CHAPTER 4

EXCIPIENTS – A PROFILE

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4.1 List of Excipients used in the research work:

Table 4.1 List of Excipients used in the experiments:

Excipients and Chemicals	Grade	Role	Manufacturers
Sodium alginate	LR	Primary polymer	LobaChem.., Mumbai
Calcium chloride dihydrate	LR	Cross linking agent	Ranchem, India
Sodium hydroxide	AR	Analysis/ Buffer	Ranchem, India
Potassium dihydrogen ortho phosphate	AR	Buffering agent	Ranchem, India
Hydrochloric acid	LR	Analysis/ Buffer	Ranchem, India
Ethylenediamine tetra acetic acid	AR	Chelating agent	S.D.Fine Chem. Ltd.
Acrycoat E30D	Solid content (28.7% w/w)	Release controlling polymer	Corel Pharmaceuticals Ahmedabad
Acrycoat L30D	Solid content (40% w/w)	Enteric coating polymer	Corel Pharmaceuticals Ahmedabad
Acrycoat S100	Solid content (95% w/w)	Slow release enteric coating polymer	Corel Pharmaceuticals Ahmedabad
Surelease	Solid content (25% w/w)	Release controlling polymer	Colorcon India Ltd.
Methocel K15M	7382 mPas.sec	Film former & Viscosity enhancer	Dow Chemical Co., India

4.2 SODIUM ALGINATE

4.2.1 Nonproprietary names

USP[1] : Sodium alginate.

BP[2] : Sodium alginate.

4.2.2 Synonyms[3]

Alginic acid, Sodium salt, Algin, Sodium polymannuronate, Satialgine S20, Album S 160 and S 15/600, Kelgin, Kelcosol, Keltone, Kelco-gel L V, HV, Sodium Alginate, Type S-11.

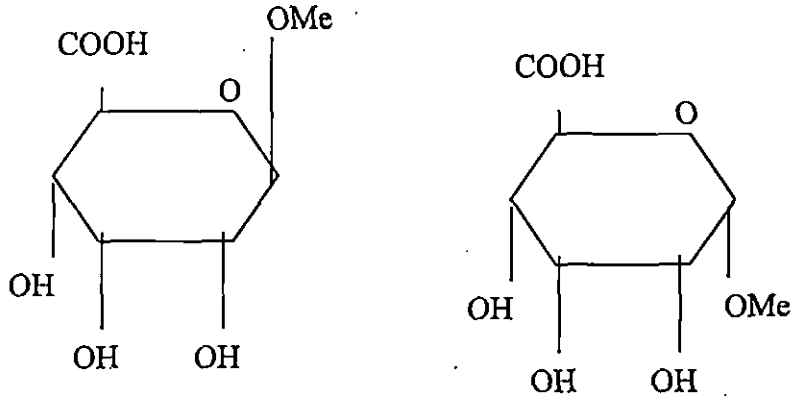
4.2.3 Sources[4,5]

Alginates are obtained from several of the larger ***phaeophyceae*** or brown algae. The most important are kelps or sea-tangles, of species of ***Laminaria,*** the common ones being ***L.digitata Lam, I Edm.***and ***L.saccharina Lam***- all of which are large olive green to brown algae belonging to the ***Laminariaceae,*** a family of ***Phaeophyceae.*** The wracks are smaller plants and the common species are ***Fucus Serratus Linn, F.vesiculosus Linn,*** all belonging to the family of ***Fucaceae.***

4.2.4 Empirical Formula ---- $(C_6H_7O_8Na)$

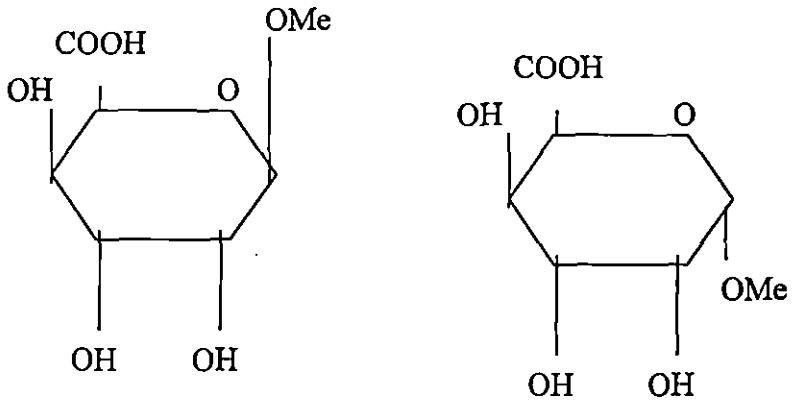
4.2.5 Structural Formula[6,7,8]

Alginic acid is a polysaccharide found originally in brown seaweed which still function as it's major polysaccharide. The polysaccharide is a linear glycuronan consisting of (1-4) linked residues of D-mannuronic acid (M) and L-guluronic acid (G) arranged in a block fashion in the polymer chain, with blocks containing one type of residue being separated by segments in which two residues alternate.



β- D Mannuronic Acid α- D Mannuronic Acid

Figure 4.1.1 Structures of Mannuronic acid



β- D Guluronic Acid α- D Guluronic Acid

Figure 4.1.2 Structures of Guluronic acid

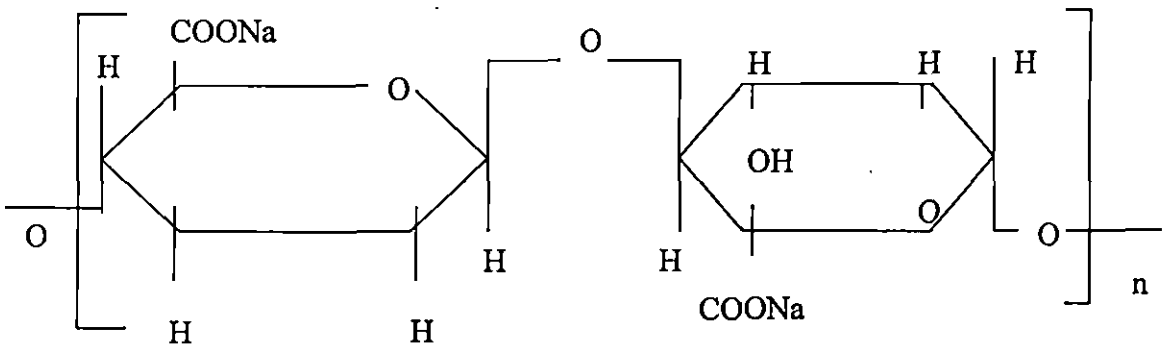


Figure 4.1.3 Structural Formula of Sodium Alginate

4.2.6 Description

Sodium alginate occurs as a white or buff powder, which is odorless and tasteless. The powder may be coarse or fine[2,3,4]. The gelling characteristics of alginate is strongly influenced by its uronic acid composition, i.e. The ratio of Mannuronic acid[6,7,8] (M) residue to Guluronic acid residue (G) commonly called as (M/G ratio). Alginates with low M/G ratio gives strong and brittle gels having a marked tendency to syneresis in excess of calcium, whereas alginates with a high M/G ratio forms elastic gels that are relatively tolerant to high levels of calcium.

