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OPTIMIZATION OF EUDRAGIT OR CELLULOSIC POLYMERS-IBUPROFEN SUSTAINED RELEASE SYSTEMS USING PRINCIPAL COMPONENT ANALYSIS

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ABSTRACT

In order to retard the release of ibuprofen from its prepared tablets Eudragit polymers including Eudragit L100, Eudragit RS, Eudragit RLPM and Eudragit RSPM as well as cellulosic polymers including ethyl cellulose 20, hydroxy propyl-methyl cellulose 606 (Pharmacoat 606) and hydroxy propyl-methyl cellulose phthalate 55 (HP 55 f) have been used as granulating agents and excipients. The principal component analysis helped to investigate 13 variables on 23 formulae (ibuprofen granulated with Eudragit polymers) and 10 variables on 31 formulae (ibuprofen granulated with cellulosic polymers). It was possible by this method to represent all the relations existing between the 13 and 10 variables on simple circles of correlations. These variables include: concentration of the drug, concentration of the polymer, dissolution of the drug at pH 1.5 and pH 7.5, the tablet breaking strength, the tablet friability, the tablet hardness/friability ratio, the time of 50 and 80% drug release, the drug release rate constant of first order kinetic at pH 1.5 and pH 7.5, the drug release rate constant of Higuchi equation and dissolution efficiency.

Principal component analysis allowed to separate the formulae according to their compression characteristics, the dissolution efficiency, the kinetic parameters, the quality and the best choosing polymer for the retardation of ibuprofen and choosing the preferable excipient for the sustained release formulations. Dissolution was identified as the predominant parameter of the system next by compression characteristics.

From the principal component analysis investigations, it could be concluded that the formula of ibuprofen granulated with 15% Eudragit RSPM and containing 23% Avicel pH 102 and the formula granulated with 3% ethyl cellulose 20 and containing 23% Avicel pH 102 were found to be the optimum formulae.

INTRODUCTION

Pharmaceutical research and development projects are often optimization problems involving a great number of variables. The techniques of optimization are well documented on the literature[1-4]. Fonner et al[5] demonstrated the applicability of mathematical techniques to pharmaceutical systems limited to two independent variables.

The multivariate statistical procedure, principal component analysis, can effactively be used to solve the problem of formulation optimization. This method first finds the function of variables that has the largest variance and then finds the function independent of the first function having the largest variance. It then finds the function independent of the first two functions with the largest variance and so on.

The role of principal component analysis in the selection of optimum pharmaceutical formulations is presented[6,7]. It was found that dissolution and disintegration of formulated tablets contributed 95.4 and 99.3% to the overall information about the formulations.

The use of multifactorial analytical method proved to be necessary in dealing with the lubrication of a tablet for cleaning contact lenses[8]. The principal component analysis helped to make a synthetic representation of the relationships existing between 15 variables selected.

Optimization of a sustained release form of sodium diclofenac was carried out[9] using a factorial design for 3 independent variables.

The present work represent the optimization of sustained release forms of ibuprofen using principal component analysis for 13 variables on 23 formulae (ibuprofen tablets granulated with Eudragit polymers) and 10 variables on 31 formulae (ibuprofen tablets granulated with cellulosic polymers).

THEORY

The type of project of concern here is one of selecting the most desirable level of ingredients or controllable process factors. That is, it is desired to quentitate a formulation that has been qualitatively determined.

The structure of the data associated with the experiment is presented in the matrix form shown in table (1). For the purpose of describing the procedure[7], let Y_{ik} ($i=1,2,\ldots,P$; $k=1,2,\ldots,N$) denote the numerical value associated with the kth experiment for the i th response variable, and let P and N represent the number of response variables and the number of experiments for each parameter considered, respectively. In this case, Table (1), P=13 and N=23. The value of Y_{ik} can be the mean of several measurements.

