

# CHAPTER I

## GENERAL BACKGROUND

### INTRODUCTION

The term disintegrant is used to refer to a substance that is added to a tablet formular for the purpose of causing the compressed tablet to break apart when placed in an aqueous environment (Gunsel et al., 1980 cited in Visavarungroj and Remon, 1990). The function of the disintegrant is to counteract the action of tablet binder and the compression forces used to form the tablet. The stronger the effect of binder, the more efficient is the disrupting effect required of the disintegrant in order to release the active ingredient into the gastrointestinal fluid (Visavarungroj and Remon, 1990).

Disintegrants have been attracting an increasing amount of attention as a result of the greater interest in drug dissolution and bioavailability. The initial investigations in this area were concerned primarily with materials that are known to swell when wetted with water. The supposition was that these agents would swell when exposed to gastric fluids and would exert sufficient pressure in the tablet to break it apart into small segments (Visavarungroj and Remon, 1990).

Sodium carboxymethylcellulose is the sodium salt of the polycarboxymethyl ether of cellulose which prepared from a reaction between alkali cellulose and sodium monochloroacetate. It is soluble in cold and hot water, and has a tendency to agglomerate on wetting with water. The hydration rate of this polymer depends on the nature of the substituent present and the degree of substitution (or moles of substituent, MS). Sodium carboxymethylcellulose is insoluble in organic solvents, but dissolve in

certain mixtures of water and water miscible organic solvents (e.g., alcohol and acetone). Sodium carboxymethylcellulose product is commercially available from various suppliers in several viscosity (molecular weight) grades (Kumar and Banker, 1993).

Although several types of sodium carboxymethylcelluloses have been employed in pharmaceuticals for many years, they have generally been used as viscosity-increasing agents or suspending agents. Internally cross-linked carboxymethylcellulose fibers have recently been introduced commercially - as Ac-di-sol<sup>®</sup> (FMC Corp., Philadelphia), listed in the USP/NF as croscarmellose sodium, Type A, and as CLD<sup>®</sup> Cellulose (Buckeye Cellulose Corp., Memphis) - for use as tablet disintegrants. The cross-linking greatly reduced water solubility while still permitting the material to swell and absorb many times its weight in water without losing individual fiber integrity (Shangraw, Wallace and Bowers, 1981).

To improve disintegration characteristics, several substances like starches, cellulose, synthetic polymers, ion exchange resins and silicon compounds have been tried. Sodium carboxymethylcellulose as such has not been exploited as disintegrant because of the formation of gel on contact with water leading to hinderance in the disintegration of tablets.

From the preliminary study, sodium carboxymethylcellulose cross-linked with sodium trimetaphosphate showed instantly swelling many times its weight when contact with water, which was similar to the property of most of the disintegrants that have been studied by many investigators.

The experimental study was divided into two parts. The first part related to the preparation of cross-linked sodium carboxymethylcellulose and the second part with the evaluation of modified sodium carboxymethylcellulose as disintegrant.