4.2.7 Method of manufacture

Sodium alginate is prepared[3] by the neutralization of purified alginic acid with sodium bicarbonate.

4.2.8 Functional category[3,4]

Suspending Agent; Viscosity builder; Disintegrant; Tablet binder; Mucoadhesive agent.

4.2.10 Pharmacopoeial specifications

Table 4.2 Official specifications of Sodium alginate as per different Pharmacopoeia

Test	USP[1]	BP[2]
Identification	+	+
Assay	90.8 – 106.0%	-
Microbial limits	< 200 viable organism per gram. *Salmonella* species and *E.coli* must be absent.	Total viable aerobic count not more than 10^3 microorganisms per gram. *Salmonella* species and *E.coli* must be absent.
Loss on drying	.< 15.0% by weight.	.< 15.0% by weight.
Sulphated ash	-	30.0 – 36.0%
Ash	18.27%	-
Lead	.< 0.001%	.< 10 ppm.
Arsenic	.< 1.5 ppm	-
Heavy metals	.< 0.004%	.< 20 ppm.

'+' sign of conformation; '-'not specified; NF – National Formulary; BP – British Pharmacopoeia; USP – United States Pharmacopoeia

4.2.11 General properties[3]

Sodium alginate is slowly soluble in water, forming a viscous, colloidal solution. It is insoluble in alcohol and in hydro-alcoholic solutions in which the alcohol content is greater than 30% by weight. It is also insoluble in other organic solvents and in acids where the pH of the resulting solution falls below 3.0. Various grades of sodium alginate are available yielding aqueous solutions of varying viscosity within a range of 20 to 400 cp in 1% solution at 20°C. Solutions are sterilized by autoclaving. Some decrease in viscosity occurs following sterilization. The extent of this loss depends on the presence of other substances added to the solution. A 1% solution in distilled water has a pH of approximately 7.2

4.2.12 Stability and Storage Conditions

Since sodium alginate is hygroscopic, the moisture content at equilibrium is a function of relative humidity. Dry storage stability is excellent when the powder is stored in a well-closed container at temperatures of 25°C or less. Solutions are most stable at pH between 4 and 10. Viscosity decreases for sodium alginate solutions above a pH of 10. Solutions should not be stored in metal containers. Preparations for external use may be preserved by

the addition of chlorocresol (0.1%), chloroxylenol (0.1%) or esters of p-hydroxybenzoic acid, or if the medium is acidic, benzoic acid may be used.[1,3,4].

4.2.13 Incompatibilities

Sodium alginate is incompatible[3] with acridine derivatives, crystal violet, phenyl mercuric nitrate and acetate, calcium salts, alcohols in concentrations greater than 5% w/v and heavy metals. High concentrations of electrolytes cause an increase in viscosity until salting-out of the sodium alginate occurs. Salting out occurs if more than 4% w/v of sodium chloride is present.

4.2.14 Safety

No satisfactory data have been reported in the literature concerning the acute oral toxicity (LD_{50}) of sodium alginates[3]. The incorporation of 5 to 15% sodium alginate in the diet of purebred beagle dogs for one year cause no harmful effects. Numerous studies have attested to the high levels of safety of sodium alginate in foods. Allergy tests conducted with sodium alginate have shown that the material is not allergenic.

4.2.15 Handling Precautions

None is reported. Sodium alginate has not been shown to possess any eye or skin irritation properties.

4.2.16 Applications in Pharmaceutical Formulations[3]

Table 4.3 Pharmaceutical Applications of Sodium Alginate

USE	CONCENTRATION (%)
Pastes and Creams	5-10
Stabilizer in Emulsions	1-3
Suspending agent	1-5
Tablet Disintegrant	2.5-10
Tablet Binder	1-3

4.2.17 Mechanism of Gelation

Circular Dichroism[7] and Nuclear Magnetic Resonance (NMR) studies have shown the reason why alginates with differing M/G ratio have different gelling characteristics. The reason is that they contain different proportions of block structure, i.e. Mannuronic acid blocks (M blocks), Guluronic acid blocks (G blocks) and alternating blocks (MG blocks). These blocks differ in their ability zones, in that G blocks aggregate readily and, with excess calcium, aggregate even further causing syneresis, where as M blocks require high level of calcium to aggregate. Alternating blocks have little tendency to aggregate.

X-ray diffraction[8] studies showed a buckled two fold conformation for poly L. Guluronic acid, which appears to persist in all of the salt forms so far studied. The evident lack of conformational mobility, which is paralled by hydrodynamic evidence of a stiff, extended chain conformation, presumably reflects the severe steric constraints of the (1-4) diaxial, inter-residue linkage. In this favored two fold conformation; polyguluronate chains display a regular array of electronegative cavities, whose size and geometry appear to be compatible with chelation of calcium. Hence, calcium binding has been interpreted in terms of an "egg-box" model, with specific site binding of cations between long, structurally and sterically regular, polyguluronate chain-sequences. (Figure 4.1.1)

This interaction between calcium ion and polyguluronate chain occurs mainly due to favorable orientation of carboxylate group in these chains. The specific interchain linkage of G chain by calcium ion results in the formation of gel network structure in the alginate (Figure 4.1.3)

4.2.18 Comments

Sodium alginate is also used as a haemostatic agent in surgical dressings. It has been reported that sodium alginate could be sterilized by ethylene oxide without loss of viscosity.

4.3 CALCIUM CHLORIDE DIHYDRATE ($CaCl_2 .2H_2O$)

4.3.1 Molecular Formula[1,2,4] $CaCl_2, 2H_2O$

4.3.2 Molecular Weight 147.0

4.3.3 Definition[1,2,4]

Calcium chloride contains not less than 97.0% and not more than the equivalent of 103.0% of $CaCl_2, 2H_2O$.

4.3.4 Characters[1,2,4]

It is a white, crystalline powder, hygroscopic.

4.3.5 Solubility

It is freely soluble in water, soluble in alcohol.