The variance (S_{ii}) and the covariances (S_{ij} $i \neq j$) associated with the P parameters are then calculated as follows:

$$\text{Variance}=S_{ij}=\left[\sum_{k=1}^{N} Y_{ik}^2 - \left(\sum_{k=1}^{N} Y_{ik}\right)^2 N^{-1}\right] (N-1)^{-1} \qquad \text{(Eq.1)}$$

where $i=1,2,\ldots,P$, and:

$$\text{Covariance}= S_{ij}(i/j)=\left[\sum_{k=1}^{N} Y_{ik}Y_{jk} - \left(\sum_{k=1}^{N} Y_{ik}\right)\left(\sum_{k=1}^{N} Y_{jk}\right) N^{-1}\right] (N-1)^{-1} = S_{ji} \qquad \text{(Eq.2)}$$

where $i=1,2,\ldots,P$ and $j=1,2,\ldots,P$

There would be a total of P variances and ½ p(p-1) covariances associated with P parameters. There will be 13 variances and 78 covariances when 16 parameters are considered. The variance and covariance quantities are then arranged in a square matrix form as follows:

$$\Sigma = \begin{bmatrix} S_{11} & S_{12}\cdots\cdots\cdots S_{1p} \\ S_{21} & S_{22}\cdots\cdots\cdots S_{2p} \\ \cdot & \\ Sp1 & Sp2\cdots\cdots\cdots Spp \end{bmatrix} \qquad \text{(Eq.3)}$$

This matrix called the variance-covariance matrix and is denoted by the greek letter Σ (sigma). The variances are arranged in the main diagonal of the matrix and the covariances are placed in their respective off-diagonal positions. Since $S_{ij}=S_{ji}(i \neq J)$, one has only ½P(P+1) distinct elements in the matrix. If there are P parameters, then the dimension of this matrix is (PXP) with P rows and P columns and there are P^2 elements in the matrix. When P=13, the dimension of Σ is (13x13) with 169 elements in the matrix.

The determinant of the matrix reduces these P^2 (here 169) elements to a single number. This number rep-

resents the variance of the entire system, usually called the generalized variance. This statistics is helpful for comparing the variances of two different systems. The primary interest here, however, is in the magnitude of the variances of the individual components and their relative information within the system under consideration. So, consider the determinant of the matrix $(\Sigma - \lambda I)$, where I is identity matrix with ones in the main diagonal and zeros elsewhere and, expressed explicity, gives:

$$\Sigma - \lambda I = \begin{bmatrix} s_{11}-\lambda_1 & s_{12} & \ldots\ldots & s_{1p} \\ s_{21} & s_{22}-\lambda_2 & \ldots & s_{2p} \\ \cdot & & & \\ \cdot & & & \\ \cdot & & & \\ s_p1 & s_p2 & & s_{pp}-\lambda_p \end{bmatrix} \qquad \text{(Eq.4)}$$

In this equation, the i's $(i=1,2,..,P)$ are unknown. By seeting

$$\Sigma - \lambda I = \Theta \qquad \text{(Eq.5)}$$

and expanding the determinant on the left, one has a polynomial equation of P th order of the following form:

$$\Sigma - \lambda I = f(\lambda) = (-\lambda)^P + a_{p-1}(-\lambda)^{P-1} + \ldots + a_1(-\lambda) + a_0 = \Theta \qquad \text{(Eq.6)}$$

where the coefficients a_i's, but for signs, the sum of all of the principal ith-order minors of the determinant of the variance-covariance matrix Σ. A Pth-order polynomial would yield P roots (zeros of the polynomial). These roots (λ_i's) are known as characteristic roots, latent roots, or eigenvalues. The term "eigenvalue" will be used in the subsequent reference to the roots. These eigenvalues ($\lambda_1, \lambda_2, \ldots, \lambda_p$) represent the variances of each "orthogonal" component of the system. The variance-convariance matrix of the orthogonal system (Λ) has the following structure:

$$\Lambda = \begin{bmatrix} \lambda_1 & 0 & 0\ldots.0 \\ 0 & \lambda_2 & 0\ldots.0 \\ \cdot & & \\ 0 & 0 & 0\ldots.\lambda_p \end{bmatrix} \qquad \text{(Eq.7)}$$