## OBJECTIVE OF THE STUDY

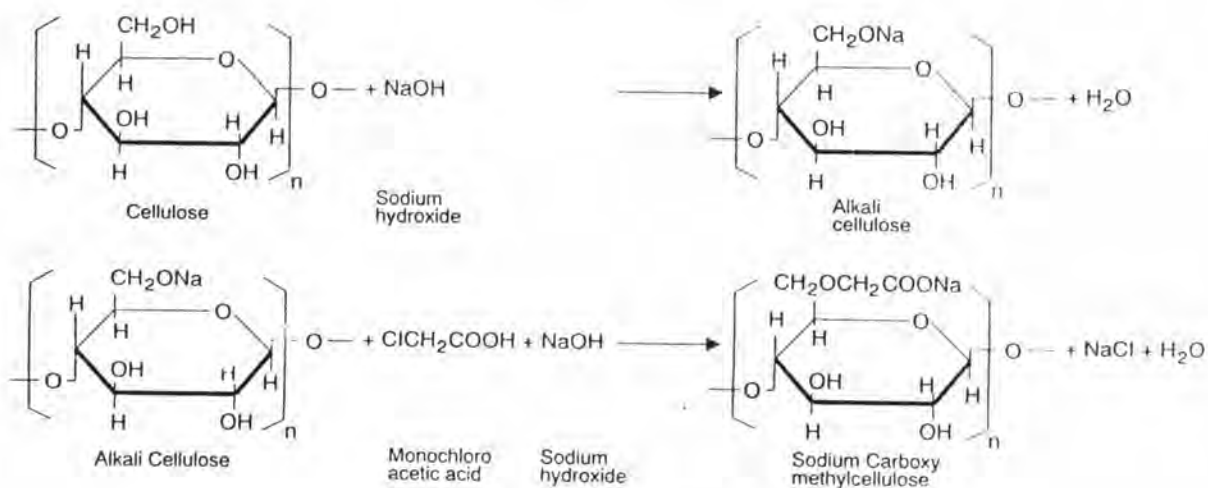
The aims of this study are:

1. To study the condition of crosslinking reaction between sodium carboxymethylcellulose and sodium trimetaphosphate.
2. To study the chemical and physical properties of sodium carboxymethylcellulose cross-linked with sodium trimetaphosphate compared with sodium carboxymethylcellulose used as starting materials and commercial disintegrants.
3. To study the disintegrating property of tablets containing sodium carboxymethylcellulose cross-linked with sodium trimetaphosphate compared with sodium carboxymethylcellulose used as starting materials and commercial disintegrants.
4. To study the effect of viscosity grade of sodium carboxymethylcellulose on disintegrating property of sodium carboxymethylcellulose cross-linked with sodium trimetaphosphate.

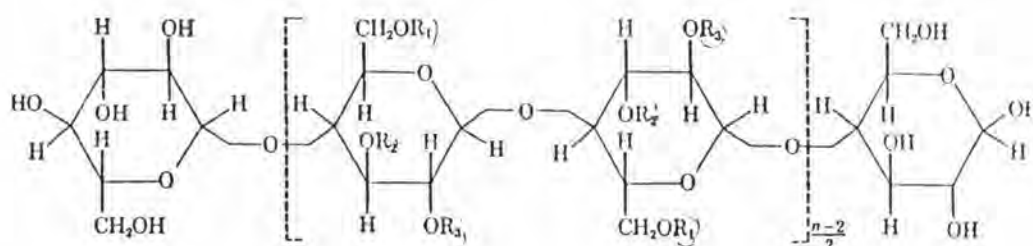
## LITERATURE REVIEW

### Sodium Carboxymethylcellulose

Sodium carboxymethylcellulose is the sodium salt of the polycarboxymethyl ether of cellulose. The most common method to prepare cellulose ethers is by nucleophilic substitution. Typically, the cellulose is first converted into an alkali cellulose, followed by a reaction with an appropriate nucleophilic agent such as monochloroacetic acid, under controlled conditions. The alkali cellulose can be prepared by treating cellulose with a base. Sodium hydroxide is usually used, but other alkali metal hydroxides can also be used. The alkali treatment also causes swelling and decrystallization of cellulose, and consequently increases the number of accessible regions in the cellulose (Nicholson and Merritt, 1985; Vigo et al., 1969 cited in Kumar and Banker, 1993). The reactions may be represented as:



The cellulose molecule consists of repeating cellobiose units, which are composed of two anhydroglucose units (Shah et al., 1981). The structure of the cellulose and carboxymethylcellulose molecules are



cellulose :  $R_1 = R_2 = R_3 = H$

carboxymethylcellulose : degree of substitution = 1 when  $R_1 = CH_2COOH$ ,  
 $R_2 = R_3 = H$

degree of substitution = 3 when  $R_1 = R_2 = R_3 = CH_2COOH$  ( $n$  = number of anhydroglucose units or degree of polymerization)

