymers swell in water up to 1000 times their original volume (and ten times their original diameter) to form a gel when exposed to a pH environment above 4.0-6.0. Since the pKa of these polymers is 6.0 ± 0.5, the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative charges, which adds to the swelling of the polymer. Such swollen particles remain discrete in various mucilaginous or colloidal dispersions. Although swelling is inherently caused by their hydrophilic nature, "maximum volume swell" does not occur in water until the
These polymers are very mild acids – weaker than acetic acid – they readily react to form salts. Aqueous dispersions of carbopol polymers have an approximate pH range of 2.8 to 3.2 depending on polymer concentration. The greater the concentration, the higher the carboxyl concentration and, therefore, the lower the pH. All the carbopol resins, when first dispersed in water or other solvent, they are tightly knotted together via hydrogen bonding, thus limiting its thickening capability. At normal use levels of up to 1% (Figure 2.13 (a)) no significant thickening occurs until the resins are partially neutralized with an appropriate base to form a salt. When this salt dissolves and ionizes, it swells into its most effective thickening form (Figure 2.13 (b)). When dispersed in water, the molecule begins to hydrate and uncoil slightly, generating an increase in viscosity. However, to achieve the highest possible performance with the polymer, the molecule must be completely uncoiled. There are two mechanisms, by which the molecule can become completely uncoiled, providing maximum thickening, emulsion formation, or bioadhesion performance (Noveon Bulletin, 2002):

- The most commonly used mechanism is accomplished by neutralizing the polymer with a suitable base. Neutralization ionizes the carbopol polymer, generating negative charges along the polymer backbone. Repulsions of these like negative charges cause the molecule to completely uncoil into an extended structure (Figure 2.13 (a) and (b)). This reaction is rapid and gives instantaneous thickening, emulsion formation or bioadhesion. This is readily done with neutralizing agents such as sodium or potassium hydroxide or amine bases such as Tris® (tris (hydroxymethyl) aminomethane). Less polar or nonpolar solvent systems should be neutralized only with amines.
• A second thickening mechanism involves the use of a hydroxyl donor in addition to the polymer. The combination of a carboxyl donor and one or more hydroxyl donors will result in thickening because of the formation of hydrogen bonds. This mechanism is time dependent and can take from five minutes to several hours to attain maximum thickening. The pH of such systems will tend to be acidic. Some commonly used hydroxyl donors are polyols (glycerine, propylene glycol, PEGs etc.), sugar alcohols (mannitol, sorbitol etc.), non-ionic surfactants with 5 or more ethoxy groups and others (See Figure 2.13 (a) and (b)).

2.8. Guar Gum

2.8.1. INTRODUCTION

Nonproprietary Names: BP: Guar galactomannans, PhEur: Guar galactomannanum, USPNF: Guar gum
Synonyms: Galactosol, jaguar gum, Meyprogat, Meyprodor, Meyprofin.
Chemical Name: Galactomannan polysaccharide
CAS Registry Number: 9000-30-0
Empirical Formula and Molecular Weight: \((C_{6}H_{12}O_{6})_n \approx 220,000\)
Guar is a legume that has been traditionally cultivated as livestock feed. Guar gum is the ground endosperm of the seeds. Approximately 85% of guar gum is guaran, a water soluble polysaccharide consisting of linear chains of mannose with 1\(\beta\rightarrow4\) linkages to which galactose units are attached with 1\(\alpha\rightarrow6\) linkages.
2.8.2. STRUCTURAL FORMULA

Guar gum (Figure 2.14) is a gum obtained from the seeds of Cyamopsis tetragonolobus (Fam. Leguminosae) by grinding the endosperms and subsequent partial hydrolysis. It consists chiefly of a high-molecular-weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages, which may be described chemically as a galactomannan. It is composed of D-galactose and D-mannose in molecular ratios of 1:1.4 to 1:2. The molecule consists of a linear chain of $\beta-(1\rightarrow4)$-glycosidically linked manno-pyranoses and single $\alpha-(1\rightarrow6)$-glycosidically linked galacto-pyranoses.

![Structural formula of guar gum](image)

Figure 2.14. Guaran/galactomannan is the principal polysaccharide in guar gum

2.8.3. MANUFACTURING

Guar gum is obtained from the ground endosperm of the guar plant, Cyamopsis tetragonolobus (Fam. Leguminosae). The seed hull can be removed by grinding, after soaking in sulfuric acid or water, or by charring. The embryo (germ) is removed by differential grinding, since each component possesses a different hardness. The separated endosperm, containing 80% galactomannan is then ground to different particle sizes depending upon final application.
2.8.4. PHYSICOCHEMICAL PROPERTIES

- Description: Odorless or nearly odorless, white to yellowish-white powder with a bland taste.
- pH (1% w/w solution): 5.5–7.5
- Solubility: Practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol. The optimum rate of hydration occurs at pH 7.5–9.0. Finely milled powders swell more rapidly and are more difficult to disperse. Two to four hours in water at room temperature are required to develop maximum viscosity.
- Viscosity (dynamic): 4.86 Pa s (4860 cP) for a 1% w/v dispersion. Viscosity is dependent upon temperature, time, concentration, pH, rate of agitation, and particle size of the guar gum powder. Synergistic rheological effects may occur with other suspending agents such as xanthan gum.

2.8.5. PHARMACEUTICAL APPLICATIONS

Guar gum has five to eight times the thickening power of starch and commonly used in cosmetics, pharmaceutical industry, food products, and also used as a source of dietary fiber. It has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose (Khullar et al., 1999). In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant (Feinstein and Bartilucci, 1966; Sakr and Elsabbagh, 1977; Duru et al., 1992), in oral and topical products as a suspending, thickening, and stabilizing agent; and also as a controlled-release carrier. Guar gum has also been examined for use in colonic drug delivery (Wong et al., 1997; Sinha et al., 2004; Toti and Aminabhavi, 2004; Tugcu Demiroez et al., 2004). Guar-gum-based three-layer matrix tablets have been used experimentally in oral controlled-release formulations (Al-Saiden et al., 2004). Therapeutically, guar gum has been used as part of the diet of patients with diabetes mellitus (Jenkins et al., 1977). It has also been used as an appetite suppressant, although its use for this purpose, in tablet form, is now banned in the UK.
2.9. Xanthan Gum

2.9.1. INTRODUCTION

Nonproprietary Names: BP: Xanthan gum, PhEur: Xanthani gummi, USPNF: Xanthan gum
Synonyms: Corn sugar gum, Keltrol, polysaccharide B-1459, Rhodigel, Vanzan NF, Xantural.
Chemical Name: Xanthan gum
CAS Registry Number: 11138-66-2
Empirical Formula & Molecular Weight: \((C_{35}H_{68}O_{29})_n\) and Approximately \(2\times10^6\)
The USPNF 23 describes xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

Natural gums occur in all life forms. We use gum arabic, gelatin or dextran, china grass (sea weed / agar), gum tragacanth in daily use for different purposes. Many types of gums can be obtained from plant sources. Their collection is costly and requires skilled labourers. Moreover, seasonal variations affect the quality and quantity of plant gums. The polysaccharides for scientific and industrial applications are obtained more conveniently from microbial sources due to several factors. They can be produced under controlled conditions from selected species using renewable sources and are biocompatible and biodegradable. These factors have accelerated the use of microbial gums such as pullulan, curdlan, scleroglucan, dextran and xanthan. Microbial polysaccharides are composed of regular repeating units of simple sugars like glucose, mannose, fructose, etc. (Lachke, 2004).

Xanthan Gum (E415), a microbial desiccation-resistant polymer was discovered 50 years ago in Illinois (USA). It is a polysaccharide produced as a secondary metabolite of a biotechnological submerged fermentation process by a micro-organism: Xanthomonas campestris (a gram negative, yellow-pigmented bacterium), in aerobic conditions (It is naturally produced to stick the bacteria to the leaves of cruciferous vegetables such as cabbage and cauliflower). Many micro-organisms, bacteria in particular, are capable of metabolizing extra-cellular polysaccharides. However, Xanthan is the only bacterial polysaccharide produced industrially on a large scale. It is a natural carbohydrate commercially produced by fermenting glucose with the appropriate micro-organisms.
2.9.2. XANTHAN STRUCTURAL UNIT

Xanthan gum, an anionic polyelectrolyte is a high molecular weight heteropolysaccharide produced by viscous fermentation. Its unique functionality compared to other commercial polysaccharides is provided by the actual structure of the xanthan gum molecule. As shown in Figure 2.15, the polymer backbone is made up of \( \beta-1, 4 \)-linked D-glucose residues and, therefore, is identical to the cellulose molecule. A trisaccharide side chain containing one glucuronic acid unit between two mannose units is linked to every second glucose unit at the number 3 position. This side chain consisting of \( \alpha \)-D-mannose, which contains an acetyl group, of \( \beta \)-D-glucuronic acid, and of a terminal \( \beta \)-D-mannose unit linked with a pyruvate group. The mannose closest to the backbone has an acetic acid ester on carbon 6, and the mannose at the end of the trisaccharide is linked through carbons 6 and 4 to the second carbon of pyruvic acid. The negatively charged carboxyl groups on the side chains cause the molecules to form very viscous fluids when mixed with water.