It is clearly seen in Eq.7 that the original system has been transformed to an orthogonal system in which the covariances of the components have been reduced to zero (hence the term orthogonal system is used). The generalized variance of the original system is identically equal to the generalized variance of the orthogonal system, that is:

$$|\Sigma| = |\Lambda| \qquad \text{(Eq.8)}$$

This clearly indicates the complete preservation of the total information of the original system in the transformed system. The orthogonal system provides an estimation of the relative contribution of each component to the overall information. Let $\Theta = \lambda_1 + \lambda_2 + \ldots + \lambda_p$; then $256\,\lambda_1\Theta^{-1}$, $256\,\lambda_2\Theta^{-1}, \ldots\ldots, 256\,\lambda_p\Theta^{-1}$ are the respective relative contribution (in percent) of each of the p components of the system to the overall information.

Now consider the structure of each component associated with each eigenvalue $\lambda_r (r=1,2,\ldots,p)$ is a set of p coefficients, $\gamma_{r1}, \gamma_{r2}, \ldots, \gamma_{rp}$; $r=1,2,\ldots,p$. This set of coefficients, called the eigenvector of eigenvalue λ_r, is a solution of the equation:

$$(\Sigma - \lambda_r I) = \Theta \quad r=1,2,.. \qquad \text{(Eq.9)}$$

where I is the identity matrix with ones in the main diagonal and zeros elsewhere. This equation is expressed explicity as follows:

$$\begin{bmatrix} S_{11}-\lambda_r & S_{12} & \cdots & S_{1p} \\ S_{21} & S_{22}-\lambda_r & \cdots & S_{2p} \\ \cdot & & & \\ Sp & Sp2 & & Spp-\lambda_r \end{bmatrix} \begin{bmatrix} \gamma_{r1} \\ \gamma_{r2} \\ \cdot \\ \gamma_{rp} \end{bmatrix} = \begin{matrix} 0 \\ 0 \\ . \\ 0 \end{matrix} \quad \text{(Eq. 10)}$$

where r=1,2,3,...,p.

By the eigenvectore it is possible to calculate the principal components. These vectors are in fact the coefficients of the linear regression between each principal component and initial variables Figs (1) & (2).

The magnitudes of the coefficients associated with those principal components that are substantially contributing to the overall information are of interest in the interpretation of the principal component analysis of the system under consideration.

The codes of a Fortran program for computing the eigenvalues and eigenvectors of a real symmetric matrix are available[10] and are suitable for adoption into any computer system.

The basis of this method can be approximately compared with the principal of a camera. A camera permits to pass from a 3 dimensions space the one in which we live, to a 2 dimensions space : the photograph. The quality of the collected information still depends on the angle of view. Correlations between the original variables and the principal components, at the same time as the co-ordinates of the formulae on them can be used to produce simple graphs in which fundamental structures of the data are recapitulated[8].

EXPERIMENTAL

The formulation selected as a model system for the optimization program was a production formula already in existence. Briefly, the process involved a wet granulation of ibuprofen with different polymers[11] Eudragit L100, Eudragit RLPM, Eudragit RSPM, ethylcellulose 20, pharmacoat 606 and HP55f. After drying, the excipient [Avicel pH 102, lactose, Emdex and Emcompress] and the lubricant [magnesium stearate] were added.

The three independent formulation variables selected for this particular study were : X_1, ibuprofen level, X_2 polymer level and X_3, diluent ratio. With the exception of those three variables, everything else in the formulation and the processing steps remained constant throughout the study including (a) the lubricant level, (b) granulating, milling, drying and blending conditions and (c) the speed of the compressing machine.