The degree of substitution refers to the average number of carboxymethyl groups that are substituted per anhydroglucose unit. Thus, sodium carboxymethylcellulose has a degree of substitution of 0.7 when an average of seven carboxymethyl groups have been substituted per 10 anhydroglucose units; it has a degree of substitution of 1.2 when an average of 12 carboxymethyl groups have been substituted per 10 anhydroglucose units. As the degree of substitution decreases, the chemical structure of sodium carboxymethylcellulose approaches the chemical structure of natural cellulose.

In etherification, the degree of substitution can be varied from 0.4 to the maximum of 1.5 (theoretical maximum 3 D.S.) depending upon the amount of sodium carboxymethyl groups added to 3 hydroxyl groups of each cellulose or anhydroglucose unit. The properties of sodium carboxymethylcellulose can be largely controlled in the reaction stage by varying the uniformity of substitution, the degree of substitution and the degree of polymerization.

The average molecular weight of sodium carboxymethylcellulose is determined by the average chain length and the degree of substitution. The viscosity of sodium carboxymethylcellulose dispersions increases as the molecular weight increases and thus is used as a measure of the degree of polymerization.

For many years, sodium carboxymethylcellulose has been used in tablets as a binder and as a viscosity builder in aqueous solutions. Sodium carboxymethylcellulose with a low sodium content and a degree of substitution below 0.2 was reported to be a suitable tablet disintegrant (Laminet, Delattre and Delaport, 1969). Although there are no reports on the effect of different grades of sodium carboxymethylcellulose having varying degree of polymerization and substitution on tablet characteristics, the physicochemical properties of cellulose are altered significantly with changes in the degree of substitution and polymerization.

In 1981, Shah et al. evaluated the effect of various grades of sodium carboxymethylcellulose on the disintegration and dissolution rates of a sulfamethoxazole tablet. They found that the highly polymerized grades of sodium carboxymethylcellulose are good disintegrating agents. The disintegration properties were significantly influenced by the degree of substitution. The gums with a low degree of substitution together with a high degree of polymerization were excellent disintegrating agents. The disintegration properties of sodium carboxymethylcellulose decreased as the degree of substitution increased and the degree of polymerization decreased. They suggested that, the minimum viscosity required for effective disintegration properties for the various grades of sodium carboxymethylcellulose should be in Table 1



**Table 1** Minimum viscosities for good disintegration properties

Degree of substitution	Minimum viscosity of 2% aqueous dispersion at 25°C using propeller-type mixer (cps)
0.4	>150
0.7	>200
0.9	>1500
1.2	>3000

A study to evaluate different viscosity grades of sodium carboxymethylcellulose as disintegrants and to determine the effect of their viscosity on tablet disintegration and dissolution properties, was presented by Khan and Rhodes (1975). Results showed significant differences in both the disintegration and dissolution of the tablets. However, there appeared to be no simple relationship between disintegration and dissolution times.

Sodium carboxymethylcellulose product is commercially available from various supplier in several viscosity grades, such as Aqualon<sup>TM</sup> under the trade name Cellulose Gum. In addition, sodium carboxymethylcellulose from Thai Cellulose Products Ltd., which is one of the Asian's industrial leaders, is marketed as Hycel CMC in several grades based on the degree of substitution, degree of polymerization, viscosity, purity, particle size and other parameters.