4.3.6 Specification[2,4]

a) **Appearance of solution:** 10.0gm calcium chloride was dissolved in carbon di-oxide free distilled water and diluted to 100 ml with the same solvent (Solution S). Solution S is clear and not more intensely coloured than reference IP standard.

b) **Acidity or alkalinity:** To 10 ml of freshly prepared solution S, 0.1ml of phenolphthalein solution 0.1% w/v is added. If the solution is red, not more than 0.2 ml of 0.01 M hydrochloric acid is required to discharge the colour and if the solution is colourless, not more than 0.2 ml of 0.01 M sodium hydroxide is required to turn it red.

c) **Sulphates:** Not more than 300 ppm.

d) **Heavy metals:** Not more than 10 ppm.

e) **Iron:** Not more than 10 ppm.

f) **Magnesium and Alkali metals:** Ignition residue weighs not more than 0.5% w/w.

g) **Assay:** 0.280 g of calcium chloride is dissolved in 100 ml of water and was determined by carrying out the complexometric titration of calcium. 1 ml of 0.1 M sodium edetate is equivalent to 14.70 mg of $CaCl_2, 2H_2O$.

h) **Storage:**[2,4] Should be stored in a well-closed container.

4.4 Aqueous Polymeric Dispersion[9]

Polymeric films are finding an ever increasing range of application in pharmaceutical research, development and dosage form design. In the coating of tablets and other solid dosage forms there is no coating methodology at present that can match film coating in production capability or economy. Polymeric film coatings have been increasingly employed to coat drug particles or drug containing pellets to produce products with a delayed or prolonged therapeutic action. Approximately 1000 pharmaceutical patents pertaining to polymeric materials as adjuvents including polymeric coatings have been issued in the last 15 to 20 years. In addition to application to any types of solid oral dosage form, polymeric films are being employed for such diverse uses as the coating of suppositories, the encapsulation of liquids and aerosol, spray bandages. As film theory and technology continue to advance, both fundamentally and selected pharmaceutical applications, increasing and more effective utility of polymeric films will be developed by pharmaceutical industry.[10]

The literature on sustained or controlled release medications has recently been extended to new drug-delivery systems employing polymeric coatings or matrix materials and a class of colloidal or near-colloidal aqueous polymer dispersions as rate-limiting film membranes. These dispersions or aqueous polymer emulsions may be prepared by emulsion polymerization of a monomer or by emulsification of a preformed polymer. The polymer emulsions prepared by emulsion polymerization contains small polymer particles averaging about 0.1 – 0.3 micron in diameter, but the precursor monomers are limited to those that are polymerizable in an aqueous medium in the presence of free radical initiators. Polymer emulsions from monomers not so polymerizable are prepared by emulsifying the previously polymerized monomers by means of any of a number of general types of emulsification procedures.[11]

4.4.1 Latexes and Pseudo latexes

Finely divided colloidal polymer dispersions are classified as true latexes or pseudo latexes largely on the basis of the technique of production. "True latex" is made by polymerization of a monomer or monomer blend, usually emulsified in an aqueous medium with the aid of anionic or non-ionic surfactants. The process requires the addition of initiators that function

by free-radical, anionic or cationic polymerization mechanisms. The polymer is usually of submicron dimensions, but there can be problems of toxicity with residual monomers.

Pseudo latexes, such as Aquacoat and Aquateric dispersions, can be prepared from any existing thermoplastic water insoluble polymer. For pharmaceutical use, ethyl cellulose, cellulose acetate phthalate, and other cellulosics are preferred, as they have a history of regulatory approval and utility in controlled-release dosage forms.

Both latexes and pseudo latexes are or may be colloidal dispersions containing spherical solid or semi-solid particles less than one micron in diameter, typically less than 0.1 micron. Both are fluid even at polymer concentration of 30%, and both systems form films by the same mechanism. The difference is that water-based latexes are limited to synthetic polymers of liquid-insoluble monomers that can be emulsified in water.

Pseudo latexes of ethyl cellulose are prepared by dissolving the polymer in a suitable solvent and introducing the organic phase into water to form an emulsion, employing sodium lauryl sulphate and cetyl alcohol as stabilizers. After homogenization, the solvent is removed by vacuum distillation, leaving a 30% solid dispersion of ethyl cellulose in water.

Particle size diameter is the key to pseudo latexes stability and subsequently film forming mechanisms. The five fold difference in particle size between latexes prepared by two different methods (minimum sizes 1 micron and 0.2 micron) is critical with respect to their stability or resistance to settling and sedimentation. According to Stoke's Law, for spherical particles,

$$\textbf{Rate of Sedimentation} = (D^2/18\eta)\,(dp-dm)\,g \qquad (4.1)$$

Where, **D** is the particle diameter.

η is the viscosity of medium,

dp and **dm** are the densities of the particles and medium respectively,

g is the gravitational constant.

The tendency of colloidal particles to settle upon standing is offset by their Brownian motion and the convection currents arising from small temperature gradient in the sample. Brownian motion, which results from the unbalanced collisions of solvent molecules with the colloidal particles, increases the intensity with decreasing particle size. One criterion for settling is that a sedimentation rate of 1mm/24 hr will be offset or nullified by the thermal convection currents and Brownian motion within the sample. Substituting the sedimentation rate into Stoke's equation enable us to determine the largest particle size that, in any particular instance, will not settle out upon standing. As a matter of fact, 1 micron diameter

particles of most polymers, the minimum size generally produced by direct emulsification method, settle at a relatively rapid rate, which can be reduced by raising the viscosity of the water phase in some manner.

It was an object of the VanderHoff invention to provide a process for the direct emulsification method of polymer preparation that would result in stable aqueous dispersions of particles averaging less than 0.5 micron in size. The polymer could be of any type and chemical composition: natural or synthetic, organic or inorganic, homopolymeric or random, block or graft co polymeric.

Ethyl cellulose was chosen as a candidate polymer by the physical pharmacy Department of Purdue University because of its history of use in controlled release dosage form and regulatory approval (21 CFR 172.868). Likewise, cellulose acetate phthalate (CAP) was chosen to form an enteric polymer aqueous dispersion.

The preparation of CAP pseudo latex is some what complex, and its final dispersion is spray-dried because of CAP's instability in water over the long term. A nonionic surfactant, pluronic F68, is preferred in preparation of the parent pseudo latex. A barrier dispersant system composed of acetylated monoglyceride and polysorbate 60 is used in spray-drying as a protective barrier.

4.4.2 Advantages of Pseudo latex Dispersions

Pseudo latex emulsions or colloidal polymer dispersions offer a variety of technical advantages over polymers available from organic solvent solution. The advantages from both (a) the rheological properties of dilute polymer dispersion, and (b) the unique method of film formation specific to latex emulsions.