The 13 parameters shown in Table (1) were measured on each of the 23 tablet formulations considered for the experiment described in detail in Table (2). The principal component analysis has been undertaken after the end of the study. Normally it have been a 2^3 or 3^3 design (8 or 27) experiments but here, all the 31 results were taken into account. So, the 10 parameters shown in Table (3) were measured on each of the 31 formulae as mentioned in detail in Tables (4-6). Thus, the data set to be subjected to principal component analysis contains 23 and 31 values for each response in Tables (3 & 7).

RESULTS AND DISCUSSION

Key for interpretation:

It is possible by principal component analysis to make simple and synthetic graphs.

First, initial variables can be represented by points in circles of linear correlations. Such a circle

has a radius of one unit and contends orthogonal axis corresponding to the principal components. An initial variable is well represented if its corresponding point is plotted near the circumference of the circle. If this well represented variable is also near a horizontal or vertical axis, this means that this axis is well explicated by this variable. Two initial variables are directly correlated if they are plotted close to one another (provided that they are also well represented), if the correlation is negative they are on opposite directions, and then if not correlated they are on orthogonal lines. In the best case only one circle can display all the relations existing between the great number of variables.

A second type of graph is the representation of all the formulae on the principal plans constitued by the principal axes corresponding to the principal components. Here also, the higher the co-ordinates (in absolute values) the best the representation. On the other side, formulae possessing the same or almost the same characteristics are plotted near one another.

Principal Component Analysis of the Eudragit Matrix System:

Principal component analysis is applied to 299 raw data obtained by determination of 13 variables on the twenty three formulae granulated with Eudragit, Table (2). The diagonalization of the matrix of correlations, Table (8), gives the results reported in Table (9). Almost 91% of the information is conserved when passing from a space of 13 dimensions which of the 13 variables to a space of 4 dimensions of the first 4 principal components. Table (9) lists the first five components, their respective eigenvalues, and the relative information calculated from them. An examination of these data shows that the total information contained in the system was contributed by these first five of the 13 principal component in the Eudragit polymer formulations. The first principal components contributed as much as 50.8% of the total information of the formulations. Component II in Table (9) contributed only 25.1% of the total information.

In the first circle of correlation, Fig. (3) the first axis corresponding to the first principal component is mainly due to some variables like hardness, hardness/friability ratio (H.F.R), (correlated together), which seem to be inversely proportional with friability. So, axis 1 is suitable to express cohesion inside the tablet or comprimability.

The variables: the percentage release of the drug at pH 7.5 (DIB), area under curve (AUC) (all together correlated and time of 80% released drug (T_{80}) which appears approximately in opposition to the first one. The second axis corresponds to the second principal component and would be called axis of dissolution. The release rate constant of first order (k_1) at pH 7.5 bring interesting information, it is significant and is best represented on this plan. As shown above, it is necessary in order to collect the maximum of information to observe these same variables under another "angle of view". This is confirmed on the second circle of correlation, Fig. (4), on which the third axis corresponding to the third principal component appears. This axis is in relation between k_1, k_2 and k_3 (all together correlated) and these parameters are approximately in opposition with T_{50} and T_{80}. The results presented in Table (8) for principal component III reveal that the release rate constant of the first order at pH 7.5 (k_2) was the predominant parameter of the component by sharing the

largest value (0.856) among the coefficients associated with the component. It can be admitted that the third principal component indicates to some extent the kinetics of ibuprofen with different types of Eudragit.

The signification of each principal component or each principal axis is very important to facilitate the interpretation of the properties of the formulae on the basis of their simple representation on the principal plans.

So, on the first plan, Fig. (5), defined by the first and second principal axis, many homogeneous populations of formulae are displayed.

Population "A" is plotted on the "negative" values side for axis 2 and on the "positive" side for axis 1. It is formed of formulae having the higher concentrations of polymers (Eudragit L100, Eudragit RLPM and Eudragit RSPM) and higher values of T_{80}. This population is characterized by the lowest release rate.