### **Crosslinking Reaction of Polysaccharide**

Cystine linkages or disulfide (SS) crosslinks in wool fibers form inter- and intramolecular crosslinks which stabilize the structure of the wool fibers. One of the methods to introduce SS-crosslinks into cellulose is to allow cellulose to react with a bifunctional crosslinking agent that contains a SS-bond in the molecule. Sakamoto, Yamada and Tonami (1970) studied the

reaction of bis( $\beta$ -isocyanatoethyl)disulfide (BIED), which is a bifunctional crosslinking agent that contains a SS-bond in the molecule, with cellulose and found that BIED reacted with cellulose both monofunctionally and bifunctionally to yield SS-containing branches and crosslinks, respectively. The reaction may be represented as:



Gum acacia has been tried to improve disintegration characteristic because of the formation of a sticky mucilage on contact with water leading to hinderance in the disintegration of tablets. The study of Trivedi et al. (1986) has revealed that cross-linked gum acacia with epichlorohydrin can be used as disintegrant. The exact mechanism by which cross-linking of gum taken place was not yet known. The possible mechanism may involved reaction of either carboxyl or hydroxyl groups, present in the polysaccharides of gum with epichlorohydrin. The epoxide group in epichlorohydrin was very reactive and the reaction may involved initial addition at the highly reactive oxide ring, that provided new hydroxyl groups for further crosslinking (Kornblum and Stoopak, 1973).

In 1898, Classen had disclosed that non-swelling starches could be prepared by treatment with formaldehyde. Felton and Schopmeyer (1943) disclosed the treatment of intact starch granules with very low levels of phosphorus oxychloride to give products with controlled swelling power and viscosity stability. Epichlorohydrin and trimetaphosphate are also used in cross-linking food and industrial starches. Other cross-linking agents include aldehydes, dialdehydes, vinyl sulfone, diepoxides, 1,3,5-trichloro- and 1,3,5-



triacryl-s-triazine, hexamethylene diisocyanate, bis-(hydroxymethyl) ethyleneurea, and *N,N'*-methylenebisacrylamide. The various urea-formaldehyde resins are also effective cross-linking agents. In general, any molecule capable of reacting with two or more hydroxyl groups can induce cross-linking reaction. This includes such relatively unreactive molecules as the aliphatic dihalides, although it is difficult to react such substances without damaging the starch granule (Hullinger, 1967).

In most cases, the manufacturer of a cross-linked starch does not attempt to determine the extent of cross-linking directly. Instead, the physical properties of the starch paste are examined. Viscosity, swelling power, solubility pattern, and resistance to shear are commonly measured. Direct analysis of the extent of cross-linking is difficult because of the very low degree of substitution in most cross-linked starches. Radioactive tracer techniques should prove useful, but none has been reported to date.

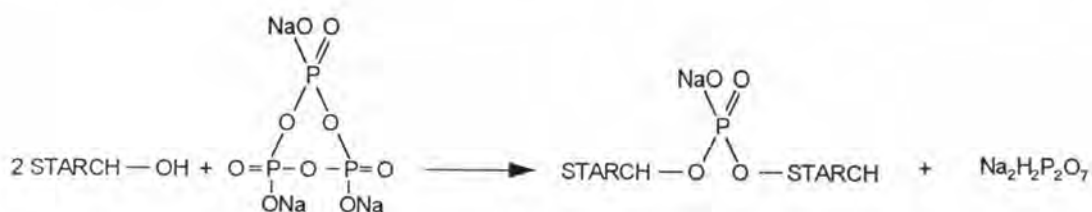
While a wide variety of chemicals have been reported to cross-linked starch, only a limited number are now of commercial significance. The most widely used are the adipic acetic mixed anhydride, which forms distarch adipates; phosphorus oxychloride or sodium trimetaphosphate, which yield distarch phosphates; and epichlorohydrin, which gives distarch glycerols (Wurzburg, 1987).

The distarch adipates are made by esterifying granule starch in aqueous suspension under mildly alkaline conditions with a mixed anhydride prepared by reacting adipic acid with acetic anhydride. Distarch phosphates may be made by reaction of starch granules in aqueous suspension with either phosphorus oxychloride or sodium trimetaphosphate under alkaline solution. Distarch glycerols may be made by treating granular starch normally in aqueous suspensions with epichlorohydrin under alkaline solutions. In addition to reacting with starch hydroxyls, a portion of the cross-linking

reagent will be hydrolyzed by water to form free adipic acid or adipate salt or phosphoric acid or its salt or glycerol, respectively. These would be present at very low concentrations since the level of reagents used in the cross-linking treatment is generally very low. Most of any residue left in the aqueous suspension is removed by washing.

