CHAPTER II

LITERATURE REVIEW

Oral Sustained Release Dosage Forms

Over the past decades, the treatment of illness has been accomplished by administering drugs to the human body via various pharmaceutical dosage forms, like tablets, capsules, pills, creams, ointments, liquid, aerosols, injectables, and suppositories. To achieve and maintain the drug concentration in the body within the therapeutic range required for a medication, it is often necessary to take this type of drug-delivery system several times a day. The limitations of conventional dosage forms appear then since they cause problems in maintaining therapeutic drug levels over only brief duration of time (Vergnaud, 1993). These limitations include:

1. The fluctuating drug levels with conventional dosage forms lead to an insufficient efficacy of therapy provoking an excessive use of drug.

2. Overdosage appearing after dissolution of drug may be responsible for a high frequency of side effects, leading to iatrogenic damage.

3. High frequency of administration of conventional dosage forms is limited by the reliability of the patient and the patient compliance.

4. A potent drug may largely lose its therapeutic efficacy through improper formulation, and thus a pharmacologically active substance is not neccessarily an effective drug.

Dosage systems able to release the drug at a constant rate for a given time period are thus of interest. The result is then a constant uniform concentration of drug in blood and tissues over a given period of time, with the following advantages:

1. Significant smaller amounts of drug are generally prescribed with a therapeutic system of drug delivery.

2. The reduced amount of drug administered reduces the problems of side effects, improving the safety of therapy.

3. The patient compliance is usually better with these types of dosage forms, as the frequency of administration is considerably lower.

The term oral sustained release is in common usage to describe orally administered drug products that modulate the time course of drug concentration on the body by releasing the drug over extended time periods. Simple oral dosage forms capable of controlling the release of the drug are often and easily obtained with monolithic devices where the drug is dispersed in a biocompatible polymer. This polymer which can be either biodegradable or nondegradable, plays the role of a polymer

matrix. Not only the polymer brings the consistency to the dosage form, but also it controlls the release of the drug. The process is generally as follows: the liquid (gastric or intestinal liquid) enters the polymer, dissolves the drug and enables the drug to leave out the dosage form through the liquid located in the dosage form. The matter transfers for the liquid and for the drug are controlled by transient diffusion, with concentration-dependent diffusivities, the diffusivity of the drug depending on the concentration of the liquid in the dosage form. The release of the drug being controlled by transient diffusion, exhibits a rather high rate at the beginning of the process which decrease with time in an exponential way. These dosage forms are very simple to prepare and rather inexpensive, but the process of release is controlled by diffusion, and the rate of release is far from being constant. In general there are many ways of preparing these dosage forms, but in the present study only the methods of matrix system and solid dispersion are focused.

Matrix System

The matrix system consists of a drug and a polymer being mixed homogeneously. The polymers used in the system may be divided into two categories, the hydrophilic or swellable polymers and the insoluble polymers. This system is normally formulated as oral dosage form in the form of capsules or tablets. In order to achieve the required drug release rate it is necessary to select the appropriate type and amount of the polymers.

Tablets containing either insoluble wax and polymer material or hydrophilic polymers are widely utilized in sustained release products. Carnauba wax, beeswax, glyceryl monostearate, stearyl alcohol, stearic acid, polyvinyl chloride, ethylcellulose and cellulose acetate are some of typical insoluble matrix materials.

Hydrophilic polymers with high gelling capacities have been studied exstensively as matrix systems to formulate an oral sustained-release formulation especially tablet dosage form. These polymers have been incorporated with drug and then being fabricated into tablets. The polymers suggested for use can be classified into three broad groups (Vazquez et al, 1992).

1. Non-cellulose natural or semisynthetic polymers

These are products of vegetable origin and are used as such - agar-agar (Vazquez et al., 1992), alginates (Nicholson et al., 1990), molasses (Uko-Nne and Mendes, 1982; Uko-Nne, Mendes, and Jambhekar, 1989a; Uko-Nne, Mendes, and Jambhekar, 1989b) - or after being transformed via semisynthesis or physical processed - Jaguar (Vazquez et al., 1992), chitosan (Bosmeier, Oh, and Pramar, 1989; Kawashima et al., 1985; Nigalaye, Adusumilli, and Bolton, 1990). Modified starches are being tried in this last respect (Herman and Remon, 1989; Herman and Remon, 1990; Herman, Remon, and DeVider, 1989; Visavarungroj, Herman, and Remon, 1990).

2. Polymers of acrylic acid

These products are arranged in the Carbomer group (American Pharmaceutical Association, 1986) and commercialized under the name of Carbopol (Perez-Marcos et al., 1991). The most-used variety is termed 934. The ionic nature of these polymers means that the gelling process is dependent on the pH of the medium.

3. Cellulose ethers

This group of semisynthetic cellulose derivatives is the one which has found the most applications in hydrophilic matrices. The ones most used are non-ionic (gelling efficacy independent of pH of medium), in particular the most viscous varieties of hydroxypropyl methylcellulose (Alderman, 1984). The methycelluloses (Ranga-Rao, Padmalatha Devi, and Buri, 1988), in contrast , have not proved especially useful in this field. In the last few years a number of interesting applications of the ionic sodium carboxymethylcellulose have been found (Baveja, Ranga-Rao, and Padmalatha Devi, 1988; Ranga-Rao, Padmalatha Devi, and Buri, 1988).

Solid Dispersions

The most widely used definition of solid dispersions is that put forward by Chiou and Riegelman (1971). The term refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting, solvent, or melting-solvent method. Depending on whether the matrix is water soluble, the drug's dissolution can be decreased or enhanced. A water-soluble carrier results in a fast

release of drug from the matrix, and a poorly soluble or insoluble carrier lead to a slower release of the drug.

Solid dispersions can be obtained by three main procedures; melting method (fusion technique), solvent method (coprecipitation technique) and melting-solvent method (Chiou and Reigelman, 1971). In melting method, the physical mixture of a drug and a carrier was heated directly until it melted. The melt mixture was then cooled and solidified rapidly in an ice bath under vigorous stirring. The final solid mass was crashed, pulverized, and sieved. Solvent or coprecipitation method entails the dissolution of a physical mixture of drug and carrier in a common solvent, followed by evaporation of the solvent and resultant coprecipitation of drug and carrier. In general the coprecipitation can be accomplished by three procedures; simple evaporation, lyophilization and spray drying. The last two procedures are appropriate for large-scale productions of coprecipitates. Melting-solvent method was first employed by Chiou and Smith (1971) . They formed solid dispersions by dissolving the solid active ingredients in a solvent and subsequently incorporating the solution into a molten carrier. The mixture was then solidified. In cases where the active constituent was a liquid, the liquid was simply mixed with the molten carrier and solidified by cooling.