Population "B", differs from the former by containing the formulae having the lower concentrations of polymers (1 and 2.5%) with 23% Avicel pH102. It is characterized by the higher dissolution at pH 7.5 (DIB).

Population "C", associates with the formulae having the higher concentrations of the drug and lower concentrations of polymers (without excipients, Avicel). These formulae showed higher friability and lower release rate than the formulae mentioned in the population "B".

Principal component analysis also permits to separate a particular population. Indeed, population "D" is completely differs from the above mentioned populations (A,B,&C) where it comprised formulae containing mixture of ibuprofen and polymers (61:15) followed by granulation with 10% Eudragit RL100 or 10% Eudragit RS100 respectively. These formulae appear completely disjoined from the others. Their position on "negative" values side for axis 1 and on the "positive"values side for axis 2. They are characterized by the best comprimability, higher hardness and higher H.F.R than the other formulae.

As seen above, these formulae must also be analysed on the second principal plan constituted of axis 1 and 3 Fig. (6).

Population "A`" present the lower release rate of ibuprofen at pH 7.5 and the formulae displaying the best agreement of a good cohesion inside the tablet.

Population "B`" associates formulae showed the highest release rate and also followed the first order release.

Population "C`" without excipients, differs from the other formulae by the higher concentration of ibuprofen, higher friability and followed first-order kinetics at pH 1.5 (k_1). Formulae (015) have the highest AUC than all other formulae. They are characterized by the higher hardness although their dissolution properties are not too bad since they have moderate release rate.

Among all the realized formulae, it is possible to select the most interesting ones displaying good compression characteristics, efficient polymers for retarding the release rate of the drug and giving satisfactory tablets, by superposing the best population of the first plan (population A) and the best population of the second plan (population A`). Formulae present at the same time in these 2 populations

having the best qualities, i.e., formulae granulated with higher concentrations of polymers for example 5, 10 and 15% of Eudragit L100, Eudragit RLPM and Eudragit RSPM.

The best two formulae which appear plotted near one to another also, having the higher co-ordinate (in absolute values), are selected for best representation. Formulae (007), (014), (005) and (021) are poltted one near the other. Formulae (007) and (014) are of the same concentration of Eudragit L100 or Eudragit RLPM polymers (15%). the same hardness, also approximately the same friability and having lower release at pH 1.5 but higher release rate at pH 7.5 than the formulae (005) and (021). Among the two remaining formulae, the first one that granulated with 5% Eudragit L100 (005) compared with the second one (021) which granulated with 15% Eudragit RSPM is finally considered as the most interesting view to the efficiency of polymers in retarding the release rate of the drug.

Principal Component Analysis of Cellulosic Matrix System:

In this study it was clearly shown that principal component analysis can play an important role in pharmaceutical formulation by identifying parameters that are substantially contributing to the overall information associated with the system.

Principal component analysis is also applied to 310 raw data obtained by determination of 10 variables on the thirty one formulae granulated with cellulosic polymers, Tables (4-6). The diagonalization of the matrix of correlation, Table (10), gives the results reported in Table (11). Almost 94% of the information is conserved when passing from a space of 10 dimensions which of the 10 variables to a space of 4 dimensions of the first 4 principal components. Table (11) shows the first five components, their respective eigenvalues and the relative information calculated from them. The total information contained in the cellulosic matrix system was contributed by these first five of the 10 principal component. The first principal component contributed as much as 55.7% of total information of the formulations. Component II in Table (11) contributed only 21.9% of the total information.

The first axis of the principal component is well represented by the cooperation of the hardness, H.F.R. and concentration of the polymer (altogether correlated) which constituted the first principal component. This axis indicates the cohesion inside the tablet (comprimability). The friability does not bring interesting information and is badly represented on this plan.