Its' major advantage over polymer solution is the concentration-viscosity relationship for pseudo latex. Water has numerous practical advantages as a coating vehicle, but its use with polymer solutions alone has been limited to low solids contents. The viscosity of such solutions rises sharply with polymers such as hydroxyl propyl methyl cellulose (HPMC) is used alone; a number of separate layers of polymer are typically built up to obtain adequate thickness for protection. During the "dry-down", long chain polymers are entangled randomly, requiring more film excipients and longer coating operations.

A direct relationship between percentage of solids and time involved in the physical coating operation is apparent. With the pseudo latex, viscosity is independent of the molecular

weight of polymer in the dispersed system. Greater concentrations (30%) of the polymers are possible at extremely low viscosities (150 cp).

Without a viscosity rate-limiting factor, more film forming polymer can be applied per milliliter of coating solution. Therefore less water needs to be driven off. This has major implications for moisture or heat sensitive drugs to be designed as controlled release dosage forms.

Another advantage of the pseudo latex emulsion formed from ethyl cellulose polymer is its permeability. It has been found that water vapour transmission rate through a pseudo latex coat is significantly more than that of mixed polymer films formed from organic solvent solution.

With pseudo latex there is a zero-order loss of water independent of the solids concentration. This is due to (a) the unique rheological characteristics of a latex emulsion, and, (b) the film formation mechanism involving coalescence of discrete submicrometer latex spheres.

At about 85% water loss, the curve begins to fall off due to particle-particle contact. Then there is a slow exponential water loss during coalescence.

With a polymer solution of ethyl cellulose, the rate of solvent loss is proportional to the vapour pressure of the solvent. As the concentration of the solids in the solution increases, the viscosity of the polymer solution increases and the vapour pressure drops. With a drop in vapour pressure there is a concurrent decrease in the rate of solvent loss. Latex emulsions give up water more quickly and completely at lower drying rates-an advantage when the rate of film deposition must be controlled.

4.4.3 Mechanism of Film Formation

A film forming polymer latex is deposited from an aqueous colloidal dispersion of discrete polymer spheres. Individual submicrometer- size spheres, each containing hundreds of polymer chains, coalesces into a continuous film as the aqueous phase evaporates. A latex dispersion consists of spheres that are suspended and separated by electrostatic repulsion. As water evaporates, interfacial tension between water and polymer pushes particles into point contact in a closed packed ordered array. A strong driving force is necessary to overcome repulsive forces, deform the particles, and cause the spheres to fuse, resulting in complete coalescence capillarity fused by high surface tension of water provides the driving force to fuse the particles, and plasticizer inclusion in the dispersion swells and softens the

polymer spheres, facilitating coalescence and reducing minimum film formation temperatures.

As evaporation proceeds the force is exerted on the spherical particles. The polymer spheres are pulled closer together as a result of surface tension (water-air interfacial tension) or capillarity as the surrounding water film constricts. Energy required for the coalescence of spheres results from the surface tension of the polymer generated by the negative curvature of the particle surface may be described by Frenkel's Equation.

$$\theta^2 = 3\gamma t / 2\pi\eta r \qquad (4.2)$$

Where θ is one-half the angle of coalescence (contact angle) at time **t**, γ is the surface or interfacial tension, **r** is the radius of a sphere and η is the viscosity of the spheres.

This equation (4.2) illustrates the inverse relationship between internal viscosity (η) of the spheres and the driving force necessary to fuse or coalesce discrete particles. This is one reason for adding plasticizer to the film. Further, it is evident that smaller-radius (submicrometer) polymer spheres require less driving force (capillarity) to completely fuse of coalesce. The degree of coalescence, characterized by the contact angle, improves as the surface tension and polymer-water interfacial tension increases.

Brown [13] demonstrated that the water-air interfacial tension (30-70 dyne/cm) is a determining force in driving coalescence as evaporation proceeds, and Voyutskii [14] theorized about the inter diffusion of polymer chains (autohesion) across what was the interface between discrete polymer spheres. Autohesion, according to Voyutskii, is the final step in the formation of integral homogenous latex films.

4.4.4 Effect of Plasticizer

It has already been emphasized that controlled release dosage form is an interactive system where time dependent drug release must be viewed from the perspective of a total delivery system. This includes the polymeric film, the substrate, physico-chemical drug characteristics and the other components, such as insoluble film additives or surfactant to promote spreading. For controlled release dosage form, polymer - plasticizer interaction in latex emulsions must be considered as it primarily affects, in concert with drug and substrate, the nature and properties of rate-limiting system. The choice and level of plasticizer for latex emulsions have a demonstrated effect on release profiles of a model drug systems studied- strong and weak basic amines with a range of ionization constants.

Strength and cohesiveness of films deposited from organic solvent are measured by adequacy of salvation and maximum polymer chain extension as reflected in the viscosity of the solution. Other physical methods have been used to appraise the relative effectiveness of plasticizer – solvent systems including birefringence, vapour pressure, infrared absorption spectra and heat of solution. These methods are useful empirical control parameters for polymer solutions; however, for latex emulsions, different methods must be used to evaluate plasticizer effectiveness. A plasticizer is a substantially non-volatile, high-boiling, non-separating substance that changes certain physical and mechanical properties of a polymer to be plasticized. Polymeric films employ plasticizers to impart flexibility, improve flow, and reduce brittleness. These changes are caused by a decrease in the cumulative intermolecular forces along the polymer chain (reduction in cohesion), which generally decreases tensile strength, lowers the softening temperature, and decrease the glass transition temperature.

The basic requirements of any plasticizer in a polymer system, including latex emulsions, are compatibility and permanency. To be compatible, the plasticizer should be miscible with polymers which indicate similar molecular forces in the two component system. It has been theorized that the most effective plasticizers will generally resemble most closely in structure the polymers they plasticize.

For pseudo latex emulsion, plasticizer selection for maximum effectiveness is conditioned by two criteria:-

a) Glass transition temperature, and
b) Relative solubility parameters (miscibility).

4.4.5 Glass Transition Temperature

Discrete polymer spheres in a latex emulsion- normally a stiff, structured crystalline polymer must be softened and swelled by plasticizer incorporated into the emulsion. Theoretically, effective plasticization of a polymer particle should reduce the critical film forming temperature of the polymer. The reduction is accomplished by decreasing the glass transition temperature (Tg), the temperature at which a polymer undergoes a marked change in material properties. Most useful plasticizer for Aquacoat includes:

- Dibutyl sebacate.
- Diethyl phthalate.

- Triethyl citrate.
- Tributyl citrate.
- Acetylated monoglyceride.