Optimization Strategy

The pharmaceutical industry is currently applying principles of optimization, which was developed by the aerospace industry to assure the performance of the many components and systems of a rocket or space vehicle with mathematical certainty, to pharmaceutical

manufacturing operation and to producrt design (Schwartz, 1990). The word optimize is difined as follows: to make as perfect, effective, or functional as possible (Schwartz, 1990). The term optimization is used often in pharmacy with respect to formulation and to processing, and one will even find it in the literature referring to any study of the formula.

In drug product design the formulator is frequently faced with many interactive effects and with competing objectives. Formulation or processing steps taken to affect one set of product properties or quality features, such as tablet hardness, resistance to friability, and good shipping and handling properties, may affect other properties, such as tablet disintegration, drug dissolution release, bioavailability, tablet weight-to-volume relationships, tablet appearance, and even processing factors. Frequently, objectives are found to be competing. For example, as the tablet is made harder to have better handling of shipping properties, the disintegration, dissolution, and bioavailability properties may become less satisfactory. Optimization is done through mathematical modeling, wherein the relationship between the controllable or independent variables (formulation and processing variables that the development pharmacist can control and vary) and the dependent variables (product quanlity features or physicochemical properties) is quantitatively established. The formulator can then study various alternatives by plugging hypothetical numbers into the model. If, for example, the tablet hardness or mechanical stability specification is relaxed slightly, and the effect on drug dissolution or bioavailability properties is greatly enhanced, this would be a good alternative to make on one property to favor another. Optimization modeling also allows placing a constraint (minimum or maximum value) on a primary objective, such as the

bioavailability property requirement, and then maximizing (making them as good as mathematically possible) the remaining features. A further advantage of optimization is that the pharmaceutical scientists can now quantitatively know how close the final product is to being an optimum product from all its various quality standpoints. Optimization may require additional work to establish the necessary relationships between independent and dependent variables, but the optimization approach first applied in the aerospace industry has obvious great potential in the pharmaceutical industry in the design of optimally safe, effective, and reliable drug products.

Optimization Methods

There are two general approaches to optimization which relate to the way in which the experimentation is conducted (Gould, 1984).

1. Model-independent methods

This approach does not rely on the generation of a model and requires only limited initial experimentation. The main body of the experimentation is then conducted within the framework of the optimization process.

2. Model-dependent methods

In this approach a mathematical model is generated following some limited experimentation. Graphical or numerical analysis of this model is then conducted which allow the optimum conditions for a series of variables to be established.

Model-Independent Optimization

The first approach to optimization is using the model independent methods, which assume nothing about the mathematic model and search, as the experimentation proceeds, for the optimum response. They are therefore interactive methods, ideally suited to formulation development. In this approach the experimentation is completed before the optimization take places. This type of optimization is represented by evolutionary operations (EVOP) and the simplex methods (Franz, Browne, and Lewis, 1990).

1. Evolutionary Operation

Evolutionary operation (EVOP) is a sequential optimization technique designed to be performed by process operators during full-scale manufacturing without endangering the final product (Franz et al., 1990). The procedure involves performing a set of experiments, typically a factorial design with a centerpoint, inside the range of operating conditions that will give acceptable product (Rubenstein, 1975). Changes in the processing variables are usually quite small, and often a large number of experiments is necessary to discern the effect of a variable from the experimental error. In an industrial process, this large number of experiments is usually not a problem since the process will be run over and over again. When one set of data has been collected at all design points, a "cycle" is said to have been completed. Usually, a single cycle is not sufficient to detect any significant change in the response, so the experiments are repeated at the same designed points (i.e. cycle 2). Additional cycles are performed until one or more processing variables,

interactions, or the mean response proves to be significantly different from the experimental error. An estimate of the experimental error is obtained from the cycle data. After a significant effect has been detected, one "phase" is said to have been completed and the processing variables are adjusted in a direction that improves the operation. The objection, as always, is to move in the direction of the optimum response. The application of this technique to tablets has been advocated by Rubenstein (1975).

2. The Simplex Method

The simplex approach to the optimum is also an experimental method and has been applied more widely to pharmaceutical systems. In brief, this method uses the results of previous experiments in a mathematically rigorous fashion to define the parameters for the next experiment in the search for the optimum response. The method derives its name from a geometric figure, defined by a number of points (vertices) equal to one more than the number of variables in the space, which moves along the response surface in search of the optimum. Thus, a simplex of two variables is a triangle, and it moves away from low responses usually by reflection as shown in Figure 1 (Gould, 1984). In the figure, the triangle ABC defines the first simplex produced from the results of three experiments. The vertex A defines the worst response and according to the simplex rules, this response is reflected through BC to D. The new simplex is then defined by vertices BCD. Vertex C is now the worst response so the simplex reflects through BD to E. By a similar process the new response moves to F and thus in three moves (experiments) the response has moved close to the optimum value. It is

also clear from Figure 1 that to locate the optimum directly, point F should be 'expanded' along the line CF to the optimum. This process of 'expansion' and also contraction greatly accelerates the rate at which the simplex approaches, and improves the way it fits, the response surface being studied.

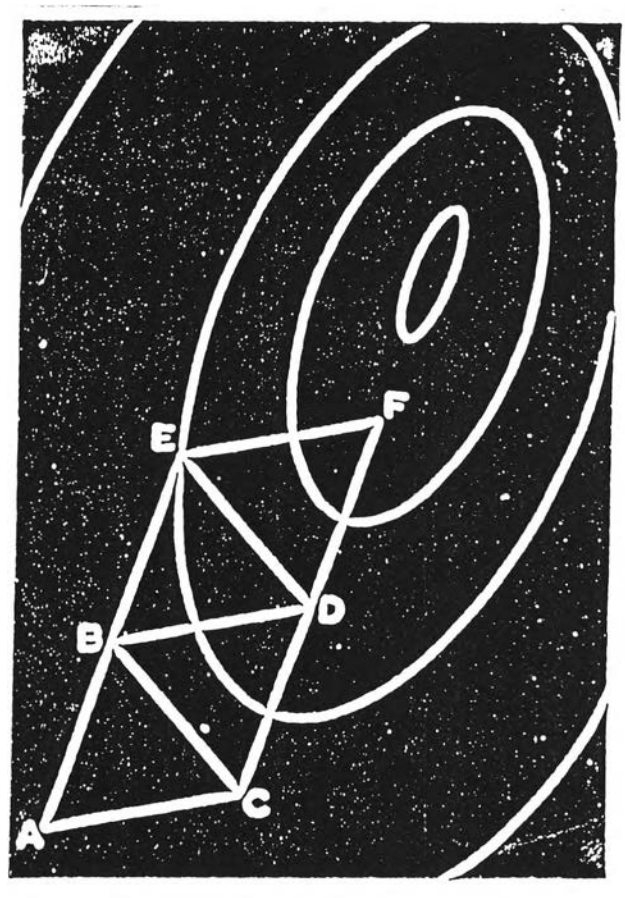


Figure 1. Progress of two-dimentional simplex toward optimum.