Now, by relating the results of the variance-analysis and the structural analysis, it may be inferred that the kinetics parameters accounted for variabilities in the second axis of principal components. This realized on the first circle of correlations Fig. (7), on which the second axis corresponding to the second principal component appears. This axis is in relation with the release rate constant of zero-order, release rate constant of first-order (correlated together) and T50 which approximately in opposition. Release rate constant of zero-order (k_1) was the predominant on the first circle than release rate constant of first-order (k_2) and Higuchi's equation (k_3) in this particular system. This may be due to the release rate constant of the Higuchi's equation (k_3) was hidden and the release rate constant (k_1)is plotted near the circumference of the circle than release rate constant (k_2), Fig.(8).

Component III in Table (11) contributed only 10.9% of the total information. A structural analysis, Table (10), reveals that "dissolution" was the predominant parameter associated with T50 of this principal component. The four parameters comprimability, kinetics, dissolution and T50 yielded a cumulative relative information of 93.5%.

Many homogeneous populations of formulae are exposed by the first principal plan, Fig.(9), that defined by the first and second principal axis.

Population "A", plotted on the "negative" values side for axis 1 and on the "positive" side for axis 2 is formed of formulae having the lowest release of the drug and good compression properties. The highest hardness and the lowest friability are obtained with formula No. (007). These formulae granulated with ethylcellulose 20 and different concentrations and types of excipients.

Population "B" included the formulae that characterized by the higher values of T50 and also bad comprimability due to higher friability and lower H.F.R. values than the other formulae. These formulae granulated with different concentrations of HP55f and containing 23% emcompress.

Population "c" having the formulae which is distinguished by the higher concentration of the drug (without excipients) and the lowest values of hardness. Tablets are not hard and the H.F.R is not very good.

On the other hand, population "D" comprises the formulae which displaying the moderate release rate of the drug (75-77%) and moderate values of friability. The release rate constant of zero-order was the predominant parameter on this population. In this population, the formulae are granulated with pharmacoat 606 and HP55f and containing the insoluble excipient (Emcompress).

Population "E" associates with formulae having good sustained release of the drug in spite of lower hardness. Population E is only constituted of formulae granulated with pharmacoat 606 and HP55f and containing the soluble excipients (lactose and Emdex).

The results obtained show that the use of wet granulation technique with different polymers as ethylcellulose 20, pharmacoat 606 and HP55f really succeed for sustained the release of ibuprofen. It must be noticed that formulae (009) and (010) containing higher concentrations of Avicel [H102 39% and 49% are also represented on this plan. These formulae appeared completely disjoined from the other. They are characterized by the higher dissolution rate (103%) although their compression properties are not too bad. The highest values of hardness, H.F.R. and the lowest friability are obtained with the two formulae.

As seen above, these formulae must also be analysed on the second principal plan constituted of axis 1 and 3 Fig.(10).

Population "A`" presents a slower and the same dissolution rate, higher values of T_{50} and reasonable compression properties.

Population "B`" associates formulae displaying the best agreement of good cohesion inside the tablet and low release rate specially in case of formulae (003), (007) and (008).

Population "C`" characterized by a higher release rate and not too bad comprimability. They are also followed zero-order kinetic.

Characteristics of population "D`" are the same and with moderate dissolution rate.

Because of their bad dissolution properties, formulae (009) and (010) are again represented apart from the others.

Among all the realized formulae, it is possible to select the best one displaying good comperession characteristics, the highest T_{50} values, the lowest dissolution rate and the efficiency of polymers for the retardation of the release and giving satisfactory tablets by choosing the best population of the first plan (population A) and the best population of the second plan (population B`). Formulae present at the same time in these two populations have the best properties. These formulae are those: (1) the formula granulated with 5% ethylcellulose 20 and containing 23% Avicel pH 102 (insoluble excipient) and (2) the formula granulated with 3% ethylcellulose 20 and containing 23% Emdex (soluble excipient).