![Structure of xanthan gum repeating unit.](image)

Approximately 60% of the terminal mannose units being pyruvylated and 90% of the proximal mannose units substituted at C6 with O-acetyl groups. It has side chains of side chains 2 mannose and 1 gluconic glucuronic acid group. It is not surprising that xanthans of different pyruvate levels (that is 1 to 6 %) display different rheological (flow) properties. Pyruvic acid attached to the terminal carbohydrate of the side chains adds another carboxylate group. The percent composition of xanthan proposed for industrial use is as follows: Glucose 37, mannose 43.4, glucuronic acid 19.5, acetate 4.5 and pyruvate 4.4%.
2.9.3. FUNCTIONALITY

Xanthan gum is mainly considered to be non-gelling and used for the control of viscosity due to the tenuous associations endowing it with weak-gel shear-thinning properties. It hydrates rapidly in cold water without lumping to give a reliable viscosity, encouraging its use as thickener, stabilizer, emulsifier, lubricant, suspending agent, and foaming agent. The consistent water holding ability may be used for the control of syneresis and to retard ice recrystallization (ice crystal growth) in freeze-thaw situations; xanthan gel strength being improved on freeze-thaw. Its most important property being its very high low-shear viscosity coupled with its strongly shear-thinning character. The relatively low viscosity at high shear means that it is easy to mix, pour and swallow but its high viscosity at low shear gives good suspension and coating properties and lends stability to colloidal suspensions. Being relatively unaffected by ionic strength, pH (1 - 13), shear or temperature it may be used in such products as salad dressings to emulsify oil and vinegar, in cosmetics, animal feeds and various industrial products. It is gluten-free but can be used as a substitute for gluten (the protein which gives wheat flour its structure). May be used alongside non-gluten containing flours to improve structure and texture in gluten-free baked goods. Xanthan gum is used as a thickener for sauces, to prevent ice crystal formation in ice cream, and as a low-calorie substitute for fat. Xanthan gum is frequently mixed with guar gum because the viscosity of the combination is greater than when either one is used alone. This unique combination of properties allows xanthan gum products to perform beyond the limits of many other commercially available hydrocolloids.

Xanthan gum is capable of synergistic interactions with galactomannans and glucomannans. It synergistically forms thermoreversible soft elastic gels with locust bean gum and guar gum on cooling mixtures. The synergy is best at high xanthan extension and is thus reduced by high salt and low pH. Xanthan gums may contain cellulase, which prevents their use with cellulose derivatives.

Xanthan gum has a relatively reproducible specification as it is produced by fermentation. Each molecule consists of about 7000 pentamers and the gum is less polydisperse than most hydrocolloids. Its natural state has been proposed to be bimolecular antiparallel double helices. It may form a very stiff intramolecular (single molecule hairpin) double stranded helical conformation by the annealing of the less stiff 'natural' denatured elongated single stranded chains. The glucan backbone is protected by the side chains which lie alongside, making it relatively stable to acids, alkalis and enzymes (this is particularly important as preparations can contain cellulase). Use of different strains or fermentation conditions may
give rise to differing degrees of acteiylation and pyruvylation, which moderates the functionality. The conversion between the ordered double helical conformation and the single more-flexible extended chain may take place over hours of annealing (equilibrating) at between 40°C - 80°C. The weakly bound network formed is highly pseudoplastic, viscosity reducing considerably with shear increase and returning in full immediately on release. High viscosity solutions (~1%) appear gel-like but still shear-thin. The rationale for this strange behavior is the hydrogen-bonded and entangled association between the side chains of the highly extended molecules, which resists dissociation. Shear thinning with greater strain is mainly due to the conformation of the side chains flattening against the backbone under shear, so reducing the intermolecular interactions.

2.9.4. PHYSICOCHEMICAL PROPERTIES OF XANTHAN

| Appearance | Cream colored powder |
| Solubility in Cold Water | Dispersed hydrated to form pseudoplastic mixtures [CP Kelco]; high water solubility |
| Salt Solution | Compatible and stable in solutions with high salt concentrations [Cp Kelco] |
| Melting point | Chars at 270°C. |
| Rheology | The presence of anionic side chains on the Xanthan gum molecules enhances hydration and makes Xanthan gum soluble in cold water. In addition, the form and the rigidity of the macromolecules determine the rheology of the solutions. See Figure 2.16 (SKW Boisystems). |

Figure 2.16. Schematic rheological behaviour of Xanthan gum-Shear dependent reversible flowing properties.

62 Section I Introduction: Polymers & Excipients
2.9.5. PHARMACEUTICAL APPLICATIONS

Xanthan gum is a hydrophilic polymer, which until recently had been limited for use in thickening, suspending, and emulsifying water-based systems. It appears to be gaining appreciation for the fabrication of matrices with uniform drug release characteristics (Tobyn et al., 1996; Sujja-areevath et al., 1998). Because drug release from xanthan gum matrices is preceded by polymer hydration, processing variables that might affect its hydration would also affect its performance as a controlled release dosage form (Billai and Yueni, 2000). It is an excellent stabilizer for pharmaceutical formulations. It uniformly suspends water-insoluble ingredients, e.g. barium sulphate in X-ray contrast media and perfectly stabilizes all kinds of pharmaceutical emulsions. In lozenges, xanthan gum prolongs the contact time of the active ingredient, in tablets xanthan gum can be used to create a retarded drug release effect. Xanthan gum swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug must diffuse. This property makes xanthan gum a useful ingredient for controlled and sustained release applications. Their compatibility with a wide variety of ingredients makes them particularly effective in these applications:

2.10. HPMC / HYPROMELLOSE

2.10.1. INTRODUCTION

Synonyms: Hydroxypropyl methylcellulose, HPMC, Methocel, Methylcellulose propylene glycol ether, Methyl hydroxypropylcellulose, Metolose, Tylopur.
Chemical Name: Cellulose hydroxypropyl methyl ether
CAS Registry Number: 9004-65-3
Empirical Formula and Molecular Weight: Hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Molecular weight is approximately 10000–150000.

Hydroxypropylmethylcellulose (HPMC) is used frequently as a rate-controlling polymer in matrix tablets. HPMC offers the advantages of being non-toxic and relatively inexpensive; it can be compressed directly into matrices and is...
available in different chemical substitution and hydration rates and viscosity grades (Mitchell et al., 1993; Perez-Marcos et al., 1994; Rekhi et al.; 1999). Methocel cellulose ethers are water-soluble polymers derived from cellulose, the most abundant polymer in nature. Methocel products are used as thickeners, binders and film formers. They also function as suspension aids, surfactants, lubricants and emulsifiers. In addition, solutions of Methocel thermally gel, a unique property that plays a key role in a variety of applications. HPMC is a very versatile material for the formulation of soluble matrix tablets. HPMC is a widely accepted pharmaceutical excipient and is included in all major compendia. Being available in a wide range of molecular weights, effective control of gel viscosity is easily provided.

2.10.2. NOMENCLATURE FOR METHOCEL PRODUCTS

Methocel is a trademark of The Dow chemical company for a line of cellulose ether products. An initial letter identifies the type of cellulose ether, its "chemistry". "A" identifies methylcellulose (MC) products. "E", "F" and "K" identify different hydroxypropyl methylcellulose (HPMC) products. Methocel E and Methocel K are the most widely used for controlled-release drug formulations. The number that follows the chemistry designation identifies the viscosity in millipascal-seconds (mPa s) of that product measured at 2% concentration in water at 20°C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the

![Figure 2.17. Structure and substitution levels in Methocel products.](image)
methoxy group (-OCH₃). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (-OCH₂CH(OH)CH₃), calculated on a dried basis.

2.10.3. POLYMER STRUCTURE AND MANUFACTURING

Methocel have the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units (Figure 2.17). During the manufacture of cellulose ethers, cellulose fibers are treated with caustic solution, which in turn is treated with methyl chloride and/or propylene oxide. The fibrous reaction product is purified and ground to a fine powder. According to the major chemical differences in their percent of methoxyl and hydroxypropoxyl substitution and degree of polymerization (measured as 2% solution viscosity), four Methocel products have been defined. Methylcellulose is made using only methyl chloride. These are Methocel A cellulose ethers (methylcellulose, MC, USP). For hydroxypropyl methylcellulose (HPMC) products, propylene oxide is used in addition to methyl chloride to obtain hydroxypropyl substitution on the anhydroglucose units (Figure 2.17). HPMC products include Methocel E (HPMC 2910, USP), Methocel F (HPMC 2906, USP), and Methocel K (HPMC 2208, USP) cellulose ethers. The hydroxypropyl substituent group, -OCH₂CH(OH)CH₃, contains a secondary hydroxyl on the number two carbon and may also be considered to form a propylene glycol ether of cellulose. The ratio of hydroxypropyl and methyl substitution influences HPMC properties such as organic solubility and the thermal gelation temperature of aqueous solutions.