With respect to pharmaceutical formulations, the simplex method was utilized by Shek, Ghani, and Jones (1980) to search for an optimum capsule formula. This report also describes the necessary techniques of reflection, expansion, and contraction regarding the appropriate geometric figures. Gould and Goodman (1983), optimized the levels of propylene glycol and ethanol to produce the maximum solubility of caffeine in a mixed cosolvent aqueous parenteral formulation.

Model-Dependent Optimization

With the model-dependent methods, experimentation at various points in the variable domains are conducted, thereby defining the universe of the response variables. For the techniques of this type, it is necessary that the relationship between any dependent variable and the one or more independent variables be known. Since much of the work in the pharmaceutics has been in the pursuit of such relationships, therefore it remains the task of the formulator to generate the relationships between the variables for the particular formulation and process. Usually, an empirical mathematical model is developed using multiple regression. In general, however, there is more than one important variables, so the experimentor must enter into the realm of "statistical design of experiments ".

Statistical Experimental design

The concept of statistical experimental design necessary for optimization techniques is that there are designs available for selecting one's experimental points so that the entire area of interest is covered or

considered and analysis of the results will allow separation of variables. The latter one will allow performance of statistical analysis which permits the experimentor to know which variable caused a specific result. Frequently a factorial design (Armstrong and James, 1990) is employed setting various levels (eg. high, medium, low) for the system variables. The other designs commonly used are the central composite design and the Plakette-Burman design (Armstrong and James, 1990). Recently, the design using Hadamard matrix with the merit of fewer experiment number has been utilized (Romero et al., 1989). In general, the experimental designs employed in optimizatin are orthogonal designs. Orthogonality can be thought of, in a geometric sense, as two perpendicular lines, neither having an effect on the direction of the other. The use of orthogonal designs not only simplfies the calculations used in the analysis but also guarantees that the treatment effects on the measured response can be estimated independently. From a statistical standpoint, this is highly desirable because independent tests of hypothesis (e.g., the F-test) can be made on each treatment in the design.

Hadamard Matrix

When studying an experimental response depending on k parameters and for which a linear model is assumed, the statistical theory of experimental design provides optimal experimental strategies (orthogonal designs) leading to the best accuracy from a minimal experiment number. The determination of an optimal strategy requires the introduction of the notion of a matrix of experiments.

Let a reduced variable X_i is associated to each parameter P_i so that:

$$X_i = \frac{2\,(P_i - P_{mean})}{P_{max} - P_{min}}$$

P_{mean} , P_{min} and P_{max} being respectively the mean, minima and maxima values of P_i. One interest of such variables is a single variation range between the levels -1 and +1 for any parameter.

Then the matrix of experiments is a matrix containing k+1 rows and k columns, each row corresponding to an experiment and each column to a variable. The term located in row i and column j has a value for the reduced variable X_i during experiment j. Ozil and Rochat (1988) has demonstrated that an optimal strategy is obtained when the matrix of experiments is an Hadamard matrix H(N). Such matrix may be built easily from a method presented by Plackette and Burman in 1946. This method is valid when k+1 is a power of 2. By this method only two formula are required:

$$H(1) = [1]$$

$$H(2n) = \begin{matrix} H(n) & H(n) \\ H(n) & -H(n) \end{matrix}$$

from which one obtained successively:

$$H(2) = \begin{matrix} H(1) & H(1) \\ H(1) & -H(1) \end{matrix} = \begin{matrix} 1 & 1 \\ 1 & -1 \end{matrix}$$

$$H(4)=\begin{matrix} H(2) & H(2) \\ H(2) & -H(2) \end{matrix} = \begin{matrix} 1 & 1 & 1 & 1 \\ 1 & -1 & 1 & -1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & -1 & 1 \end{matrix}$$

and so on. In Hadamard matrix H(N) the number of parameters that can be studied accurately on their main effects is equal to N-1.

When the reduced variables X_i are used for studying the main effects of four parameters, the linear model becomes:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + \text{Residue}$$

and its determination implies the evaluation of 5 coefficients, i.e. 5 experimints at least. Since four parameters are studied then the Hadamard matrix H(8) must be used as an optimal strategy for studying a response depending on these four parameters. This matrix can be built easily by addition of 3 dummy variables X_5, X_6 and X_7 yielding the matrix of a system with 7 parameters as an Hadamard martix H(8).

$$H(8)=\begin{matrix} H(4) & H(4) \\ H(4) & -H(4) \end{matrix}$$

$$= \begin{matrix} & 1 & 2 & 3 & 4 & 5 & 6 & 7 \\ 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 \\ 1 & 1 & -1 & -1 & 1 & 1 & -1 & -1 \\ 1 & -1 & -1 & 1 & 1 & -1 & -1 & 1 \\ 1 & 1 & 1 & 1 & -1 & -1 & -1 & -1 \\ 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 \\ 1 & 1 & -1 & -1 & -1 & -1 & 1 & 1 \\ 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 \end{matrix}$$

The suppression of the first column and of the three ones corresponding to the dummy variables leads to the matrix of experiments (D) :

$$D = \begin{matrix} 1 & 2 & 3 & 4 \\ 1 & 1 & 1 & 1 \\ -1 & 1 & -1 & 1 \\ 1 & -1 & -1 & 1 \\ -1 & -1 & 1 & 1 \\ 1 & 1 & 1 & -1 \\ -1 & 1 & -1 & -1 \\ 1 & -1 & -1 & -1 \\ -1 & -1 & 1 & -1 \end{matrix}$$

When coming back to the original units of variables, the experiments to be performed are obtained easily. For this matrix each row represents an experiment while each column represents the levels of four parameters to be studied. Such a design allows one to optimize the data exploitation according to the model:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_5X_5 + b_6X_6 + b_7X_7$$

Evidently each individual term appearing in the sum: $b_5X_5 + b_6X_6 + b_7X_7$ has no physical sense but this sum replaces the experimental error ε and so should negligible if the proposed model is valid.

Factorial Design

Factorial designs are widely used in experiments involving the study of the effects of two or more factors. By a factorial design all possible combinations of the levels of the factors are investigated. For

example, if there are ***a*** levels of factor A and ***b*** levels of factor B, then each complete trial of the experiment contains all ***ab*** treatment combinations.

The effect of a factor is defined to be the change in response produced by a change in the level of the factor. This is frequently called a main effect because it refers to the primary factors of interest in the experiment. The main effect of factor A could be thought of as the difference between the average response at the first level of A and the average response at the second level of A. In some experiments the difference in response between the levels of one factor is not the same at all levels of the other factors. When this occurs, there is an interaction between the factors.