4.4.6 Relative Solubility Parameters

Theoretically speaking, the suitability of a given plasticizer can be determined by miscibility based on solubility parameters as investigated by Hildebrand and Scott[15]. These can be calculated for polymer and plasticizer or found in the literature. In their calculation, Hildebrand and Scott relied on:

a) The molar energy of evaporation, and,
b) The density of cohesive energy as termed in an equation defining the solubility parameter of a known plasticizer.

Physical data are given for five plasticizers useful in sustained or controlled release applications of pseudo latexes for oral solid dosage form in Table 4.4 & 4.5.

Table 4.4 Physical constants of some common Plasticizers

Name of Plasticizer	B.P.(°C)	Vapour Density (Air = 1)	Vapour Pressure (mm Hg)	Water Solubility	Molecular Weight
Dibutyl sebacate	349	10.8	10 at 200°C	Negligible	282
Diethyl phthalate	298	7.66	100 at 220°C	Insoluble	222
Triethyl citrate	294	9.70	1 at 107°C	6.5%	276
Tributyl citrate	170	12.4	1 at 170°C	Insoluble	344
Acetyl tributyl citrate	173	14.1	0.8 at 170°C	Insoluble	402

Table 4.5 Solubility Parameter of some plasticizers

Plasticizer	Solubility Parameter $(J/m^3)^{1/2} X 10^{-3}$	Solubility Parameter $(Cal / cm^3)^{1/2}$
Ethyl cellulose	21.1	10.3
Diethyl phthalate	20.5	10
Dibutyl phthalate	19.00	9.3
Dibutyl sebecate	18.8	9.2

4.4.7 ACRYCOAT E30D – THE FIRST AQUEOUS POLYMERIC DISPERSION

Solvent based acrylic polymers have been used in the pharmaceutical industry for coating purposes for over 20 years. Recently, however, due to toxicity and environmental concerns, organic solvent-based coatings, including the acrylics, have given way to water-based system.

Acrycoat E30D, which contains 30% solids, is one of the first aqueous polymeric dispersions; it was marked initially in Europe and later in the United States for pharmaceutical applications in the name of Eudragit NE30D. It is prepared by emulsion polymerization and consists of neutral copolymers of ethyl acrylate, methyl methacrylate esters that are insoluble over the entire physiological pH range. It is thus suitable for the development of pH independent modified-release oral dosage forms, provided that the solubility of the drug is pH independent. Generally the polymeric dispersions has been combined with hydrophilic substances, such as polyethylene glycol, sugar and polyvinyl pyrolidone (PVP) and hydrophobic, water insoluble additives such as kaolin, talc and magnesium trisilicate to provide sustained release preparations. Also, properly formulated, the dispersion can be used to mask the taste and odour of the various bioactive agents. Some of the commonly used acrylic polymers are listed in Table 4.6.

4.4.8 Processing Conditions[9]

One of the most significant differences between aqueous polymeric solutions and dispersions is the role of water during film formation. In solutions, water is a solvent and drying is accompanied by an excessive increase in viscosity, which in turn suppresses the rate of evaporation. Excess energy is therefore required to drive off the water. In contrast, in polymeric dispersions, water is only as a dispersion medium and does not solvate the polymers. Consequently, less heat is needed to evaporate the water. This results in significant reduction in the processing time. These properties are especially critical when dealing with highly water-soluble or moisture sensitive compounds.

During the coating of pellets the product temperature should be kept around 26°C, especially when the coating is done in laboratory size coating machines. If the product temperature is maintained very high, the coating materials become tacky owing to the low glass transition temperature of the polymer. This leads to the pellets aggregation. The same criteria apply to tablets coated in a coating pan, where the temperatures of the cores should

be kept between 25°C and 30°C, particularly at the start of the drying process. Since the minimum film-formation temperature of the polymer is 20°C, these temperatures are not only high enough to drive off the water at a reasonable rate, but are also within the optimum temperature range for the formation of a continuous film. Further more, as long as it does not lead to drug migration into the film coat or instability of moisture-sensitive compounds operation at low temperature favors gradual spreading of the coating dispersions over the cores. This is followed by water evaporation, polymer deformation and fusion. As a result, a smooth and coherent film that is free from imperfections is formed.

4.4.9 Formulation Variables[9]

Although Acrycoat E30D dispersions can be theoretically used as is, in practice, it poses severe restrictions on the processing conditions. It also provides coatings that are highly impermeable to drug when used alone. It is therefore formulated with other pharmaceutical excipients to circumvent these practical problems.

Programmable release profiles can be obtained from Acrycoat E30D formulation upon addition of water soluble or water insoluble additives. While the conditions under which drug release is achieved are different for coatings that contain water soluble than those with water insoluble additives, the release rate is controlled in each by the proportion of the additives incorporated in the formulation. As the quantity of additive in the film coat is increased, the percentage drug released per unit time is correspondingly increased. Until a point is reached the integrity of the film is no longer maintained and immediate release is achieved. Another variable that affects the release rate is film thickness. An increasing film thickness is always accompanied by a decrease in release rate.

Plasticizers are generally incorporated into polymeric dispersions to soften the polymeric micropellets and enhance the film formation. While this is always true with pseudo latexes such as Aquacoat, addition of plasticizers to Acrycoat E30D formulations is not only unnecessary but may also be detrimental because it can increase the viscosity of the formulation and negate the distinct advantage of the dispersion over the polymeric solution. Incorporation of plasticizers can also augment the inherent tackiness of the film and complicate the coating process.

4.4.10 Mechanism of Drug Release[9]

During coating, the intermittent layering of the coating formulation on the substrate eventually produces a coating material that is characterized by channels and tortuous paths. The phenomenon is more pronounced with polymeric dispersions such as Acrycoat E30D than with solvent based coatings. In addition, the porosity of Acrycoat E30D coating can be increased through the incorporation of additives. pH sensitive and/or water soluble hydrophilic additives dissolve in the dissolution medium and leach out, thereby creating a micro porous membrane. Water insoluble additives also increase the porosity of Acrycoat coating by introducing imperfections. Therefore, during dissolution testing, predominant mechanism of drug release is believed to be the diffusion through the water filled pores as opposed to drug partition into, diffusion through and partition out of insoluble polymeric films.