There is considerable variation in the rate at which these chemicals cross-linked starch. The reaction rate with phosphorus oxychloride and adipic acetic mixed anhydride is very rapid. That portion which does not react with the starch is rapidly hydrolyzed. The rate of reaction with sodium trimetaphosphate is somewhat slower, while the rate with epichlorohydrin is much slower. The difference, however, can be minimized by the used of higher reaction temperatures and alkalinity when reacting with epichlorohydrin. The rate and extent of reaction with epichlorohydrin was studied by Hamerstrand et al. (1960) by determining the quantity of epichlorohydrin which had not reacted with starch in the reaction filtrates. At 25 °C, when approximately 1% NaOH and 0.024 to 1.14% epichlorohydrin on the weight of dry starch were used, 18-hour reaction time was required to react about 80% of the added epichlorohydrin with the starch. The theoretical number of anhydroglucose units per cross-link varied from 50 to 2360. Kuniak and Marchessault (1972) reported that, depending upon conditions of time, temperature, and mole ratio of all reactants, from 5 to 25% of the applied epichlorohydrin is bound in the starch as a glycerol monoether substituent.

The reaction between starch and sodium trimetaphosphate are shown as follows:



Starch phosphate esters which are cross-linked have unusual properties which make them suitable for a number of industrial uses. They are more resistant to gelatinization and pastes made therefrom have increased stability as concerns breakdown by heating compared to untreated starch. In fact, depending upon the degree of cross linking, starch esters may be prepared which are nongelatinizable in boiling water. Starch in the granule stable containing a sufficient number of distarch phosphate groups will not gelatinize even when boiled in water. Such a product may be used as an inert dusting powder, unaffected by moisture or temperature, such as is used for dusting and lubrication of surgeon's gloves which may be sterilized in the autoclave and the starch will not lose its lubricating or de-tackifying effect (Kerr and Cleveland, 1957).

The most important problem of using carboxymethyl tapioca starch as disintegrant was its solubility produced viscous gel barrier around granules and tablet. To overcome this problem a crosslinking of carboxymethyl tapioca starch by suitable crosslinking agent should be done. Teruya (1995) studied carboxymethyl tapioca starch cross-linked with sodium trimetaphosphate and found that cross-linked carboxymethyl tapioca starch with the degree of crosslinking of 0.95% phosphate provide a good disintegrant properties. The comparative study of physico-chemical properties of cross-linked carboxymethyl tapioca starch and other commercial modified potato starches (Explotab<sup>®</sup> and Primojel<sup>®</sup>) was shown that cross-linked carboxymethyl tapioca starch exhibited some physico-chemical properties better than carboxymethyl potato starches such as water uptake, bulk swelling, hydration capacity, cold water soluble, sodium chloride content and percent compressibility while viscosity and sorption isotherm of these disintegrants more closely resembled. Cross-linked carboxymethyl tapioca starch exhibited disintegrant property superior than carboxymethyl potato starches in dicalcium phosphate and erythromycin stearate tablets and equivalent to Explotab<sup>®</sup>, Primojel<sup>®</sup> and Ac-di-sol<sup>®</sup> in paracetamol tablets at the same level of concentration.

## **Cross-linked Sodium Carboxymethylcellulose**

A cross-linked form of sodium carboxymethylcellulose, marketed as Ac-di-sol<sup>®</sup> by FMC, is listed in the USP/NF as croscarmellose sodium, Type A (USP p1922), and is used as a dissolution aid and disintegrant in tablets and capsules. Ac-di-sol<sup>®</sup> shows dissolution/disintegration properties independent of tablet hardness, and is highly effective in wet granulation and direct compression products.