1. Full Factorial

The full factorial design is designated by the following nomenclature:

$$N = L^k$$

where

k = number of variables
L = number of variable levels
N = number of experimental trials

The optimization procedure is facilitated by construction of an equation that describes the experimental results as a function of the factor levels. A polynomial equation can be constructed, in the case of a factorial design, where the coefficients in the equation are related to the effects and interactions of the factors. The equation that can be constructed from a two-level factorial (2^k) experiment is of the following form:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + ... + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + ... + b_{123}X_1X_2X_3 + ...$$

where Y is the measured response, X_i is the level of the ith factor, b_i , b_{ij} , b_{ijk} , ... represent coefficients computed from the responses of the fomulations in the design, b_0 represents an intercept.

The use of three-level factorial (3^k) designs are useful for obtaining curvature in a model since it implies non-linear relationships between the factors and the response. It should be noted that only first-order regression models can be obtained from unaugmented 2^k designs.

1.1 Construction of 2^k Factorial Design

Prior to construct the 2^k factorial design, the following agreements are made. The levels of any factor are assigned by + for high level and by - for low level. As shown in Table 1 for 2^3 factorial design, the low and high levels of factors in a particular run are denoted by the absence and presence of the letter, respectively. For example, if all factors are at their low level, the run is denoted as (*1*). If factor A is at its high level, and B and C are at their low levels, the notation ***a*** is used. If factors

Table 1. Eight Experiments for a 2^3 Factorial Design.

Combination	A	B	C
(1)	-	-	-
a	+	-	-
b	-	+	-
ab	+	+	-
c	-	-	+
ac	+	-	+
bc	-	+	+
abc	+	+	+

Table 2. Transformed Levels of Factors Showing Signs to Be Used to Determine Effects and Polynomial Coefficients.

Combination	A	B	C
(1)	-1	-1	-1
a	+1	-1	-1
b	-1	+1	-1
ab	+1	+1	-1
c	-1	-1	+1
ac	+1	-1	+1
bc	-1	+1	+1
abc	+1	+1	+1

A and B are at their high levels, and C is at its low level, the notation ***ab*** is used, and so on.

The 2^k factorial design can be constructed in the following manner: the four experiments of (1), a, b, ab for the 2^2 design, the eight experiments of (1), a, b, ab, c, ac, bc, abc for the 2^3 design, the sixteen experiments of (1), a, b, ab, c, ac, bc, abc, d, ad, bd, abd, cd, acd, bcd, abcd for the 2^4 design, ..., and so on.

For using factorial designs in optimization the levels of the factors are coded so that the high level of each factor is +1, and the low level of each factor is -1 (Bolton, 1984). This procedure requires a transformation of each factor or parameter (P_i) to a reduced variable, X_i. In general, the formula for the transformation is

$$X_i = \frac{2\,(P_i - P_{mean})}{P_{max} - P_{min}}$$

P_{mean} , P_{min} , and P_{max} being respectively the mean, minima and maxima values of P_i.

The reason for the transformation is to allow for easy calculation of the coefficients in the polynomial equation. The coded values also result in orthogonality (independence) of effects. The transformation of the high and low factor levels to +1 and -1 also results in easy calculation of the variance of the coefficients. After transformations, the levels of the factors are as shown in Table 2.

2. The One-Half Fractional of the 2^k Design

2.1 Constructing One-Half Fractions

A one-half fraction of the 2^k design of the highest resolution may be constructed by writing down a basic design consisting of the runs for a full 2^{k-1} factorial and then adding the k th factor by identifying its plus and minus levels with the plus and minus signs of the highest-order interaction ABC..... (K-1). Therefore, the 2^{4-1} fractional factorial as shown in Table 3 is obtained by writing down the full 2^3 factorial as the basic design and then equating factor D to the ABC interaction. The alternate fraction would be obtained by equating factor D to the -ABC interaction.

2.2 Design Resolution

Designs of resolution III, IV, and V are particularly important. The definitions of these designs and an example of each follow.

2.2.1 Resolution III designs

These are designs in which no main effects are aliased with any other main effect, but main effects are aliased with two-factor interactions and two-factor interactions may be aliased with each other. The 2^{3-1} design is of resolution III (2_{III}^{3-1}). In this design it is impossible to differentiate between the effects of A and BC, B and AC, and C and AB.

Table 3. The 2^{4-1} Design.

	Basic Design				Treatment
Run	A	B	C	D = ABC	Combination
1	-	-	-	-	(1)
2	+	-	-	+	ad
3	-	+	-	+	bd
4	+	+	-	-	ab
5	-	-	+	+	cd
6	+	-	+	-	ac
7	-	+	+	-	bc
8	+	+	+	+	abcd

2.2.2 Resolution IV designs

These are designs in which no main effect is aliased with any other main effect or with any two-factor interaction, but two-factor interactions are aliased with other. A 2^{4-1} design with I = ABCD is of resolution IV ($2I_V^{4-1}$). In this design it is impossible to differentiate between the effects of AB and CD, BC and AD, and AC and BD.

2.2.3 Resolution V designs

These are designs in which no main effect or two-factor interaction is aliased with any other main effect or two-factor interaction, but two-factor interactions are aliased with three-factor interactions. A 2^{5-1} design with I = ABCDE is of resolution V (2_V^{5-1}). In this design each main effect and two-factor interaction can be identified.

2.3 Projection of Fractions into Factorials

Any fractional factorial design of resolution R contains complete factorial designs in any subset of R-1 factors. This is an important and useful concept. For example, if an experimenter has several factors of potential interest but beleives that only R-1 of them have important effects, then a fractional factorial design of resolution R is the appropriate choice of design. If the experimenter is correct, then the fractional fatorial design of resolution R will project into a full factorial in the R-1 significant factors.

Central Composite Design

An experimental design for fitting a second-order model must have at least three levels of each factor. There are many designs that could be used for fitting a second-order model and the central composite design is probably the most widely-used experimental design for fitting a second-order response surface (Montgomery, 1991). This design consists of a 2^k factorial or fractional factorial (coded to the usual +1 notation) augmented by 2k axial points ($\pm \alpha$, 0, 0, ... , 0), (0, $\pm \alpha$, 0, ... , 0), (0, 0, $\pm \alpha$, ... , 0), ... , (0, 0, 0, ... , $\pm \alpha$) and nc center points (0, 0, ... , 0). The basic second-order central composite design is used to estimate curvature in a continuous response (i.e., dependent variable) according to the model described below:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + \ldots + b_kX_k + b_{12}X_1X_2 + \ldots + b_{(k-1)k}X_{k-1}X_k + b_{11}X_1^2 + b_{22}X_2^2 + \ldots b_{kk}X_k^2 + \varepsilon$$

where

Y_i = estimate of response (i.e., dependent variable)

X = independent variable

b_0 = overall mean response

b_i = regression model coefficients

k = number of independent variables

ε = random error

The number of experimental trials (N) in a composite design is given by:

$$N = 2^{k-F} + 2k + C$$

where

F = fraction of the full factorial

C = number of centerpoint replicates

The major advantage of designs of this type is the reduction in the number of experimental trials required to estimate the squared terms in the second-order model. Table 4 compares the number of experimental trials required for a three-level factorial or fractional factorial designs and a typical composite design with a single centerpoint ($2^{k-F} + 2k + 1$) for up to five independent variables (Franz et al., 1990).