2.10.4. POLYMER PROPERTIES

2.10.4.1. Molecular Weight and Viscosity

HPMC, being a semi-synthetic material derived from cellulose, is a linear polymer comprised of etherified anhydroglucose rings. For products typically used in controlled release applications, the degree of polymerization (DP) is adjusted to a range between 100 and 1500. The difference in molecular weight of various Methocel products is reflected in the viscosity of an aqueous solution of a standard concentration. Viscosity of polymer solutions is the result of hydration of polymer chains, primarily through H-bonding of the oxygen atoms in the numerous ether linkages, causing them to extend and form relatively open random coils. A given hydrated random coil is further H-bonded to additional water molecules, entrapping water molecules within, and may be entangled with
other random coils. All of these factors contribute to larger effective size and increased frictional resistance to flow.

There are slight differences in the hydration rates of the different polymer substitutions, in practice there is little effect seen on the release rate during the first 10 minutes. Table 2.3 gives idea about the comparative hydration rates of different Methocel products based on substitution type.

Table 2.3. Rates of hydration of Methocel grades by substitution type.

<table>
<thead>
<tr>
<th>Product</th>
<th>% Methoxyl</th>
<th>% Hydroxy-propoxyl</th>
<th>Type</th>
<th>Relative rate of hydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methocel K Premium</td>
<td>19-24</td>
<td>7-12</td>
<td>HPMC</td>
<td>Fastest</td>
</tr>
<tr>
<td>Methocel E Premium</td>
<td>28-30</td>
<td>7-12</td>
<td>HPMC</td>
<td>Next fastest</td>
</tr>
<tr>
<td>Methocel F Premium</td>
<td>27-30</td>
<td>4-7.5</td>
<td>HPMC</td>
<td>Slower</td>
</tr>
<tr>
<td>Methocel A Premium</td>
<td>27.5-31.5</td>
<td>0</td>
<td>MC</td>
<td>Slowest</td>
</tr>
</tbody>
</table>

One possible explanation for differences in performance of the various HPMC substitution types may be the mobility of water within the gel layer, which is lower within the Methocel K4M Premium containing matrix, leading to greater diffusional resistance to water. This directly reduces the diffusion of drug out of the matrix and indirectly affects the state of hydration within the gel, thus affecting that component of drug release due to erosion of the dosage form.

2.10.4.2. Hydration and Erosion Rates

The kinetics of gel growth is also very similar for all substitution types of HPMC; the observed apparent differences in swelling behavior are attributed to differential expansion of the glassy core (Rajabi-Siahboomi et al., 1994). The amount of water bound to HPMC is related to both the substitution and the polymer molecular weight. Within the gel layer, there obviously exists a moisture gradient from the outside surface in contact with liquid to the inner dry core. Water appears to exist in at least three distinct states within a hydrated gel of pure polymer (Mccrystal et al., 1997). Upon complete polymer hydration at the outer surface, chain disentanglement begins to occur, i.e., erosion of the matrix. The rate of erosion is related to molecular weight over a wide range by an inverse power law. In addition, erosion rate is affected by the composition and ionic strength of electrolytes in the liquid medium and, by the composition and level of drugs and other additives within the matrix.

To achieve controlled release through the use of a water-soluble polymer such as HPMC, the polymer must quickly hydrate on the outer tablet skin to form a gelatinous layer. A rapid formation of a gelatinous layer is critical to prevent
wetting of the interior and disintegration of the tablet core. Once the original protective gel layer is formed, it controls the penetration of additional water into the tablet. As the outer gel layer fully hydrates and dissolves, a new inner layer must replace it and be cohesive and continuous enough to retard the influx of water and control drug diffusion. Although gel strength is controlled by polymer viscosity and concentration, polymer chemistry also plays a significant role. Evidence suggests that the chemistry of HPMC encourages a strong, tight gel formation compared to other cellulosics. As a result, drug-release rates have been sustained longer with HPMC than with equivalent levels of methylcellulose (MC), hydroxyethylcellulose (HEC), or carboxymethylcellulose (CMC). For these reasons, HPMC is very often the polymer of choice over other cellulosics.

2.10.5. FACTORS AFFECTING THE DRUG RELEASE

The mechanisms by which dissolution profile is controlled in matrix tablets are dependent on many variables, to a greater or lesser extent. The key factors that may affect the dissolution profile are:

2.10.5.1. Hydrophillic 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, present throughout the tablet, hydrates on the outer tablet surface to form a gel layer (Figure 2.18). 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 (if insoluble).

2.10.5.2. Selection of Methocel Polymers Type

The flexibility in using Methocel products in controlled release matrix tablets stems from the different types of polymer grades. The two polymer grades of Methocel most commonly used in controlled-release applications are K (HPMC 2208, USP) and E (HPMC 2910, USP). A fast rate of hydration followed by quick gelation and polymer/polymer coalescing is necessary for a rate-controlling
Initial Wetting
Tablet surface wets and METHOCEL Premium polymer starts to partially hydrate, forming a gel layer. Initial burst of soluble drug from the external tablet layer is released.

Expansion of Gel Layer
Water permeates into the tablet increasing the thickness of the gel layer, and soluble drug diffuses out of gel layer.

Tablet Erosion
Outer layer becomes fully hydrated and is released into the gastric fluids. Water continues to permeate toward the tablet core.

Soluble Drug is released by diffusion from the gel layer and by exposure through tablet erosion.

Insoluble Drug is released by exposure through tablet erosion.

Figure 2.18. Drug release from matrix tablets.

polymer to form a protective gelatinous layer around the matrix. This prevents the tablet from immediately disintegrating, resulting in premature drug release. As mentioned above, the hydration rates of the various grades of Methocel products differ based on varying proportions of the two chemical substituents, hydroxypropoxy and methoxyl substitution, attached to the cellulose backbone of HPMC. The hydroxypropoxy substitution is relatively hydrophilic in nature and greatly contributes to the rate of hydration of Methocel. The methoxyl substitution is relatively hydrophobic in nature and does not contribute significantly to the rate of hydration of Methocel. And therefore, Methocel K products usually establish the gel barrier the quickest, while Methocel F products have the slowest rate of hydration.

Increasing viscosity yields slower drug release as a stronger more viscous gel layer is formed, providing a greater barrier to diffusion and slower attrition of the tablet. The fine tuning of modified release systems may be achieved by blending different viscosity grades of Methocel where the desired dissolution rate is not obtained with a single viscosity grade of Methocel. The controlled release profiles
obtained by direct compression or conventional granulation are very similar and provide a good correlation. The uniform distribution of Methocel throughout the matrix is the most important manufacturing factor.

2.10.5.3. Polymer Level

There must be sufficient polymer content in a matrix system to form a uniform barrier that protects the drug from immediately releasing into the dissolution medium. If the polymer level is too low, a complete gel layer may not form (Cheong et al., 1992). Because hydrophilic matrix tablets containing HPMC absorb water and swell, the polymer level in the outermost hydrated layers decreases with time. The outermost layer of the matrix eventually becomes diluted to the point where individual chains detach from the matrix and diffuse into the bulk solution. The polymer chains break away from the matrix when the surface concentration passes a critical polymer concentration of macromolecular disentanglement (Harland et al., 1988; Bonderoni et al., 1992; Ju et al., 1995). The polymer concentration at the matrix surface is defined as the polymer disentanglement concentration.

It is important to note that polymer level in a formulation may not always affect drug release in the same way because of potential drug/excipient/polymer interactions, but most studies indicate that higher polymer levels result in slower release rates. This effect of slower release for higher polymer levels is due to the longer period of time required to reach the disentanglement concentration at the tablet surface, which in turn equates to greater resistance to surface erosion. There is a threshold level of retardation of drug-release rate that is achievable where a further increase in polymer loading does not result in further decrease in drug-release rate. This is because drug release does not result solely from polymer erosion, but also from drug diffusion through the hydrated polymer layers. An increase in polymer level also tends to decrease the sensitivity of the formulation to minor variations in the raw materials or the manufacturing process.

2.10.5.4. Effect of Particle Size

The particle size of HPMC polymer can greatly influence polymer performance in the hydrophilic matrix. Fractions of HPMC polymers with smaller particle size have more surface area relative to equivalent weights of fractions with larger particle size. The greater surface area provides for better polymer-water contact, thus increasing the overall rate at which complete polymer hydration and gelation occurs. This leads to the more effective formation of the protective gel barrier so critical to the performance of hydrophilic matrix tablets.
Tablets made with very coarse polymer particles (>177 mm) disintegrate and result in immediate drug release. A sufficient amount of polymer surface area is not exposed to the infusing medium to allow a protective gel layer to form. However, matrices containing smaller polymer particles, and therefore having a greater total surface area, hydrate fast enough and form a protective gel that slow down both water penetration into the tablet and drug release out of the matrix. In case of more soluble drug, the formulation is more susceptible to polymer particle size. There is more spread between the release profiles for the different sieve cuts for release of active drug. This suggests that more soluble drugs require a faster rate of gel formation to sufficiently control drug release (Mitchell et al., 1993).