Cross-linked sodium carboxymethylcellulose may be used as a tablet disintegrant in concentrations as low as 1%, although a 2% level is recommended for tablets made by direct compression, a 3% level for those made by wet granulation (Shangraw, Wallace and Bower, 1981).

The effectiveness of cross-linked sodium carboxymethylcellulose at such low concentration levels can be attributed to its fibrous nature, which allows intraparticulate wicking of water into tablet matrices by single fibers rather than by a continuum of many individual and more spherical particles, as is the case with starch grains (Shangraw, Wallace and Bower, 1981).

Gissinger and Stamm (1980) concluded that cross-linked sodium carboxymethylcellulose (Ac-di-sol<sup>®</sup>) was superior to non-cross-linked material. They found that cross-linking improved both the swelling and water uptake of this material.

Gorman and co-workers (1982) published a report in which evaluated two cross-linked sodium carboxymethylcellulose. The two disintegrants (Ac-di-sol<sup>®</sup> and CLD-2<sup>®</sup>) differed cross-linkage levels, fiber length, bulk swelling, and water uptake. The authors did not identify the role of fiber length in disintegrant action for this disintegrant.

low viscosity in solution) and a maize starch modified by milling with water to break the amyloplasts and agglomerating the fragments under pressure (Starx<sup>®</sup> 1500).

2. Celluloses and derivatives of cellulose: microcrystalline cellulose (Avicel<sup>®</sup>), methylcellulose, different carboxymethylcellulose with different degrees of substitution and water solubilities (CMC Na, Nymcel<sup>®</sup>), cross-linked carboxymethylcellulose (Ac-di-sol<sup>®</sup>), hydroxypropylcellulose (L-HPC<sup>®</sup>), mixture of sodium carboxymethylcellulose and microcrystalline cellulose (Avicel<sup>®</sup> RC 591).

3. Macromolecules which are different from the two others groups: alginic acid, guar gum (Vidogum<sup>®</sup> KL 175), casein formaldehyde (Esma spreng), pectins, cation exchange resin (Amberlite<sup>®</sup> IRP 88), cross linked polyvinylpyrrolidone (Polyplasdone<sup>®</sup> XL).

4. Finely divided solids: one is composed with magnesium and aluminium silicates (Veegum<sup>®</sup> F), the other one is a colloidal silicon dioxide (Aerosil<sup>®</sup> 200).

### **Mode of Incorporation**

Wet granulation is an often-used technique for manufacture of tablets. The disintegrant in wet granulation can be incorporated either extragranularly, intragranularly, or distributed between the two phases. Much work has been done on the effect of mode of incorporation of disintegrants in wet granulation (Sakr and Farrag, 1975; Shotton and Leonard, 1976; van Kamp et al., 1983; Gordon et al., 1990). Sakr and Farrag (1975) and Gordon et al. (1990) found intragranular inclusion to be superior with extragranular inclusion. Miller et al. (1980) and Shotton and Leonard (1976), however, found the combined inclusion to result in faster dissolution than the separate



modes of incorporation, and van Kamp et al. (1983) concluded that method of addition of disintegrants had little effect on the dissolution characteristics. These apparent differences could be attributed to the method of manufacture or to the physicochemical characteristics of the tablet ingredients.

For identical amounts of disintegrant, wet-granulated paracetamol tablets containing disintegrants in the combined mode disintegrate faster than the extragranular mode followed by the intragranular mode (Khattab, Menon and Sakr, 1993). The differences between the extragranular and intragranular modes of inclusion can be explained (Shotton and Leonard, 1976). Due to the disintegrant particles being confined to spaces between the granules in the extragranular mode, an easier passage for water penetration is present for the formation of a continuous hydrophilic capillary system throughout the tablet. Intragranular disintegrants are confined within the granules thus presenting a less wettable matrix and subsequent absence of a continuous hydrophilic network.