While the axial points can assume any location in the design a specific type of central composite design, an orthogonal central composite design, has proven to be particularly advantageous (Franz et al., 1990). Designs of this type have the advantage of having all terms (including squared terms) in the model orthogonal to each other and, therefore, all effects can be estimates independently (i.e., uncorrelated estimates of the model coefficients can be obtained). This is accomplished by locating the axial points at a distance, α, from the centerpoint as shown in Table 5. The design layout for a general central composite design with three independent variables (k = 3) is presented in Table 6.

The central composite design is made rotable by the choice of α. The value of α for rotatability depends on the number of points in the factorial or fractional factorial portion of the design; in fact , $\alpha = (nf)^{1/4}$

Table 4. Comparison of the Number of Experimental Trials Required for a Three-Level Factorial Design (3^{k-F}) Versus a Typical Composite Design ($2^{k-F} + 2k + 1$).

Number of Independent Variables, k	3^{k-F} Factorial	$2^{k-F} + 2k + 1$ Composite
2	9	9
3	27	15
4	81	25
5	243	43
5	81[a]	27[b]

[a] One-third fractional factorial three-level design (3^{5-1})

[b] Half fractional factorial-based design (2^{5-1})

Table 5. Comparison of Axial Point Distances α for Two Types of Composite Designs for Up to Eight Variables.

k	Orthogonal Central Composite[a]	Rotatable Central Composite
2	1.000	1.414
3	1.216	1.682
4	1.414	2.000
5	1.596	2.378
5[b]	1.547	2.000
6	1.761	2.828
6[b]	1.724	2.378
7[b]	1.885	2.828
8[b]	2.029	3.364

[a]Assume a single centerpoint (C = 1)

[b]Basic design is a half-fractional factorial

Table 6. Design Layout for an Orthogonal Composite Design Where k = 3 and C = 1.

Trial	Variable Level X_1	X_2	X_3	
1	-1	-1	-1	
2	+1	-1	-1	
3	-1	+1	-1	
4	+1	+1	-1	
5	-1	-1	+1	2^3 Full Factorial
6	+1	-1	+1	
7	-1	+1	+1	
8	+1	+1	+1	
9	$+\alpha$	0	0	
10	$-\alpha$	0	0	
11	0	$+\alpha$	0	
12	0	$-\alpha$	0	Axial Points or Extreme
13	0	0	$+\alpha$	
14	0	0	$-\alpha$	
15	0	0	0	Centerpoint

yields a rotable central composite design where nf is the number of points used in the factorial or fractional factorial portion of the design.

Multiple Regression in Optimization

1. First Order Relationships Between Independent and Dependent Variables

If the independent and dependent variables are connected by straight-line relationships, these relationships can be represented by linear programming. Many pharmaceutical problems are problems of opimization and many pharmaceutical relationships are linear or can be made linear using simple mathematical transformations such as taking logarithms. However, linear programming has received surprisingly little attention in the pharmaceutical literature. The first stage of model-dependent optimization is to obtain experimental data, and this is best achieved by means of a proper statistical experimental design. The next stage of the optimization procedure is to carry out multiple regression analysis. This involves fitting the values of a dependent variables and the independent variables into a polynomial equation of the form:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + \ldots b_kX_k + \varepsilon$$

Multiple regression analysis is used to obtain the values of the coefficients b_0 , b_1 , b_2 ,. .. , and b_k.

If interactions between independent variables are occurred, the relationship between a response and the independent variables is given by an equation of the form:

$$Y_i = b+b_1X_1+b_2X_2+...+b_kX_k+b_{12}X_1X_2+...+ b_{(k-1)k}X_{k-1}X_k+ \varepsilon$$

Solving this equation by multiple regression gives the values of b_0, b_1, b_2, ... b_{k-1}, and b_{12}, b_{23} ,..., $b_{(k-1)k}$, respectively.

2. Second-order Relationships Between Independent and Dependent Variables

In many cases there is a linear relationship between independent and dependent variables, or where an interaction occurs between them. Such a relationship sufficiently accurately reflects the actual situation, and a first-order relationship is adequate to locate the approximate area in which the optimum is to be found. In the great majority of formulation problems, this is probably sufficient. If however the relationships between the independent variables and the dependent variables are nonlinear, then it may be advantageous to assume a second-order relationship. In this case a suitable statistical experimental design must be chosen such as three level factorial design or central composite design. Multiple regression relates each dependent variable to the various independent variables by equation:

$$Y_i = b_0 + b_1X_1+ b_2X_2 ... + b_kX_k + b_{12}X_1X_2 + ... + b_{(k-1)k}X_{k-1}X_k + b_{11}X_1^2 + b_{22}X_2^2 + ... + b_{kk}X_k^2 + \varepsilon$$

Multiple regression of the experimental data gives the coefficients, the task can be facilitated by using a computer multiple regression program. As the number of independent variables is increased, so does the complexity of the second-order model used to describe them. A system using five independent variables was described by Schwartz et

al. in 1973 (Schwartz, Flamholz, and Press, 1973). Each dependent variable was fitted into an equation of all independent variables. The obtained second-order polynomial equation contained twenty-one unknown coefficients and hence a central composite design of twenty-seven experiments was chosen to provide sufficient data points for these to be calculated.

Testing Hypothesis Concerning Regression Coefficients in Multiple Linear Regression (Neter, Wasserman, and Kutner, 1987)

Consider a first-order multiple regression model with k independent variables:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + \ldots b_kX_k + \varepsilon$$

1. Test Whether All $b_k = 0$

This is the overall F test of whether or not there is a regression relation between the dependent variable Y and the set of independent variables. The alternatives are:

$$H_o : b_1 = b_2 = \ldots\ldots = b_{p-1} = 0$$
$$H_a : \text{not all } b_{k\ (k=1,\ \ldots\ldots,\ p-1)} \text{ equal } 0$$

and the test statistic is:

$$F^* = \frac{SSR(X_1, \ldots, X_{p-1}) / p-1}{SSE(X_1, \ldots, X_{p-1}) / n-p}$$

$$= \frac{MSR}{MSE}$$

If H_o holds, $F^* \sim F_{(p-1,\ n-p)}$. Large values of F^* lead to H_a conclusion.