Table 4.6 Polyacrylates used in Pharmaceuticals and Cosmetics

Grade	*Form of Supply*	*Polymer Content (% w/w)*	*Solubility*	*Solvents*	*Applications*	*Pharmaceutical Monogram*	*Storage Condition*	*Shelf Life*
Acrycoat L100	White Powder	95%	Insoluble in Gastric Fluid Soluble in intestinal fluid of pH 6.0 and upwards.	Alcohols, Acetone with 3% water	Enteric Coatings, Insulating layers, as binder for enteric granules, pH dependent release system	Methacrylic Acid Co-polymer Type 'A' USP. /NF.	Not above 40°C	5 years
Acrycoat L12.5	Solution in Isopropanol	12.5%		Alcohols Acetone				
Acrycoat L30D	Milky Aqueous Dispersion	30%	Soluble in water at pH 5.5 and upwards	Water, Alcohols, Acetone		Methacrylic Acid Co-polymer Type 'C' USP. / NF.	5°C to 40°C	2 years
Acrycoat L100D	White Powder	95%	Soluble in water at pH 5.5 and upwards	Water, Alcohols, Acetone				5 years
Acrycoat S 100	White Powder	95%	Insoluble in Gastric fluid Soluble in Intestinal fluid at pH 7.0 and upwards.	Alcohols, Acetone, with 3% water	Enteric coatings with slow release coating resist to tropical conditions, Sustained release formulations, pH dependent release systems.	Methacrylic Acid Co-polymer Type 'B' USP. /NF.	5°C to 40°C	5 years
Acrycoat S 12.5	Solution in Isopropanol	12.5%		Alcohols, Acetone.				
Acrycoat E 30D	Milky Aqueous Dispersion	30%	Swellable, soluble in water in any pH	Water, Alcohols, Acetone	Film Coatings, Sustained release, pH independent, transdermal systems	"Polyacrylate dispersion 30%" Ph.Europe	5°C to 40°C	2 years
Acrypol 934/974	White Powder	98%	Soluble in water, benzene, cyclohexane	Water, Hydroalcoholic solvents, Oil-water, Water-oil Systems.	Gels, Suspensions, Topical Preparation	'Carbomer' USP. /NF. Contains 56% to 68% carboxylic content or Polyacrylic acid.	Not above 40°C Protect from moisture	5 years
Acrypol 934P/974P					High purity oral pharma grade for Gel, Suspension, Controlled Release tablet, Taste masking			
Acrypol 940/980					Cosmetics, Topical Preparations			
Acrypol 941/971					Low viscous gels, Emulsion Stabilizer			

4.5 AQUEOUS POLYMERIC DISPERSIONS USED IN THE STUDIES

4.5.1 ACRYCOAT E30D (30% w/w POLYACRYLATE AQUEOUS DISPERSION)

Description:

ACRYCOAT E30D is an aqueous dispersion of a neutral acrylic co-polymer. Solubility is not pH dependent and films readily permeable to gastric juices. pH independent polymer for rapidly disintegrating film coating.

Features:

Clear colourless transparent lacquer films are formed. Colours can be added with pigment or food colours. Films permeable to gastric juices.

Solubility:

The aqueous dispersion is miscible with water in any proportion. A clear or slightly opalescent viscous dispersion can be obtained by mixing one part of ACRYCOAT E30D with five parts of acetone or Isopropanol.

Applications:

- Coating of tablets, pills, granules and powders, protecting the drug from surrounding environment, particularly air, moisture, light, thus provides required stability.
- Masking unpleasant taste and odour, thus overcoming non-compliance to patients.
- Providing product 'identity' for differentiating products from manufacturing and storage.
- Imparting cosmetic elegance to product appearance, masking of noticeable visible differences in tablet core from batch to batch.
- Reducing risk of interactions between incompatible ingredients.
- Improving mechanical integrity, eliminating possibility of abrasions, chipping etc.
- Isolating porous cores.

- Extending and improving storage properties.
- To improve compression characteristic during tableting (hardness, surface uniformity).

Controlled Release Tablets:

- As a binder and film former in the manufacture of porous matrix. Tablets or pellets (wet granulation) with delayed release of the active substance.
- As a film former, mixed with other dispersions to control permeability.

Transdermal Systems:

- To regulate release of drug from transdermal systems through the membrane.
- To improve the skin tolerability of transdermal therapeutic systems with occlusive properties.

Advantages:

- Less proportion of polymer is required.
- Low temperature for film formation.
- Neutral (pH independent) film formation.
- Stability over a broad temperature range.
- Exhibits excellent colour value and self gloss.
- Marginal weight gain in tablets.
- Hydrophobic.

Specifications:

Appearance	- milky white liquid.
Odour	- aromatic.
Content	- 28.5 to 31.5% w/w dry polymer.
Solubility	- water, alcohols, acetone.

Toxicity:

ACRYCOAT E30D is a high molecular weight polymer. It is not absorbed by body tissues and is totally safe for human consumption. Test for toxicological tolerance shows that it does not have any pronounced physiological action and is non-toxic.

Plasticizer:

Plasticizers are not necessary but permeabilities of polymer can be regulated by addition of polyethylene glycols, vinyl alcohol or pyrolidone as water soluble additives.

Precaution:

Coagulation may occur during formulation due to electrolytic effect, pH changes and foam formation by high speed stirring.

4.5.2 ACRYCOAT L30D (METHACRYLIC ACID CO-POLYMER, TYPE – C)

Acrycoat L30D, a 30% w/w aqueous dispersion of copolymer of poly (methacrylic acid ethylacrylate) esters. Copolymers of methyl methacrylic acid and ethyl acrylate as ester components with methacrylic acid are used as enteric coatings, because they contain carboxylic groups that are transformed to carboxylate groups in the pH range of 5-7 by salt formation with alkali and amines. In pure water and diluted acids they form water insoluble films resistant to gastric juices. They are popularly applied in formulating preparations which shows pH dependant drug release.

Description:

ACRYCOAT L30D is an aqueous dispersion of a neutral co-polymer which conforms to USP /NF specifications of 'METHACRYLIC ACID CO-POLYMER', TYPE – C.

Features:

- **Appearance:** ACRYCOAT L30D forms colourless and transparent film in presence of plasticizers. Pigments can be added to colour the film.

- **Solubility:** ACRYCOAT L30D films are insoluble in pure water, in buffer solutions below pH 5.5 and gastric juices. ACRYCOAT L30D films are soluble in neutral to weakly alkaline region of the digestive tract, in intestinal fluids and buffer solutions above pH 5.5.

Applications:

- Enteric coating for resistance to gastric fluid, (to protect active drug from influence of acid, prevent irritation of gastric mucosa).
- Film coating of tablets, pills for protecting the drug from surrounding environment, particularly air, moisture, light, thus providing required stability.
- Masking unpleasant taste and odour, thus overcoming resistance to drug in ingestion.
- Providing product 'identity' for differentiation of products from manufacturing and storage.
- Imparting cosmetic elegance to product appearance, masking of any noticeable differences in tablet core from batch to batch.
- Reducing risk of interactions between incompatible ingredients.
- Improve mechanical integrity, eliminating possibility of abrasions, chipping etc.
- Insulating hygroscopic cores.
- Isolating porous cores.
- Extending and improving storage properties.