### **Evaluation of swelling of disintegrant**

Possible mechanisms proposed for disintegrant action are rapid water uptake into compacts, swelling of disintegrant particles, swelling of deformed disintegrant particles, porosity and capillary action, particle repulsion, heat of wetting, breakage of physico-chemical bonds, gas release, melting and enzymation action (Caramella et al., 1990; Pesonen, Paronen and Ketolainen, 1989). Even though there has been a strong debate on that in the literature, swelling is probably the most widely accepted mechanism of disintegrant action. This is also due to the fact that particle swelling is directly linked to another claimed mechanism of disintegrant action, that is water uptake mechanism. In fact it has been definitely demonstrated by many excellent works that an efficient swelling promotes a rapid water uptake into compacts.

Many attempts have been made to qualify swelling, but only recently have sophisticated methods been brought to bear on the problem. In the past, investigators have used sedimentation volume of a slurry as a measure of swelling. This test gives a fair appraisal of swelling capacity but does not provide for dynamic measurement of the swelling itself. As a result, many disintegrant studies could not correlate rank-order sedimentation volume with disintegrant efficiency. In the opinion of a few authors, much of the controversy concerning the rate of swelling in the disintegration process is due to the fact that some confusion has persistently been made between swelling extent and swelling efficiency. These two properties are not necessarily related to each other.

#### Swelling extent

The methods for the quantitative evaluation of disintegrant swelling (swelling extent) may be grouped into :

1. Methods for the evaluation of intrinsic swelling, that is individual particle volume increase
2. Methods for the evaluation of swelling in bulk, that is water uptake capacity of disintegrant powder bed

The former method are mostly based on microscopic observation of particles, even though instrumental method, that is based on the employment of a coulter counter or laser diffraction apparatus, have also been proposed. These methods, with a few exceptions, mainly provide an evaluation of particle swelling in static condition, that is at the equilibrium.

The latter methods may be, in tern, classified into :

1. Static methods, like hydration capacity and sedimentation volume
2. Dynamic methods, like water uptake of powder bed, swelling of pure disintegrants tablets and dilatometry

Whereas static methods provide only for the quantification of the amount of water uptaken at the equilibrium, dynamic methods provide for the evaluation not only of the extent (amount of water uptaken or extent of expansion) but also of the rate of swelling process (Kanig and Rudnic, 1984).

Both sedimentation volumes and bulk swelling rates were evaluated by Rudnic et al. (1982), who found a poor correlation between the static test (sedimentation) and disintegrant efficiency. For bulk swelling test, they found that it was dependent upon a number of variables such as water transport through a gel layer and rates of hydration.

### **Swelling efficiency**

Unlike the methods for the quantitative evaluation of swelling, the approaches for the evaluation of swelling efficiency are far less common, although a few of them have been described in the literature. For instant, List and Muazzam (1979) was the first who proposed to measure the swelling pressure inside tablet; other authors, Columbo et al. (1980) and Gould and Tan (1985) took up and exploited these concepts.

All the methods for the evaluation of swelling efficiency rely upon the measurement of a pressure or a force inside disintegrating tablets, meaning that they may be considered dynamic methods in the etymological sense of the word. Caramella et al. (1984) concluded that a disintegrant is likely to be effective in a given formulation only when it promotes a rapid force development inside the compact. Even limited swelling material (sometimes called non-swelling disintegrant) can act as efficient disintegrants because the swelling force depends rather more on the energy of swelling than on the extent of swelling. In addition, List and Muazzam (1979) concluded that disintegrants capable of producing a significant force of swelling generally are more effective disintegrants.

These investigators developed a novel method of evaluating intrinsic swelling using high speed cinemicroscopy and computerized image analysis. Although these method allowed for more accurate and precise measure of swelling, they concluded that bulk swelling and intrinsic swelling produced similar rank order disintegrant swelling rates.