2. Test Whether a Single $b_k = 0$

This is the partial F test of whether a particular regression coefficient b_k equals zero. The alternatives are:

$H_o : b_k = 0$

$H_a : b_k \neq 0$

and the test statistic is:

$$F^* = \frac{SSR\ (X_k / X_1, \ldots, X_{k-1}, X_{k+1}, \ldots, X_{p-1}) / 1}{SSE(X_1, \ldots X_{p-1}) / n-p}$$

$$= \frac{MSR\ (X_k / X_1, \ldots, X_{k-1}, X_{k+1}, \ldots, X_{p-1})}{MSE}$$

If H_o holds, $F^* \sim F_{(1,\ n-p)}$, Large values of F^* lead to H_a conclusion. Computer packages which provide extra sums of squares permit use of this test.

An equivalent test statistic is:

$$t^* = \frac{b_k}{s(b_k)}$$

If H_o holds, $t^* \sim t_{(n-p)}$. Large values of t^* lead to H_a conclusion.

Since the two tests are equivalent, the choice is usually made in terms of available information provided by the computer package output. The values of F* and t* usually can obtain from a statistical computer program and these values will be compared to the values of $F_{(p-1,n-p)}$, $F_{(1,n-p)}$, or $t_{(n-p)}$ obtained from the statistical F-table or t-table.

Note:

$p = k + 1$

n = the number of the experiments

k = the number of the independent variables

MSE = error mean square or residual mean square

MSR = regression mean square

SSE = error sum of squares or residual sum of squares

SSR = regression sum of square

s^2 = sample variance

Optimization Using Search Methods

In search methods the response surfaces, as defined by the appropriate equations, are searched by various methods to find the combination of independent variables yielding the optimum. A search method of optimiztion was applied to a pharmaceutical system and was reported by Schwartz et al. (1973) . It takes five independent variables into account and is computer assisted. It was proposed that the procedure described could be set up such that persons unfamiliar with the mathematics of optimization and with no previous computer experience

could carry out an optimization study. The steps necessary to complete such a study may be summarized as follows.

1. Select a system.
2. Select variables:
   a. Independent
   b. Dependent
3. Perform experiments and test product.
4. Submit data for statistical and regression analysis.
5. Set specifications for feasibility program.
6. Select constraints for grid search.
7. Evaluate grid search printout.
8. Request and evaluate related graphical plots.

The key to successful application of the experimental optimization techniques is based on adequate experimental design. The selection of an appropriate statistical experimental design relies on the number of independent variables being studied and also the nature of the relationships between the interested responses and those independent variables. Increasing the number of the studied variables results in more experiments being performed in order to yield adequate data to build the empirical equations of the response surfaces. The resulting data obtained from the designed experiments are derived, usually by multiple regression to yield a mathematical model for each response variable. The accuracy of the equation is evaluated by the R-square or the index of determination, which is an indication of the fit.

For the optimization itself, two major steps are used: the feasibility search and the grid search. A feasibility program can be used to locate a set of response constraints which are just at the limit of possibility. One selects the several values for the responses of interest (i.e., the responses one wish to constrain) and a search of the response surface is made to determine whether a solution is feasible. The selected constraints are fed into the computer and are relaxed one at a time until a solution is found. In general, this type of computer program is designed so that it stops after the first possibility therefore it is not a full search. The solution obtained may be one of many possibilities satisfying among the constraints.

The next step, the grid search is necessary if one wants to search for alternative solutions that satisfy the constraints. By this method the experimental range is divided into a grid of specific size and methodically searched. Based on an input of the desired criteria, the program prints out all solutions that meet the constraints. In addition to providing a printout of each solution, the grid search program also gives the corresponding values for the responses. At this point the experimenter can trade off one response for another. Thus the best or most acceptable formulation is selected from the grid search printout to complete the optimization. Graphic approaches are also available and graphic output is provided by a plotter from computer programs. The output includes plots of a given response as a function of two variables while the remaining variables are held at some desired levels. Response surface plots and contour plots are generated in this manner.

This approach demonstrates the fact that using only a part of this procedure will represent a step forward over the trial-and-error method of formula and process modification. It is not necessary to carry these studies to completion. For example, once the designed experimentation has been completed one might be able to accomplish the task simply by analyzing the graphs: therefore, further mathematical treatment or search programs will not be necessary.

Formulation of Controlled Release Solid Dispersions

In general, capsule and tablet are two oral dosage forms which can be formulated from controlled release solid dispersions. While the capsule dosage form is quite easy to prepare the formulator must recognize the effects of capsule shell on the drug release rate. In another hand, the tablet dosage form is more complicated since several factors in tabletting can have influences on drug release from the tablets. These factors include tablet compression force, type and amount of tablet excipient and the method of tablet manufacturing. These factors must be investigated thoroughly before any optimized controlled release solid dispersion tablet formualtion can be formulated successfully.

1. Tabletting of Controlled Release Solid Dispersions

There are some limitations in fabrication controlled release solid dispersions into tablet dosage form.

1.1 Only direct compression or dry granulation method can be used in manufacturing of solid dispersion tablets. Wet granulation

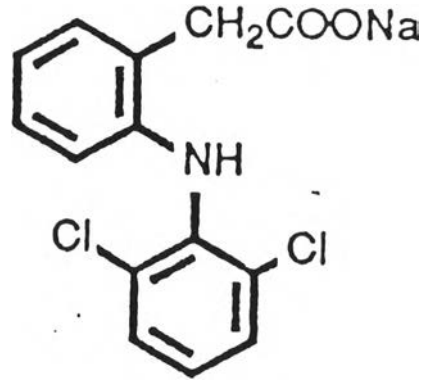
method involves with utilization of solvent and thus can't be used otherwise the system of solid dispersions will be destroyed.

1.2 Since the dose of sustained release tablets is quite high therefore the amount of any carrier being used in the solid dispersion system is limited. Hence, the appropriate carrier of highly effective ought to be chosen in order to lower the amount of the carrier required to be employed.

1.3 The method of preparing solid dispersions also plays an important role in determining the solid dispersion tablet formulation. In general, coprecipitation method using simple evaporation and melting method give solid dispersions of adequate dense but quite sticky while coprecipitation method utilizing spray drying or freeze drying yields nonstickly solid dispersions of quite bulky. The bulkiness of solid dispersions is an important factor to be considered upon choosing the direct compessible diluent for a solid dispersion tablet formulation. The diluents of high density are required in the tablet formulation of high bulk solid dispersions. Stickiness of the obtained solid dispersions is another factor to be considered since it will cause problems in tablet manufacturing.