Table (1): Data Matrix of Formulation of Ibuprofen With Different Types of Eudragit.

Experiment Number (Formulation)	Reponse Variables												
	(CDI)	(CPO)	(DIA)	(DIB)	(HRD)	(FRB)	(HFR)	(T_{50})	(T_{80})	(K_1)	(K_2)	(K_3)	(AUC)
1	Y_{11}	Y_{21}	Y_{31}	Y_{41}	Y_{51}	Y_{61}	Y_{71}	Y_{81}	Y_{91}	$Y_{10.1}$	$Y_{11.1}$	$Y_{12.1}$	Y13.1
2	Y_{12}	Y_{22}	Y_{32}	Y_{42}	Y_{52}	Y_{62}	Y_{72}	Y_{82}	Y_{92}	$Y_{10.2}$	$Y_{11.2}$	$Y_{12.2}$	$Y_{13.2}$
3	Y_{13}	Y_{23}	Y_{33}	Y_{43}	Y_{53}	Y_{63}	Y_{73}	Y_{83}	Y_{93}	$Y_{10.3}$	$Y_{11.3}$	$Y_{12.3}$	$Y_{13.3}$
4													
.													
.													
.													
23	$Y_{1.23}$	$Y_{2.23}$	$Y_{3.23}$	$Y_{4.23}$	$Y_{5.23}$	$Y_{6.23}$	$Y_{7.23}$	$Y_{8.23}$	$Y_{9.23}$	$Y_{10.23}$	$Y_{11.23}$	$Y_{12.23}$	$Y_{13.23}$

Table (2): The Composition of the Different Formulae Used in the Preparation of Controlled Release Tablets Containing Different Ratio and Types of Eudragits.

Formulae No.	Ibuprofen (%)	Eudragit (granulating) agent (% w/v)	Excipient (% w/w)
(1)	76	1 Eudragit L100	23 Avicel pH102
(2)	99	1 ≈	----
(3)	76	2.5 ≈	23 Avicel pH102
(4)	99	2.5 ≈	----
(5)	75	5 ≈	23 Avicel pH102
(6)	76	10 ≈	23 Avicel pH102
(7)	76	15 ≈	23 Avicel pH102
(8)	76	1 Eudragit RLPM	23 Avicel pH102
(9)	99	1 ≈	----
(10)	76	2.5 ≈	23 Avicel pH102
(11)	99	2.5 ≈	----
(12)	76	5 ≈	23 Avicel pH102
(13)	76	10 ≈	23 Avicel pH102
(14)	76	15 ≈	23 Avicel pH102
(15)	76	1 Eudragit RSPM	23 Avicel pH102
(16)	99	1 ≈	----
(17)	76	2.5 ≈	23 Avicel pH102
(18)	99	2.5 ≈	----
(19)	76	5 ≈	23 Avicel pH102
(20)	76	10 ≈	23 Avicel pH102
(21)	76	15 ≈	23 Avicel pH102
(22)	61	15 Eudragit RL100	23 Avicel pH102 +15 Eudragit RLPM
(23)	61	15 Eudragit RS100	23 Avicel pH102 +15 Eudragit RSPM

Table (3): Response Variables of Formulations of Ibuprofen With Ethylcellulose 20, Pharmacoat 606 and $HP_{55}f$.

Symbolic Designation	Response Variables	Units
X_1(CDI)	Concentration of the Drug(Ibuprofen)	Milligram(mg)
X_2(CPO)	Concentration of the Polymer	Milligram(mg)
Y_1(HRD)	Tablet Breaking Strength	Kilograms
Y_2(DIS)	Dissolution of the Drug(Shift Dissol)	Percentage
Y_3(FRB)	Friability of the Tablets	% Wt. Loss
Y_4(HFR)	Hardness/Friability Ratio	Kg/% Wt. Loss
$Y_5(T_{50})$	Time of 50% Drug Release	Minutes
$Y_6(K_1)$	Release Rate Constant of Zero-Order	Milligram/hr.
$Y_7(K_2)$	Release Rate Constant of First-Order	$hr.^{-1}$
$Y_8(K_3)$	Release Rate Constant of Higuchi's Equation	$Mg.Cm.^{-2}Min^{-\frac{1}{2}}$