Advantages:

- Miscible with water in any proportion.
- Small quantity required, hence reducing volume of dispersion for coating.
- Low temperature required for film forming.
- Exhibits excellent colour value.
- Stability over a wide temperature range.
- Marginal weight gain in tablets.
- Hydrophobic.

Specifications: ACRYCOAT L30D

Appearance - milky white liquid.

Odour - mild aromatic or slightly aromatic.

Content - 28.5 to 31.5% w/w dry polymer.

Acid Value - 300 – 330 mg KOH/gm dry polymer.

Solubility - water, alcohols and acetone.

Toxicity:

ACRYCOAT L30D is a high molecular weight polymer. It is not absorbed by body tissues and is totally safe for oral consumption. Test for toxicological tolerance shows that it does not have pronounced physiological action and is non-toxic.

Plasticizer:

ACRYCOAT L30D film is brittle in nature. To improve film elasticity use of plasticizer is strongly recommended. The recommended plasticizers are polyethylene glycol, triacetin, triethyl citrate etc. Usually 10% of plasticizer is sufficient, but can be increased to 25%.

4.5.3 ACRYCOAT S100 (METHACRYLIC ACID CO-POLYMER TYPE - B)

Acrycoat S100, a free flowing powder containing 95% w/w solid polymer is sparingly soluble in water but soluble in alcohol and acetone with 3% v/v water. Being copolymers of Methacrylic acid, they are widely used as slow release enteric coating in tablet and capsule manufacturing industry. They are insoluble in gastric fluid but freely soluble in intestinal fluid of pH 7 and above. They are popularly applied in formulating sustained release pH dependant formulations.

Description:

ACRYCOAT S100 is an anionic co-polymer which conforms to USP /NF specifications of 'METHACRYLIC ACID CO-POLYMER' TYPE- B. It is insoluble in acids and pure water, soluble in neutral to weakly alkaline medium.

Features:

- Appearance: ACRYCOAT S100 films are colourless and transparent, desired colour can be obtained by adding pigments.
- Solubility: Insoluble in water, in buffer solution below pH 7.0 and gastric fluids. Soluble in the region of the intestinal tract, where the fluids are neutral to weakly alkaline and in buffer solutions above pH 7.0.

Applications:

- Enteric coating for resistance to gastric fluid, (to protect active drug from influence of acids, prevent irritation of gastric mucosa), or to delay drug release in the intestine, when thick coatings are applied.
- Enteric coating of tablets, pills for protecting the drug from surrounding environment, particularly air, moisture, light thus maintaining required stability.
- Masking unpleasant taste and odour, thus overcoming non-compliance to patients.
- Providing product 'identity' for differentiation of products from manufacturing and storage.
- Imparting cosmetic elegance to product appearance, masking of any noticeable differences in tablet core from batch to batch.
- Reducing risk of interactions between incompatible ingredients.
- Improves mechanical integrity, eliminating possibility of abrasions, chipping etc.
- Insulating hygroscopic cores.
- Isolating porous cores.
- Extending and improving storage properties.
- As a binder of film former in the manufacture of porous matrix tablets (wet granulations) with delayed release of the active substance.
- Used to sustain the release of drug from tablets, granules etc.

Advantages:

- Option of solvent or semi aqueous media.
- Less quantity required, reducing volume of solution, so shortening production time.
- Stability over a broad temperature range.

- Exhibits excellent colour value.
- Marginal weight gain in tablets.
- Hydrophobic.

Specifications:

Appearance	-	white, fine, free flowing powder.
Odour	-	weakly aromatic.
Content	-	min. 95% dry polymer.
Acid Value	-	180 – 200 mg KOH/gm dry substances.
Solubility	-	Isopropyl alcohol, acetone, methanol, Ethanol etc.

Toxicity:

ACRYCOAT S100 is a high molecular weight polymer. It is not absorbed by body tissues and is totally safe for human oral consumption. Test for toxicological tolerance show that it does not have pronounced physiological action and is non-toxic.

Plasticizer:

ACRYCOAT S100 films are brittle to improve film elasticity, use of plasticizer is strongly recommended. The recommended plasticizers are poly-ethylene glycol, dibutyl phthalate, castor oil, diethyl phthalate, triacetin, triethyl citrate etc. Usually 10% of plasticizers will be sufficient, but if necessary, can be increased upto 25%.

4.6 SURELEASE (AQUEOUS ETHYL CELLULOSE DISPERSION)

Definition:

Surelease[9,16] is a complete, optimally plasticized aqueous dispersion of Ethylcellulose (Ethylcellulose is a partly O-ethylated cellulose) designed specifically for modified release and taste masking application. Using Ethylcellulose as the rate-controlling polymer, Surelease brings technological advances with dependable, reproducible extended release profile that are consistent from laboratory to pilot and production scale processes. It is a complete, ready to use system.

Composition:

Surelease is composed of water, ethyl cellulose, oleic acid, dibutyl sebacetate or esters of fatty acids and ammonia hydroxide.

Polymer:

Ethylcellulose has long history of use in the pharmaceutical industry as a controlled release polymer. It forms a relatively impermeable barrier. Due to its water insolubility, it has been finely dispersed in the Surelease system. It provides a highly durable film with excellent surface integrity. Dissolution profiles are independent of pH. Reduction of solid content from 25% to 15% w/w by distilled water facilitates ease of spraying.

Plasticizer:

Dibutyl sebacetate, esterified fatty acids and oleic acid are the plasticizers for the Surelease formulations. In the manufacturing process they are incorporated in the dispersed polymer particles to achieve a consistent and effective plasticizer level.

Advantages:

a) **Environment friendly and easy to use.**
b) **Consistent and reproducible drug release profiles**
c) **Aqueous form of dispersions.**
d) **Internationally regulatory acceptance.**
e) **Optimally formulated system.**

Applications:

a) **Coating of particles, pellets and tablets using fluidized bed technique.**
b) **As a binder for wet granulation in the development of matrix tablets.**
c) **Taste masking.**
d) **Release controlling polymer.**

Specifications:

# Description:	Off white turbid liquid that dries to a clear film
# Identification:	Solid content - 24 -26 % w/w
# pH:	9.5 – 11.5
# Specific Gravity:	1.00 – 1.05

Mechanism of drug release:

Surelease forms a virtually insoluble membrane around the core of the drug. The drug must then diffuse through the membrane and into the surrounding fluid.

Shelf-life and Storage:

The shelf-life is 18 months from the date of manufacture. The polymer is to be stored in a sealed containers avoiding exposure to heat and moisture. Need not to freeze.