1.4 The influences of tablet ingredients on drug release must be recognized. Tablet excipients such as disintegrant, dry binder and lubricant also have effects on drug release from the controlled release solid dispersion tablets. Another factor which has significant effect on drug release is compression force.

Diclofenac Sodium



$C_{14}H_{10}C_{12}NO_2Na$

Diclofenac sodium is a synthetic, nonsteroidal anti-inflammatory, and analgesic compound. It is an odorness. white to off-white crystalline, slightly hygroscopic powder (Adeyeye and Li, 1990). The pK_a of diclofenac sodium in water is 4 and the partition coefficient in n-octanol/aqueous buffer pH is 13.4. Diclofenac sodium is poorly soluble in acidic medium but more solubility is obtained in alkani medium. Its melting point is about 283-285 ^oC (Windholz, 1983).

Diclofenac sodium is completely absorbed from the gastrointestinal tract after oral administration having the half-life of approximately two hours (Adeyeye and Li, 1990). The usual dose of diclofenac sodium is three times a day for a conventional 25 mg enteric coated tablet. Sustained release diclofenac sodium tablet is available commercially in the dose of 100 mg (Reynolds, 1989).

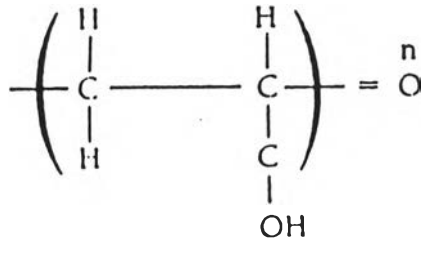
Carbomer

(Carbopol 934)

Empirical Formula
$-(C_3H_4O_2)_x\cdot(-C_{12}H_{18}-Sucrose)_y-$

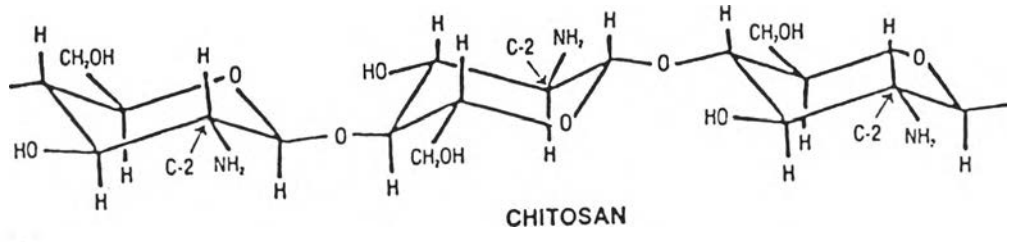
Molecular Weight
Carbomer 934: 3×10^6
Carbomer 940: 4×10^6
Carbomer 941: 1×10^6

Structural Formula



Carbomer or carboxypolymethylene is a synthetic, high molecular weight, cross-linked polymer of acrylic acid copolymerized with approximately 0.75-2% w/w of polyalkylsucrose (American Pharmaceutical Association, 1986). It is a white, fluffy, acidic, hygroscopic powder with a slight characteristic odor. Carbomer is available under the commercial name Carbopol. There are three varieties of carbomer of different molecular weights and viscous capacities which are distributed naming Carbopol 934, Carbopol 940, and Carbopol 941, respectively. Carbomer is soluble in water, alcohol and glycerine. One gram of carbomer is neutralized by approximately 400 mg of sodium hydroxide. Neutralized aqueous gels of carbomer are more viscous between pH 6 and pH 11. The viscosity is considerably reduced if the pH is <3 or >12. Of the many polymers used in the formulation of hydrophilic matrix tablets, the Carbomers occupy an important position and are still studied.

Chitosan



Chitosan is generally obtained from natural chitin after N-deacetylation by an alkaline treatment (Rinaudo and Domard, 1989). Chitin is the second most abundant natural biopolymer, cellulose being the most abundant. Chitin is widely distributed througout nature. The most easily exploited sources are the protective shells of crustaceans such as crabs and shrimp. Chitosan, being a high molecular weight polymer, is a linear polyamine whose amino groups are readily available for chemical reactions and salt formation with acids. Values fo pK_a going from 6.6 to 7 were given in the literature. Since chitosan can be viewed as a cellulose derivative, the primary (C-6) and secondary (C-3) hydroxy groups can be used to make derivatives. Chitosan has rather specific solution properties. First, when in the free amine form, chitosan is not soluble in water at neutral pH's. At acidic pH's, the free amino groups ($-NH_2$) become protonated to form cationic amine groups ($-NH_3^+$). Table 7 lists some key solution behavior of the two amine forms of chitosan (Standford, 1989).

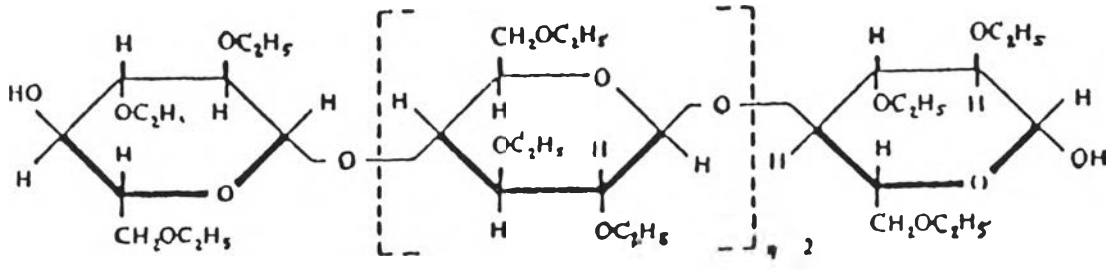
Table 7. Chitosan Solution Properties

Free Amine ($-NH_2$)	Cationic Amine ($-NH_3^+$)
- Soluble in acidic solutions	- Soluble at pH's < 6.5
- Insoluble at pH's > 6.5	- Forms viscous solutions
- Insoluble in H_2SO_4	- Solutions shear thining
- Linited solubility in H_3PO_4	- Forms gels with polyanions
- Insoluble in most organic solvents	- Will remain soluble in some alcohol-water mixtures

Chitosan is being evaluated in a number of medical applications. These include wound dressings, hemostatic agents, drug delivery systems, and as hypocholesterolemic agent (Standford, 1989). In these uses chitosan's key properties are: 1) biocompatibility, 2) non-toxicity, its degradation products are known natural metabolites, 3) Its ability to improve wound healing and/or clot blood, 4) ability to absorb liquids and to form protective films and coatings, 5) selective binding of acidic lipids, thereby lowering serum cholesterol levels. In pharmaceutical field, chitosan beads can be used as a biocompatible matrix to deliver drugs. Due to chitosan's ability to be depolymerized by lysozyme, an enzyme found in various mammalian tissues, drug impregnated chitosan beads can be used as a bioerodible system to deliver pharmaceuticals.