2.10.5.5. Effects of Binders and Lubricants on Direct Compression

The preparation of hydrophilic matrix tablets using Methocel cellulose ethers is most easily accomplished by directly compressing a dry mixture of drug, HPMC, and other excipients. HPMC has good compaction characteristics; however, some formulations may require a binder to increase tablet strength. One useful excipient for direct compression is microcrystalline cellulose (MCC), now available in a wide variety of grades, differing in parameters such as mean particle size, particle size distribution, density, and moisture. Newer materials consist of MCC co-processed with other excipients. As a result, there exists a range of flow properties and compressibilities for MCC products that results in differing tablet strengths and manufacturing constraints, which potentially could affect drug dissolution. MCC may function in some formulations as a binder and/or disintegrant, depending on the level. MCC exhibits disintegrating properties at levels as low as 10% (Peck et al., 1989). Generally, neither MCC particle size nor the MCC density had a significant effect on drug release.

Lubricants are added to reduce sticking to the punch faces and to allow easy ejection of the tablet during tablet formation. Magnesium stearate, a boundary-type lubricant, is the lubricant of choice because its plate-like crystalline structure readily deforms in shear during the mixing and compaction process, thereby coating the powder and tooling surfaces. The obvious concern here is that over lubrication could lead to coating of this hydrophobic material on the surfaces of the tablet and thereby retard release. This would be not only a function of lubricant level, but also a function of blend time with the lubricant since increased mixing can lead to increased shearing of the magnesium stearate particles. Sheskey et al. found that magnesium stearate levels from 0.2 to 2.0% and blend times of 2 to 30 minutes had only a slight impact on drug-release rates (Sheskey et al., 1995). Other formulation variables such as filler type and drug solubility
had a much greater impact on drug release. Tablets containing lubricant plus unmilled dibasic calcium phosphate anhydrous are harder than those prepared using spray-dried lactose, regardless of drug type or mixing conditions. These results may be because dicalcium phosphate has a "brittle fracture" mechanical property, which allows for the formation of new clean surfaces available for bonding during the tablet compression state. As expected, tablet ejection forces were influenced to the greatest extent by the level of lubricant in the formulation.

2.10.6. ADVANTAGES OF METHOCEL

2.10.6.1. Simple Formulations

The recommended guidelines to formulate a robust modified release matrix is to use at least 20% and preferably 30% Methocel, keeping the formula and process as simple as possible. Many products may be prepared by direct compression, however, if required simple granulation with water or common organic solvents may be used. The actual method of production (direct compression or wet granulation) frequently has little or no impact on the final release rate for a given formula.

2.10.6.2. Manufacture of matrix tablets

Primary control of the release should be achieved by the Methocel content, varying the ratio of drug to polymer. The formulation should then be investigated to see if the release rate is affected by particle size of the drug and other components. The components and dissolution test method, should then be standardised to ensure reproducibility of the formulation and release profile. Tablet shape and surface characteristics, plus the chemical nature of the Drug/Excipient may affect formulation of the pseudo gel and hence the dissolution rate.

HPMC polymers are very versatile release agents. They are nonionic, so they minimize interaction problems when used in acidic, basic, or other electrolytic systems. HPMC polymers work well with soluble and insoluble drugs and at high and low dosage levels. In addition, they are tolerant of many variables in other ingredients and production methods. And HPMC products typically provide outstanding controlled release performance by themselves, eliminating the potential performance variations that may arise in multi-polymer systems.
2.11. Ethylcellulose

2.11.1. INTRODUCTION

Nonproprietary Names BP: Ethylcellulose, PhEur: Ethylcellulosum, USPNF: Ethylcellulose
Synonyms: Aquacoat ECD, Aqualon, Ethocel, Surelease.
Chemical Name: Cellulose ethyl ether
CAS Registry Number: 9004-57-3
Empirical Formula and Molecular Weight: Ethylcellulose with complete ethoxyl substitution (DS=3) is \(C_{12}H_{23}O_9(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5\) where \(n\) can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of \(\beta\)-anhydroglucose units joined together by acetal linkages.

![Figure 2.19. Structural formula of ethylcellulose.](image)

Ethylcellulose (shown in Figure 2.19) is a tasteless, free-flowing, white to light tan-colored powder widely used in oral and topical pharmaceutical formulations as a coating agent, flavoring fixative, tablet binder, tablet filler, viscosity-increasing agent.

2.11.2. MANUFACTURING

Ethylcellulose is prepared by treating purified cellulose (sourced from chemical-grade cotton linters and wood pulp) with an alkaline solution, followed by ethylation of the alkali cellulose with chloroethane as shown below, where \(R\) represents the cellulose radical: \(RONa + C_2H_5Cl \rightarrow ROC_2H_5 + NaCl\). The manner in which the ethyl group is added to cellulose can be described by the degree of substitution (DS). The DS designates the average number of hydroxyl positions on the anhydroglucose unit that have been reacted with ethyl chloride. Since each anhydroglucose unit of the cellulose molecule has three hydroxyl groups, the maximum value for DS is three.
2.11.3. PHYSICOCHEMICAL PROPERTIES

- Solubility: It is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

- Viscosity: The viscosity of ethylcellulose is measured typically at 25°C using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene : 20% ethanol (w/w). Grades of ethylcellulose with various viscosities are commercially available. They may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging from 7 to 100 mPa s (7–100 cP). Specific ethylcellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and durable films.

2.11.4. PHARMACEUTICAL APPLICATIONS

The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules (Bodmeier and Paeratakul, 1994; Narisawa et al., 1994; Dressman et al., 1995; Sadeghi et al., 2001). Ethylcellulose coatings are used to modify the release of a drug (Goracinova et al., 1996; Sadeghi et al., 2001), to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former (Klinger et al., 1990; Katikaneni et al., 1995; Pollock and Sheskey, 1996; Kulvanich et al., 2002). Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility by the addition of hypromellose or a plasticizer (Saettone et al., 1995; Beck and Tomka, 1996). An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents.

Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those situations,
instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression. High-viscosity grades of ethylcellulose are used in drug microencapsulation (Lavasanifar et al., 1997). Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area.

In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wet-granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution. Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances (Friedman et al., 1988). In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used (Ruiz-Martínez et al., 2001). Ethylcellulose has been studied as a stabilizer for emulsions (Melzer et al., 2003). Ethylcellulose is additionally used in cosmetics and food products. Ethylcellulose has also been used as a backing membrane on mucoadhesive patches intended for buccal administration. The membrane had high tensile strength, and provided excellent unidirectional drug flow (Sharma and Hamsa, 2001). Studies have also suggested ethylcellulose for use in floating microparticles based on low-density foam powder, for gastroretentive drug delivery systems (Streubel et al., 2002).

2.12. Polymethacrylates

2.12.1. INTRODUCTION

Nonproprietary Names:
Acidum methacrylicum et methylis methacrylas polymerisatum 1:2
Copolymerum methacrylatis butylati basicum
Polyacrylatis dispersion 30 per centum
USP-NF: Ammonio methacrylate copolymer, Methacrylic acid copolymer, Methacrylic acid copolymer dispersion


Chemical Name and CAS Registry Number: Different Polymethacrylates has different chemical names and CAS registry numbers. Some of these are given in following Table 2.4.
Table 2.4. Chemical name and CAS Registry Number of polymethacrylates.

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Trade name</th>
<th>Molecular Mass</th>
<th>CAS number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) 1:2:1</td>
<td>Eudragit E 100</td>
<td>150 000</td>
<td>24938-16-7</td>
</tr>
<tr>
<td></td>
<td>Eudragit E 12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eudragit E PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(ethyl acrylate, methyl methacrylate) 2:1</td>
<td>Eudragit NE 30 D</td>
<td>800 000</td>
<td>9010-88-2</td>
</tr>
<tr>
<td></td>
<td>Eudragit NE 40 D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methacrylic acid, methyl methacrylate) 1:1</td>
<td>Eudragit L 100</td>
<td>135 000</td>
<td>25806-15-1</td>
</tr>
<tr>
<td></td>
<td>Eudragit L 12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eudragit L 12.5 P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methacrylic acid, ethyl acrylate) 1:1</td>
<td>Acryl-EZE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acryl-EZE MP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eudragit L 30 D-55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eudragit L 100-55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eastacryl 30 D</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kollicoat MAE 30 D</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kollicoat MAE 30 DP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methacrylic acid, methyl methacrylate) 1:2</td>
<td>Eudragit S 100</td>
<td>≥100 000</td>
<td>25086-15-1</td>
</tr>
<tr>
<td></td>
<td>Eudragit S 12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eudragit S 12.5 P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7:3:1</td>
<td>Eudragit FS 30D</td>
<td>≥100 000</td>
<td>26936-24-3</td>
</tr>
<tr>
<td>Poly(ethyl acrylate, methyl-methacrylate, trimethylammonioethyl-methacrylate-chloride) 1:2:0.2</td>
<td>Eudragit RL 100</td>
<td>≥100 000</td>
<td>33434-24-1</td>
</tr>
<tr>
<td></td>
<td>Eudragit RL PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eudragit RL 30 D</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eudragit RL 12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eudragit RD 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1</td>
<td>Eudragit RS 100</td>
<td>≥100 000</td>
<td>33434-24-1</td>
</tr>
<tr>
<td></td>
<td>Eudragit RS PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eudragit RS 30 D</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eudragit RS 12.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acrylate polymers and their derivatives, collectively known as Eudragit polymers, were the first synthetic polymers used in pharmaceutical coatings (Zelko et al., 2002). Eudragit® is the trade mark of acrylic resins carrying carboxyl groups, free or in the form of esters, or containing basic moieties, widely used for designing new pharmaceutical dosage forms, according to the possibility to form a film coating or to control the delivery of the active agent as a function of pH (Sancin et al., 1999).