4.7 METHOCEL K15M (HYDROXY PROPYL METHYL CELLULOSE)

Non proprietary names:

USP[1] : Hydroxypropyl methyl cellulose. BP[2] : Hypromellose.

Definition[1,2,3]:

Hydroxypropyl methyl cellulose (HPMC) is partly O-methylated and O-(-2-hydroxypropylated) cellulose. It is available in general grades, which vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of apparent viscosity, in mPas (milli Pascal), of a 2% w/w aqueous solution at 20°C. HPMC, defined in the USP XXII, specifies the substitution type by appending a four digit number to the nonproprietary name, e.g. HPMC 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxy group ($OCH_2CHOHCH_3$), calculated on a dried basis. Molecular weight is approximately 10,000 – 15, 00,000. HPMC is an odorless and tasteless, white or creamy-white coloured fibrous or granular powder[3,4].

Specifications[2,3,4]

#	Acidity/alkalinity	: pH: 5.5 – 5.8 for a 1% w/w aqueous solution.
#	Ash	: 1.5% - 3.0%, depending upon the grade.
#	Auto ignition temperature	: 360°C.
#	Density (tapped)	: 0.50 – 0.70 g/cm^3 for Pharmacoat.[17]
#	Melting point	: browns at 190 – 200°C; chars at 225 – 230°C.
#	Glass transition temperature	: 170 – 180°C.
#	Specific Gravity	: 1.26.

Solubility : Soluble in cold water, ethanol and dichloromethane, insoluble in chloroform, ethanol, and ether

Advantages:

a) **Non toxic.**
b) **Non irritant, especially to eyes.**
c) **Consistent viscosities.**
d) **Safe for use in pharmaceuticals, cosmetics as well as food products.**
e) **Soluble in cold water.**
f) **Dissolution rate shifts with pH, hence suitable for slow release enteric formulations.**
g) **Being nonionic, doesn't form complex with metallic salts and ionic organic compounds.**

Applications:

a) **Tablet binder**[18,19]
b) **Film Coating**[20-24]
c) **Extended Release matrix**[25-28]
d) **Thickening agent for ophthalmic preparations**
e) **Film former**
f) **Emulsifier**
g) **Suspending agent in topical gels**
h) **Stabilizing agent in ointments**
i) **Protective colloid in suspension**
j) **Adhesive in plastic bandages**
k) **Wetting agent in hard contact lenses**
l) **Cosmetics and Food products**

Stability and Storage:

Solutions are stable at pH 3-11. At higher temperature, the viscosity of solutions reduces. Upon heating and cooling a reversible sol to gel transformation occurs. Aqueous solutions are liable to enzyme resistant but liable to microbial spoilage, hence preservatives are used in eye preparations. HPMC powder should be stored in well closed container, in a cool, dry place.

4.8 REFERENCES

1. *United States Pharmacopeia* XXV, United States Pharmacopoeial Convention, Inc., Asian Edition, 2002, 882-883, 2617, 2643-2644.
2. *British Pharmacopoeia*, British Pharmacopoeia Commission, London, 2000, 841, 1376, 1604.
3. A.Wade and P.J.Weller, *Handbook of Pharmaceutical Excipients*, 2nd Edition, American Pharmaceutical Association, Washington & The Pharmaceutical Press, London, 1994, 229, 428, 562.
4. *Indian Pharmacopoeia*, Vol. 1, Controller of Publication, New Delhi, 1996, 127, 382, 680.
5. T.E.Wallis, *A Textbook of Pharmacognosy*, 5th edition, CBS Publishers and Distributors, 1985, 467-69.
6. E.R.Morris, D.A. Rees, D.Thom, *Carobohydrate Research*, **66**, 1978, 145-54.
7. D.Thom, G.T.Grant, E.R.Morris and D.A.Rees, *Carobohydrate Research*, **100**, 1982, 29-41.
8. A. Penman and G.R.Sanderson, *Carobohydrate Research*, **25**, 1972, 273-82.
9. James W. Mc. Ginity, *Aqueous polymeric coatings for pharmaceutical dosage forms*, 2nd Edition, Marcel Dekker, 1997, 355, 381.
10. J.W.Nicholson and E.A.Wasson, *Film Spreading and Film Formation by Waterborne Coatings in Surface Coatings*, Chapter 2, **Vol. 3**, Kluwer Academic Publishers, 91-123, 1990.
11. J.Bandrup and E.H.Immergut (Eds.), Polymer handbook, 3rd Edition, Wiley, New York, 1973.
12. J.W. Vanderhoff, E.B. Bradford and W.K. Carrington, *J. Polymer Science*, Polymer Symposium, **41**, 1973,155-174.
13. H.R. Brown, C. Creton and V.R. Deline, *Macromolecules*, **27 (7)**, 1994, 1774-1780.
14. S.S. Voyutskii, *J. Polymer Science*, **32 (125)**, 1958, 528-530.
15. J. H. Hildebrand and R. L. Scott, *Solubility of Nonelectrolytes*, 3rd Edition, Rheinhold Publishing Company, New York, 1949
16. *Surelease Product Bulletin*, Colorcon, West Point, USA, 1995.
17. R.C.Rowe, *J.Pharmacy Pharmacology*, 1977, **29**, 723 - 726.
18. H.C.Wilson and G.W.Cuff, *J.Pharmaceutical Sciences*, 1989, **78**, 582 – 584.
19. Z.T.Chouhan, *J.Pharmaceutical Sciences*, **69**, 1980, 1-4.

20. R.C.Rowe, *J.Pharmacy Pharmacology*, **32**, 1980, 116 – 119.
21. G.Banker, G.Peck, S.Jan and P.Pirskitikulr, *Drug Development & Industrial Pharmacy*; **7**, 1981,693 – 716.
22. A.O.Okhamafe and P.York, *J.Pharmacy Pharmacology*, **34** (suppl), 1982, 53.
23. D.A.Alderman and G.J.Schulz, **US Patent 4816298**, 1989.
24. M.K.Patel, **US Patent 4916161**, 1990.
25. J.G.Hardy, J.W.Kennrley, M.J.Taylor, C.G.Wilson and S.S.Davis, *J.Pharmacy Pharmacology*, **34** (Suppl.), 1982, 91.
26. J.F.Hogan, *Drug Development & Industrial Pharmacy*, **15**, 1989,975 – 999.
27. A.C.Shah, N.J.Britten, L.S.Olanoff and J.N.Badalament, *J.Controlled Release*, **9**, 1989,169 – 175.
28. H.C.Wilson and G.W.Cuff, *J.Pharmacy Pharmacology*, 1989, **78**, 582 – 584.