Ethylcellulose

(Ethocel 10 cps)

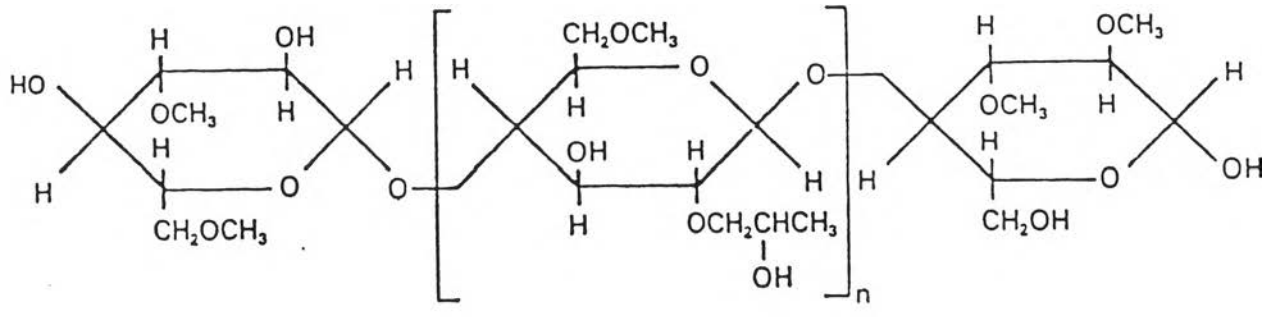


Ethylcellulose resins (Ethocel) result from the reaction of ethyl cholride with alkali cellulose. Common raw materials are cotton linters and wood pulp. Ethylcelluose is a tasteless, free-flowing, white to light tan powder. It is insoluble in water, glycerin and propylene glycol, but soluble in varying degrees in certain organic solvents, depending upon ethoxyl content. Ethycellulose is essentially non-toxic. Properties of ethylcellulose, such as tensile strength, elongation, and flexibility, depend largely upon the degree of polymerization, which can be measured by viscosity. Therefore, within each type based on ethoxyl content there exist low to high viscosity types, based on degree of polymerization. In pharmaceutical industry ethycellulose has been used as binder in tablets, coating material for tablets, coating material for stabilization, coating to prevent unpleasant taste, coating for drug microcapsules, and thickening agent in creams, lotions or gels (American Pharmaceutical Association, 1986).

Ethocel resins are identified by a number indicative of viscosity range. They are produced and marketed in a number of different viscosity gradients, viscosity increases as the length of the polymer molecule increases. Ehocel Standard 10 is a product having viscosity in a range of 9 - 11 cps. It is available in Premium grade for FDA compliance.

Hydroxypropyl Methylcellulose

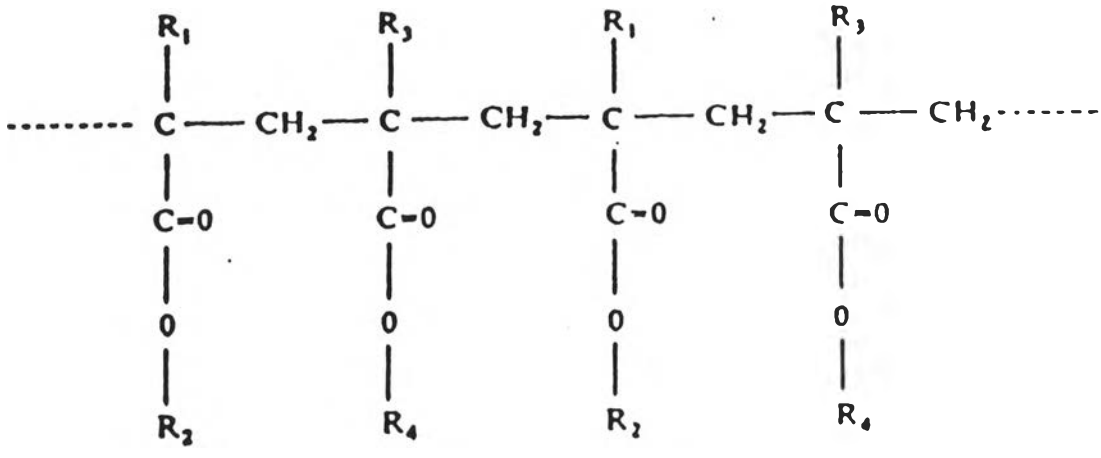
(Methocel E4M)



Hydroxypropyl methylcellulose is non-ionic water soluble ether of methylcellulose. Hydroxypropyl methylcellulose products are available in various viscosity types, ranging from 5 to 15,000 cps, naming Methocel E, F, J, and K. Hydroxypropyl methylcellulose is an odorless, tasteless, white or creamy-white fibrous or granule powder which dissolves slowly in cold water, forming a viscous colloidal solution. It is insoluble in hot water, alcohol, and chloroform but soluble in mixtures of methyl alcohol and methylene chloride (Windholz, 1983). Lower viscosity grades are used in aqueous film coating and higher viscosity grades are used in solvent film coating. High viscosity grades are also used to retard the release of water-soluble drugs (American Pharmaceutical Association, 1986). Methocel E4M has viscosity in the range of 3500-5600 cps. The Premium grades of Methocel hydroxypropyl methylcellulose products are accepted as additives for a variety of food and drug uses.

Methacrylic Acid Copolymer

(Eudragit RS 100)



Type RS: R_1 = -H, $-CH_3$

R_2 = $-CH_3$, $-C_2H_5$

R_3 = $-CH_3$

R_4 = $-CH_2CH_2N(CH_3)_3^+Cl^-$

Methacrylic acid copoymer or polymethacrylates are prepared by polymerization of acrylic and methacrylic acids or their esters; e.g., butyl ester or dimethylaminoethyl ester. Several types of methacrylic acid copolymer are available in commmercial place including type E, type L, type S, and type RS (American Pharmaceutical Association, 1986). Eudragit RS is a anionic polymer synthesized from acrylic and methacrylic acid ester with a low content of quaternary ammonium groups. The ammonium groups are presented as salts and give rise to the permeability of the lacquer films. Eudragit RS acrylic resins form water-insoluble films with defined permeability to water and to dissolved drugs, independent of pH values.

Eudragit RS 100 is colorless, transparent to slightly opaque granules with a weakly aromatic odor. It is soluble in acetone, methyl alcohol, and methylene chlorides, as well as solvent mixtures of approximately equal parts of acetone/isopropyl alcohol and isopropyl alcohol/methylene cholride. Eudragit RS 100 is recommended for application in the field of controlled drug release due to its defined permeability to water and to dissolved drug.