2.12.2. STRUCTURAL FORMULA

Figure 2.20 is the basic structure for all types of polymethacrylates. As shown below, depending on the function groups attached, different types of polymethacrylates with different physicochemical properties can be produced for variable applications.
Figure 2.20. Structural formula of polymethacrylates.

For Eudragit E:
\[ R_1, R_3 = \text{CH}_3 \\
R_2 = \text{CH}_2\text{CH}_2\text{N(CH}_3\text{)}_2 \\
R_4 = \text{CH}_3, \text{C}_4\text{H}_9 \]

For Eudragit L and Eudragit S:
\[ R_1, R_3 = \text{CH}_3 \\
R_2 = \text{H} \\
R_4 = \text{CH}_3 \]

For Eudragit FS:
\[ R_1 = \text{H} \\
R_2 = \text{H}, \text{CH}_3 \\
R_3 = \text{CH}_3 \\
R_4 = \text{CH}_3 \]

For Eudragit RL and Eudragit RS:
\[ R_1 = \text{H}, \text{CH}_3 \\
R_2 = \text{CH}_3, \text{C}_2\text{H}_5 \\
R_3 = \text{CH}_3 \\
R_4 = \text{CH}_2\text{CH}_2\text{N(CH}_3\text{)}_3\text{Cl}^- \]

For Eudragit NE 30 D and NE 40 D:
\[ R_1, R_3 = \text{H}, \text{CH}_3 \\
R_2, R_4 = \text{CH}_3, \text{C}_2\text{H}_5 \]

For Acryl-EZE and Acryl-EZE MP, Eudragit L 30 D-55 and Eudragit L 100-55, Eastacryl 30D, Kollicoat MAE 30 D and Kollicoat MAE 30 DP:
\[ R_1, R_3 = \text{H}, \text{CH}_3 \\
R_2 = \text{H} \\
R_4 = \text{CH}_3, \text{C}_2\text{H}_5 \]

Some of acrylate polymers can be considered as polycations (Eudragit types E, RL, RS, NE) and the others as polyanions (Eudragit types L, S, and L 100-55). The first ones have positively charged groups: dimethylamino groups in Eudragit type E, or quaternary amino groups in Eudragit types RL, RS and NE. The second ones have negatively charged groups: carboxyl groups in Eudragit types L and S both (Moustafine et al., 2005).

Eudragit RS and RL are neutral biocompatible copolymers synthesized from acrylic and methacrylic acid esters. The structures of Eudragit RS and RL differ only in the extent of the quaternary ammonium substitutions, with Eudragit RS
containing much less such substitution than Eudragit RL. The most interesting among acrylic polymers were high permeable Eudragit RL and low permeable Eudragit RS.

2.12.3. MECHANISM OF DRUG RELEASE FROM EUDRAGIT

Eudragit RL and RS, both are insoluble in water and digestive juices, but both swell and are permeable, which means that the drugs can be released by diffusion. Therefore, the permeability of the drug through Eudragit RS and/or RL is independent of the pH of the digestive tract. The degree of permeability depends on the relative proportion of quaternary ammonium groups in Eudragit (Wu et al., 2003).

Formulations with Eudragit RS give slower rates than those prepared with Eudragit RL (Oth and Moes, 1989). It could be explained considering the chemical structure of Eudragit. The Eudragit RL and RS are synthesized from acrylic and methacrylic esters with high and low content of quaternary ammonium groups (1/20 and 1/10) and result in microspheres with different water permeability. Increasing ratio of Eudragit RS increased MDT, may be due to the less hydrophilic nature and thereby decreased water permeability of Eudragit RS compared to Eudragit RL, which can decrease the permeation of dissolution medium through the polymer matrix.

Eudragit S 100 is known to be insoluble in pure water and at acidic pH but becomes soluble in neutral to weakly alkaline media, starting from pH 7. Therefore, its association to a drug provides a resistance to gastric juice and prevents the release of the drug until pH rises above 7, that is in the physiological medium of the intestine.

2.12.4. PHARMACEUTICAL APPLICATIONS

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents (Lehmann, 1984; Cameron and McGinity, 1987; Beckert et al., 1996; Jovanovic et al., 1997; Gupta et al., 2001b; Gupta et al., 2001a). Depending on the type of polymer used, films of different solubility characteristics can be produced.

Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10–50%. Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel
formulations for rectal administration (Umejima et al., 1993). Table 2.5 summarizes the properties and applications of majority of the commercially available polymethacrylates.

**Table 2.5. Summary of properties and uses of commercially available polymethacrylates.**

<table>
<thead>
<tr>
<th>Type</th>
<th>Supply form</th>
<th>Solubility/permeability</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit E 12.5</td>
<td>Organic solution</td>
<td>Soluble in gastric fluid to pH 5</td>
<td>Film coating</td>
</tr>
<tr>
<td>Eudragit E 100</td>
<td>Granules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit E PO</td>
<td>Powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit L 12.5 P</td>
<td>Organic solution</td>
<td>Soluble in intestinal fluid from pH 6</td>
<td>Enteric coating</td>
</tr>
<tr>
<td>Eudragit L 12.5</td>
<td>Powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit L 100</td>
<td>Powder</td>
<td>Soluble in intestinal fluid from pH 5.5</td>
<td>Enteric coating</td>
</tr>
<tr>
<td>Eudragit L 100-55</td>
<td>Powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit L 30 D-55</td>
<td>Aqueous dispersion</td>
<td>Soluble in intestinal fluid from pH 5.5</td>
<td>Enteric coating</td>
</tr>
<tr>
<td>Eudragit S 12.5P</td>
<td>Organic solution</td>
<td>Soluble in intestinal fluid from pH 7</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit S 12.5</td>
<td>Powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit Fluor</td>
<td>Aqueous dispersion</td>
<td>Soluble in intestinal fluid from pH 7</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eudragit Fluor</td>
<td>Powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit RL 100</td>
<td>Granules</td>
<td>High permeability</td>
<td>Sustained release</td>
</tr>
<tr>
<td>Eudragit RL PO</td>
<td>Powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit RL 30 D</td>
<td>Aqueous dispersion</td>
<td>High permeability</td>
<td>Rapid disintegrating film</td>
</tr>
<tr>
<td>Eudragit RD 100</td>
<td>Powder</td>
<td>High permeability</td>
<td></td>
</tr>
<tr>
<td>Eudragit RS 12.5</td>
<td>Organic solution</td>
<td>Low permeability</td>
<td>Sustained release</td>
</tr>
<tr>
<td>Eudragit RS 100</td>
<td>Granules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit RS PO</td>
<td>Powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit RS 30 D</td>
<td>Aqueous dispersion</td>
<td>Swellable, permeable</td>
<td>Sustained release, tablet matrix</td>
</tr>
<tr>
<td>Eudragit NE 30 D</td>
<td>Aqueous dispersion</td>
<td>Soluble in intestinal fluid from pH 5.5</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Eastacryl 30 D</td>
<td>Aqueous dispersion</td>
<td>Soluble in intestinal fluid from pH 5.5</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Kollicoat 30 D</td>
<td>Aqueous dispersion</td>
<td>Soluble in intestinal fluid from pH 5.5</td>
<td>Enteric coatings</td>
</tr>
<tr>
<td>Kollicoat 30 DP</td>
<td>Powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acryl-EZE MP</td>
<td>Powder</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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2.13. References


B F GOODRICH BULLETIN, 2001. Polymers for Personal Care - Toxicity of the Carbopol Resins as a Class, Polymers for Personal Care - Toxicity of the Carbopol Resins as a Class, B F Goodrich Company, Cleveland, OH, TDS-93.


SKW BOISYSTEMS, Satiaxane-Xanthan gum for food applications, Satiaxane-Xanthan gum for food applications, SKW Boisystems -Business Unit Texturant Systems, France.


3. LITERATURE SURVEY

The influence of water-soluble and insoluble excipients on dynamics of hydration, front movement, erosion, and drug release from hydrophilic matrix tablets containing water-soluble drug was studied by Jamzad and his co-workers (Jamzad et al., 2005). They found significant release differences between tablet batches and this was consistent with changes in swelling rate, gel thickness, and swelling front movement within the tablets. They have concluded that unlike in conventional dosage forms inclusion of excipients in hydrophilic controlled-release tablets containing water-soluble drugs should be carefully analyzed as their various physico-chemical properties may have significant implications on swelling dynamics, front movement, drug release kinetics, and consequently in vivo performance.

Mulhbacher et al. have investigated the swelling characteristics, which allow a better understanding of the mechanisms involved in the control of the drug release from the cross-linked high amylase starch based polymeric matrices (Mulhbacher et al., 2004). They observed that the drug loading did not change the equilibrium swelling ratio but affected the initial swelling velocity, seemingly due to the competition between drug and polymer for water uptake, a phenomenon probably influenced by the loading and the drug solubility. It was also shown that the increase of ionic strength would slightly increase the drug release time probably by decreasing the amount of free water still available to solubilize the drug present into the matrix.

Zuleger and his coworkers have explained swelling investigations to clarify the drug release mechanism by diffusion, erosion and polymer particle erosion, in order to reveal differences in the swelling behavior responsible for the diverging drug release mechanisms (Zuleger et al., 2002). For that they determined the expansion factor, texture analysis, visual swelling observation of dye containing tablets sandwiched between Plexiglas discs and photomicroscopy. Altogether they allowed the investigation of dimensional changes, swelling velocity, thickness, appearance and strength of the gel layer and front movements. A combination of the different techniques proved to be helpful to provide information necessary for a broad understanding of the complex phenomenon of swelling. Intensive swelling was observed for matrices with diffusion controlled release (e.g. MHPC 100000), while
erosion controlled systems (e.g. Pharmacoat 606) were characterized by limited swelling and fast polymer erosion. They impeded the swelling, weakened the gel layer and caused attrition of polymer material, thus only a thin gel layer was formed.

Siepmann et.al have calculated the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles using mathematical model (Siepmann et al., 2000). They showed that a broad spectrum of drug release patterns can be achieved by varying the size and shape of the tablet. The effect of the initial matrix radius on release was found to be more pronounced than the effect of the initial thickness. The practical benefit of the proposed method is to predict the required size and shape of new controlled drug delivery systems to achieve desired release profiles, thus significantly facilitating the development of new pharmaceutical products.

The influence of chitosan and sodium alginate and formulation variables on the formation and drug release from pellets prepared by extrusion/spheronisation was studied by Chatchawalsaisin, J. et al. (Chatchawalsaisin et al., 2004). They used 0–16% of chitosan, −16% of sodium alginate, 30–70% of microcrystalline cellulose and the pH 2.2–5.4 of binder liquids for pellet preparation and the maximum mean dissolution time obtained was only 0.75 h. The levels of drug, chitosan, and sodium alginate significantly influenced the in vitro dissolution of paracetamol pellets. They concluded that there was no implication of the interaction between oppositely charged polymers, in terms of retarding the drug release from pellets.

Hodsdon A. C. et al have studied the the influence of pH on the sustained-release performance and internal gel structure of sodium alginate matrices (Hodsdon et al., 1995). They showed that the differences observed in release profiles of the drug at acidic and neutral pH might be more a result of a change in the quality and integrity of the gel barrier formed under acid conditions. The faster drug release was observed at pH 1.2 is a reflection of the inferior barrier properties of this composite layer, relative to those of the continuous gel layer formed at pH 7.5.

Miyazaki, S. et al prepared directly compressed oral mucoadhesive alginate-chitosan tablets and found that increasing the chitosan content in the tablets and/or the viscosity grade of the alginate decreases the in vitro release rate.(Miyazaki et al., 1995). Prepared formulations released the drug within 3-6 h. On contact of the tablets with water, the sodium alginate rapidly hydrates and swells to form a visible
gel layer over the tablet surface. The rate of penetration of the medium into the tablets, and hence the rate of release of dissolved drug, are a function of the amount of the hydrophilic sodium alginate dispersed throughout the matrix.

Sustained release of water-soluble drug from directly compressed alginate tablets were studied by Holte, Ø et al (Holte et al., 2003) with different grades of alginate. Sustained drug release up to 16 h was achieved using sodium alginate in combination with dibasic calcium phosphate. Among the grades of alginate investigated, no significant difference in the resulting drug release profiles from the tablets was found, indicating that equilibrium gel properties of the alginate do not affect drug release rates from compressed powder mixtures including alginate.

Tablet formulations containing different ratios of sodium alginate and calcium gluconate were prepared by direct compression method (Güngör et al., 2003) and found suitable for the design of sustained release preparation of mefenamic acid. The researchers also found that although in absence of bivalent calcium ions formulation can show a significant decrease in the extent of drug release due to hydrogel matrix formation as a result of the gelation of sodium alginate upon exposure to aqueous media.

Chlorhexidine buccal tablets prepared using drug-loaded chitosan microspheres were evaluated by Giunchedia et al (Giunchedia et al., 2002). Their release behavior is quite different probably owing to the presence of the anionic polymer (sodium alginate) mixed with the cationic polymer (chitosan) and a consequent ionic interaction between them.

Hejazi and Amiji have prepared gastro-retentive drug delivery systems using chitosan as a carrier (Hejazi and Amiji, 2003). Chitosan microspheres were prepared and evaluated by Sinha et al (Sinha et al., 2004). Sustained release characteristics and pharmacokinetic parameters of ketoprofen suppositories using chitosan have also been reported (Tarimci and Ermi, 1997).

Hasana et. al. showed controlled release of Metoclopramide HCl when embedded in a hydrophilic matrix of chitosan and sodium alginate (Hasana et al., 2003). The in vitro release data was found to be first order according to the Higuchi mechanism. An in vivo evaluation of the metoclopramide controlled release matrix on humans effectively delayed absorption, reduced the peak plasma concentrations and

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maintained higher concentrations during the elimination phase when compared to the immediate release formula.

Comparative studies on polyelectrolyte complexes and mixtures of chitosan–alginate and chitosan–carrageenan as prolonged diltiazem clorhydrate release systems has been carried out by Tapiaa et. al. The swelling behavior of the chitosan–carrageenan and chitosan–alginate systems was analyzed by using the Hopfenberg model which permits to separate the diffusional contribution, $k_f$, from the relaxational contribution, $k_r$, involved in solvent penetration/sorption in glassy polymers. The chitosan–alginate system was found better than the chitosan–carrageenan system as prolonged drug release matrix because the drug release was controlled at low percentage of the polymers in the formulation, the mean dissolution time was high, and different dissolution profiles could be obtained by changing the mode of inclusion of the polymers. Good agreement between $t_d$ and $k_f/k_r$ values for the system chitosan–alginate was found, which means that the swelling behavior of the polymers controlled the drug release from the matrix. In the case of the system chitosan–carrageenan, the high capacity of carrageenan promoted the entry of water into the tablet and therefore the main mechanism of drug release would be the disintegration instead of the swelling of the matrix (Tapiaa et al., 2004).

With a view to the application in oral drug delivery formulations, the possibility to form interpolyelectrolyte complexes of Eudragit E 100 with sodium alginate was investigated by Moustafine et. al. (Moustafine et al., 2005). It was concluded from the study that the interaction or binding ratio of a unit molecule of alginate with eudragit was largely affected by the pH value of the media. Based on the results of elementary analysis and FT-IR, the interaction ratio of each component in the solid complexes was very close to that observed in turbidity and apparent viscosity measurements thus proving that the synthesized products actually can be considered as interpolyelectrolyte complexes.

The influence of chitosan and sodium alginate and formulation variables on the formation and drug release from pellets prepared by extrusion/spheronisation was undertaken by Chatchawalsaisin et. al. Statistical analysis of the results indicated that the formulation variables of the type and level of the polymer, the proportion of the model drug, and the proportion of the microcrystalline cellulose influenced the quantity of liquid binder required to produce a good formulation, the steady-state extrusion force, the pellet perimeter, the apparent pellet density and the porosity of
the pellets. The proportion of the drug, chitosan and sodium alginate content of the formulation significantly influenced the in vitro dissolution of the model drug and the drug release mechanism differed with the formulation variables. There was no significant advantage to be gained by using a mixture of the two polymers in terms of retarding drug release (Chatchawalsaisin et al., 2004).

Varshosaz, J and Dehghan, Z. have prepared the buccoadhesive controlled-release tablets for delivery of nifedipine by direct compression of carboxymethyl cellulose (CMC) with carbomer (CP), which showed superior bioadhesion properties compared to polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxypropylmethyl cellulose (HPMC) (Varshosaz and Dehghan, 2002). The tablets showed the drug release between 5-12 h. The tablets containing just carbopol were too eroding with a fast release rate of drug while, the tablets containing 15% carboxymethyl cellulose and 35% carbopol, found to be optimum showing sustained drug release with zero-order release kinetic.

Tapia-Albarran and Villafuerte-Robles have studied amoxicillin sustained release matrix tablets containing different proportions of Carbopol 971P NF (Tapia-Albarran and Villafuerte-Robles, 2004). Carbopol 971P NF in a range from 180 to 680 mg showed increasing values of the exponent indicative of the release mechanism (n) and decreasing release constant values (k) as the matrix polymer content increased. The release constant (k) and the exponent (n) were found to be logarithmically related.

In vitro dissolution of metronidazole from sustained release floating tablets was studied by Cedillo-Ramirez et al. with varied proportions of sodium bicarbonate and Pharmatose (Cedillo-Ramirez et al., 2006). Methocel matrices showed greater hydration volumes and greater drug dissolution compared to Carbopol matrices. After adding increasing quantities of Pharmatose to matrices containing sodium bicarbonate, hydration volume decreased while dissolution increased. These results were attributed to water-filled pores that formed following the Pharmatose dissolution and to reduced polymer proportions. Carbopol matrices showed greater susceptibility to the added Pharmatose, becoming more erodible and releasing higher quantities of drug. The greater Carbopol susceptibility to added Pharmatose was attributed to its faster hydration. Methocel matrices hydrate rapidly only at the surface, delaying hydration and Pharmatose dissolution.
Starch/Carbopol spray-dried mixtures as excipients for oral sustained drug delivery was evaluated by Pringels et al. (Pringels et al., 2005). The influence of the Amioca/Carbopol 974P ratio and the pH and ionic strength of the dissolution medium on the drug release was investigated. The matrices composed of the spray-dried mixtures with 10% or 15% Carbopol 974P sustained the drug release over the longest time period. At this Carbopol concentration, shear viscosity measurements indicated the formation of an optimal network between the polymer chains of Amioca starch and Carbopol 974P, forming a rigid gel layer offering resistance to erosion during the dissolution experiments.

In the present study, investigation of the possibility of interaction of verapamil hydrochloride with Carbopol 934P using differential scanning calorimetric analysis and Fourier transform infrared analysis was performed by Elkheshen, S. A. Results revealed that the drug-to-polymer ratio had the most influential effect on both the extent of interaction between the drug and the polymer and the rate of water uptake of the polymer matrix. On the other hand, the pH of the medium had the most significant effect on the rate of drug release. Interaction of the tertiary amine nitrogen of the drug with the anionic carboxyl group on the polymer, forming an insoluble complex, reduced the rate of drug release. This interaction also led to neutralization of the carboxyl group and suppression of the electrostatic repulsion between the anionic groups, which reduced the uncoiling and chain relaxation of the polymer and consequently decreased the swelling of the matrix (Elkheshen, 2001).

Santos et al. have prepared xanthan gum based pellets by extrusion spheronisation using lactose monohydrated, tribasic calcium phosphate and β-cyclodextrin as other excipients (Santos et al., 2004). Drug diffusion and erosion were competing mechanisms of drug release from those tablets. The tablets prepared from the pellets showed drug release up to 24 h.

Ibuprofen mini-matrices using xanthan gum as one of the matrix former has been prepared by hot-melt extrusion technique and evaluated by a group of researchers (Brabander et al., 2003) and its bioavailability was also assessed (Brabander et al., 2004). The formulation with xanthan gum as the hydrophilic excipient was able to maintain the ibuprofen plasma levels during 24 h. The comparative pharmacokinetic evaluation of the developed formulations with the marketed formulation showed 80% bioavailability for the developed formulations.
The synergistic gelation effects of the xanthan gum and galactomannans have been employed to produce sustained release tablet and capsule formulations by Ughini et al (Ughini et al., 2004). Developed formulations gave 30-90% of drug release within 24 h. Analysis of release data indicated a rather zero-ordered drug release with the erosion mechanism playing a dominant role. They concluded that the final drug release can be tailored by adjusting the matrix former polymer level and/or addition of a dissolution agent to speed up the drug release.

Relationship between swelling, erosion and drug release in three hydrophilic natural gum mini-matrix by wet granulation have been studied in detail by Sujja-areevath and his co-workers (Sujja-areevath et al., 1998). They investigated Xanthan, locust bean and karaya gums and found that xanthan gum has the ability to hydrate more rapidly than the other two gums used. With xanthan and karaya gums, Fickian diffusion is dominant during the first half of the dissolution period, while erosion predominates during the latter half facilitating an approach toward zero-order release. However, with locust bean gum erosion is dominant throughout the dissolution period.

Spiclin et al have used xanthan gum for the preparation of Sodium ascorbyl phosphate containing topical microemulsions (Spiclin et al., 2003). For o/w microemulsions a wider range of thickening agents were tested, but only xanthan gum was found appropriate, although microemulsions were not transparent.

Recently starch has been studied as a matrix-forming excipient for sustained oral dosage forms and Leticia Sánchez et al have studied a new technique for the production of cold water-swellable starch using gelatinization and freeze-drying processes (Sánchez et al., 1995). They concluded that this modified starch does not show acceptable flow properties but inclusion of HPMC can improve this problem and successfully used for the sustained release formulation development.

Michailova et al have discussed the influence of hydrogel structure on the processes of water penetration and drug release from mixed hydroxypropylmethyl cellulose/thermally pregelatinized waxy maize starch hydrophilic matrices (Michailova et al., 2001). They reported that the kinetic swelling properties of mixed HPMC/thermally pregelatinized waxy maize starch hydrogels directly influence the drug release behaviour and the structural features of the formed gel layer. This mixed matrix defines them as ‘filled’ composite systems with poor adhesion between
the surface of the elastic waxy maize starch 'filler' and the continuous HPMC phase. The pregelatinized waxy maize starch shows a stronger influence on the velocities of both water penetration and drug release from mixed matrices.

The properties of native starch, maize, potato, rice and tapioca (cassava) starch, in tablet formulations on compaction was studied by Bos et. al. Rice starch showed much better compactibility as compared to maize, potato and tapioca starch. Moreover, its binding capacity proved to be almost insensitive to mixing with magnesium stearate. This in contrast to the dramatic decrease in crushing strength of potato starch tablets containing the lubricant. The compactibility of the starches was found to be strongly affected by the equilibrium moisture content of the starches, which is dependent on the relative humidity of the atmosphere under which the powders were stored. All starches showed adequate capacity for water uptake to act as a disintegrant. Rice starch exhibited worst flowability, caused by its fine particle size as compared to the other starches. Granulation of rice starch changed it into a potential filler-binder in tablets prepared by direct compression (Bos et al., 1987).

Once-daily propranolol extended-release tablet dosage form were designed and in vitro/in vivo investigation was carried out by Huang et. al. Formulations containing HPMC, Microcrystalline cellulose (MCC) and lactose were developed and in vitro studies, the response surface methodology and multiple response optimization utilizing the polynomial equation were used to search for the optimal formulation with specific release rate at different time intervals. The mechanism of drug release from HPMC matrix tablets followed non-fickian diffusion. In the vivo study, the MRT was prolonged for matrix tablets when compared with commercial immediate release tablets. Furthermore, a linear relationship between in vitro dissolution and in vivo absorption was observed in the beagle dogs (Huang et al., 2004).

Vueba et. al. reported the study of different ketoprofen : excipient formulations, in order to determine the effect of the polymer substitution and type of diluent on the drug-release mechanism (Vueba et al., 2004). They used substituted cellulose—methylcellulose, hydroxypropylcellulose and hydroxypropylmethyl cellulose were used as polymers, while lactose monohydrate and b-cyclodextrin as diluents. Polymers MC25 and HPC were found not to be appropriate for the preparation of modified release hydrophilic matrix tablets, while HPMC K15M and K100M showed to be advantageous. The analysis of the release profiles concluded that the type of
polymer did not influence the release mechanism of the drug. Moreover, the drug-release process was found to be slightly influenced by the type of diluent, either lactose or β-cyclodextrin.

Verma and Garg developed and evaluated extended release formulation of glipizide based on osmotic technology (Verma and Garg, 2004). The effect of different formulation variables, namely, level of solubility modifier in the core, membrane weight gain, and level of pore former in the membrane, were studied. Drug release was found to be affected by the level of solubility modifier in the core formulation. Drug release from the developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred.

Swelling and release mechanism study of matrices containing NaCMC and HPMC were evaluated by Conti et. al. Matrices showed a similar swelling trend at pH 4.5 and 6.8, while they have different behaviour in acidic fluid. At pH 1 the gel layer formed by NaCMC is characterized by a rigid structure of a partially chemically crosslinked hydrogel while HPMC matrices form a physical not crosslinked gel. At pH 4.5 and 6.8, all the systems show the typical morphological behaviour of a swellable matrix in which the macromolecular chains in the gel network are held together by weak bondings (physical gel). In these buffers, MB systems maintain a constant drug release rate coupling diffusion and erosion mechanism: the gel and infiltrated layers thicknesses are maintained constant and a zero-order release kinetics was achieved (Conti et al., 2007).

Effect of varying the restriction degree of 4-aminopyridine release from HPMC matrices on the mechanism controlling the process was explained by Martinez-Gonzalez et. al. The increase of the HPMC matrix content reduced the release rate of the drug. The release mechanism showed a linear trend toward higher release exponent \( n \) values with a continuous reduction of drug release. The addition of increasing proportions of citric acid produced the opposite. An increasing drug release rate produced logarithmic decreasing \( n \) values. The results demonstrate that every restriction of the drug release rate is associated with increasing values of the mechanism-indicating exponent \( n \). This relationship means a logarithmic movement away from a release mechanism controlled by diffusion toward a mechanism controlled by relaxation, erosion and dissolution of the polymeric matrix as the drug

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release rate is restricted. These results are attributed to an increasing hydration and dissolution of the polymeric matrix, as the drug release is subject to limitation (Martinez-Gonzalez and Villafuerte-Robles, 2003).

To decrease the sensation of roughness when a tablet, which is rapidly disintegrated by saliva (rapidly disintegrating tablet), is orally taken, Ishikawa et. al. prepared rapidly disintegrating tablets using microcrystalline cellulose (Avicel PH-M series), a new type of pharmaceutical excipient that is spherical and has a very small particle size (particle size, 7-32 microm), instead of conventional microcrystalline cellulose (PH-102) used in the formulation of tablets containing acetaminophen or ascorbic acid as model drugs for tableting study. It was found that particle size is an important factor for tablet preparation using microcrystalline cellulose. Rapidly disintegrating tablets was prepared by the direct compression method when suitable excipients such as fine microcrystalline cellulose (PH-M-06) and spherical sugar granules were used (Ishikawa et al., 2001).

The effect of shape and porosity on the compression behaviour and tablet forming ability of granular materials formed from microcrystalline cellulose was investigated by Johansson et. al. The dominant mechanism during compression appeared to be permanent deformation. However, during compression of high porosity granules, fragmentation or attrition seemed to occur alongside deformation. Tablets formed from granules had a closer pore structure than those formed from pellets of equal intragranular porosity and the granules seemed to deform to a higher degree during compression. The total tablet porosity was almost independent of the intragranular porosity and the shape of the granules before compression. They suggested that the degree of granule deformation was controlled by the intragranular porosity and voidage of each bed of granules before compression. The tensile strength of the tablets was also dependent on the porosity and the shape of the granules; tablets formed from irregular granules were stronger than those formed from pellets of an equal intragranular porosity (Johansson and Alderborn, 2001).

Obae et. al have studied morphological effect of microcrystalline cellulose particles on tablet tensile strength. They found that the morphology of MCC particles was one of the most important factors affecting tensile strength. tensile strength increased with an increase in the ratio of length/width for particles (Obae et al., 1999).
The role of intra- and extragranular microcrystalline cellulose in tablet dissolution was studied by Li et al. The intra-extragranular distribution of MCC was found critical to the compactibility and initial dissolution rates from these tablets. Intragranular MCC reduced drug dissolution, the effect being most marked in the case of the slightly soluble hydrochlorothiazide. For formulations containing intragranular MCC, the granulating fluid level on tablet dissolution was also important, since an increase in fluid level resulted in slower drug dissolution from both the loose granules and the tablets compressed from them. Conversely, extragranular MCC tended to increase both dissolution rates and compactibility. It may be concluded that the appropriate distribution of MCC between and within granules may optimize both dissolution and compactibility without changing overall tablet composition (Li et al., 1996).

The effect of tablet formulation and hardness on in vitro release of cephalexin from Eudragit L100 based extended release tablets was discussed by Saravanan et al. The dissolution results showed that a higher amount of Eudragit in tablet composition and higher tablet hardness resulted in reduced drug release. An increased amount of microcrystalline cellulose in tablet composition resulted in enhanced drug release (Saravanan et al., 2002).

A pH-dependent colon-targeted oral drug delivery system using methacrylic acid copolymers in view of manipulating drug release using Eudragit L100 and Eudragit S100 combinations have been reported by Khan et al. The dissolution profiles of the drug obtained from the studied tablets demonstrated that the release of the drug could be manipulated by changing the Eudragit L100-Eudragit S100 ratios in the combinations within the pH range between 6.0 and 7.0 in which the individual polymers are soluble, and a coating formulation consisting of a combination of the two polymers can overcome the issue of high gastrointestinal (GI) pH variability among individuals (Khan et al., 2000).

Relationship between drug dissolution and leaching of plasticizer for pellets coated with an aqueous Eudragit S100:L100 dispersion was suggested by Bando et al. The plasticizer content in the film coating influenced the dissolution profile of theophylline from pellets coated with Eudragit S100:L100 (1:1). A large amount of the triethyl citrate was leached from the enteric films before drug release was initiated and a triethyl citrate level of approximately 30% in the films, based on the polymer weight, was the critical amount of triethyl citrate for initiating drug release during dissolution.
testing at pH 6.0. While enteric films are more soluble and dissolve faster at higher pH values, the kinetics of plasticizer release was one of the important factors controlling the dissolution of drugs at pH 6.0, at which pH the enteric polymers were insoluble (Bando and McGinity, 2006).

The effects of carrageenans, and cellulose ethers on the drug release rates of ibuprofen controlled release tablet matrices prepared by direct compression were investigated by Nerurkar et al (Nerurkar et al., 2005). They found that the combination of Viscarin and HPMC gave almost linear release profiles over the entire range of concentration that was studied. The least effective combination was methylcellulose in combination with HPMC. Most of the formulations released ibuprofen by an anomalous (non-Fickian) transport mechanism, except those matrices that contained methylcellulose and Gelcarin (in a 1:1 and 1:2 ratio), which showed zero-order release. They concluded that both lambda and iota carrageenan can be used in combination with cellulose ethers for the formulation of controlled-release ibuprofen tablets.

Katharina M. Picker have used carrageenan in mixture with microcrystalline cellulose and studied its functionality for making tablets (Picker, 1999). He found that the tablets produced from pure k-carrageenan deformed more elastically than pure MCC, the tablets produced were stable but not at the same degree as those made from MCC. He reported that tablets made from k-carrageenan showed less 'fusion' and thus more mechanical interlocking is responsible for their stability. Moreover, he concluded the change in release was in accordance with a change in swelling of tablets made of the binary mixtures.

Guar gum-based three-layer matrix tablets for oral controlled delivery of highly soluble metoprolol tartrate as a model drug was evaluated by Al-Saidan and his team (Al-Saidan et al., 2004). Due to the delayed $T_{max}$, lower $C_{max}$, decreased $K_{a}$, unaltered bioavailability and prolonged half-life from guar gum three-layer matrix tablets in comparison with the immediate release tablet dosage form, they concluded that guar gum three-layer matrix tablets were able to provide oral controlled delivery of highly water-soluble drug such as metoprolol tartrate in humans.

Most computations in the field of in vitro/in vivo correlations can be handled directly by Excel worksheets, without the need for specialized software. He illustrated a summary of Excel features, applications for numerical computation of AUC and
Mean, Wagner–Nelson and Loo–Riegelman absorption plots, and polyexponential curve fitting (Langenbucher, 2002). He also explained how to handle computational in vitro/in vivo correlation problems by Microsoft Excel with respect to distribution functions and moments (Langenbucher, 2003b).

According to Langenbucher, convolution and deconvolution are the classical in-vitro-in-vivo correlation tools to describe the relationship between input and weighting/response in a linear system, where input represents the drug release in vitro, weighting/response any body response in vivo (Langenbucher, 2003a). While functional treatment, e.g. in terms of polyexponential or Weibull distribution, is more appropriate for general survey or prediction, numerical algorithms are useful for treating actual experimental data. Deconvolution is not considered an algorithm by its own, but the inversion of a corresponding convolution. He suggested the MS Excel can be used as a useful tool for all these applications.

Xiaohong Qi et al have predicted drug concentration profiles of 2,3,5,6-tetramethylpyrazine following transdermal application using convolution method (Qi et al., 2003). The influence of first pass metabolism on the development and validation of an IVIVC for metoprolol extended release tablets has been reported by Sirisuth et. al. using using the convolution integral (Sirisuth and Eddington, 2002). Veng-Pedersen has presented an overview of noncompartmentally-based modeling which is a modeling that makes use of systems analysis, predominantly linear systems analysis (Veng-Pedersen, 2001).

Koester et. al. have reported the bioavailability of carbamazepine:β-cyclodextrin complex in beagle dogs from hydroxypropylmethylcellulose matrix tablets using the statistical software Bioeqv 3.4. (Koester et al., 2004). Corrigan et.al. have used PCDCON software for establishment of IVIVC in his research work on the influence of dissolution medium buffer composition on ketoprofen release from ER products (Corrigan et al., 2003). Evaluation of novel starch acetate–diltiazem controlled release tablets in healthy human volunteers was carried out by Korhonen using Hill's equation (Korhonen et al.). were explained by Uppoor have explained regulatory perspectives on in vitro (dissolution) / in vivo q (bioavailability) correlations (Uppoor, 2001).
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