Table (4) The Composition of the Different Formulae Used in the Preparation of the Tablets Containing Ethylcellulose20, as a Granulating Agent

Formula Number	Ibuprofen (%W/W)	Ethylcellulose20* (%W/V)	Excipients+1%Mg.Stearate (W/W)
(1)	76	1	23% AvicelpH102
(2)	76	3	23% AvicelpH102
(3)	76	5	23% AvicelpH102
(4)	76	3	23% Lactose
(5)	60	5	39% Lactose
(6)	76	3	23% Emcompress
(7)	76	3	23% Emdex
(8)	60	5	39% Emdex
(9)	60	5	39% AvicelpH102
(10)	50	5	49% AvicelpH102
(11)	99	1	----------

Ethylcellulose20* was used as the granulating agent.

Table (5) The Composition of the Different Formulae Used in the Preparation of the Tablets containing Hydroxypropyl-Methylcellulose (Pharmacoat 606)

Formula Number	Ibuprofen (%W/W)	Pharmacoat606* (%W/V)	Excipients+1%Mg.Stearate (W/W)
(12)	76	1	23% Lactose
(13)	76	3	23% Lactose
(14)	76	5	23% Lactose
(15)	76	5	23% Emdex
(16)	76	5	23% AvicelpH102
(17)	76	3	23% Emcompress
(18)	76	5	23% Emcompress
(19)	71	5	23% Emcompress+5% HPMC
(20)	66	5	23% Emcompress+10%HPMC
(21)	99	1	----------
(22)	99	5	----------

Pharmacoat606* was used as a granulating agent

Table (6) The Composition of the Different Formulae Used in the Preparation of the Tablets Containing Hydroxypropyl-Methylcellulose Phthalate($HP_{55}f$)

Formula Number	Ibuprofen (%W/W)	$HP_{55}f$* (%W/V)	Excipients+1% Mg.Stearate (W/W)
(23)	76	1	23% Emcompress
(24)	76	3	23% Emcompress
(25)	76	5	23% Emcompress
(26)	76	3	23% Emdex
(27)	76	5	23% Emdex
(28)	76	3	23% Lactose
(29)	76	5	23% Lactose
(30)	76	5	23% AvicelpH102
(31)	99	1	----------
(32)	99	5	----------

$HP_{55}f$* was used as a granulating agent.

Table (7):Response Variables of Formulations of Ibuprofen With Different Types of Eudragit.

Symbolic Designation	Response Variables	Units
X_1(CDI)	Concentration of the Drug(Ibuprofen)	Milligram(mg)
X_2(CPO)	Concentration of the Polymer	Milligram(mg)
Y_1(DIA)	Dissolution of the Drug at pH1.5	Percentage
Y_2(DIB)	Dissolution of the Drug at pH7.5	Percentage
Y_3(HRD)	Tablet Breaking Strength	Kilograms
Y_4(FRB)	Friability of the Tablet	Percent Wt.Loss
Y_5(HFR)	Hardness/Friability Ratio	Kg/%WT. Loss
$Y_6(T_{50})$	Time of 50% Released Drug	Minutes
$Y_7(T_{80})$	Time of 80% Released Drug	Minutes
$Y_8(K_1)$	Release Rate Constant of First-Order Kinetic at pH 1.5	$Min^{-1} x\ 10^{-5}$
$Y_9(K_2)$	Release Rate Constant of First-Order Kinetic at pH 7.5	$Min^{-1} x\ 10^{-3}$
$Y_{10}(K_3)$	Release Rate Constant of Higuchi's	$Mg.Cm^{-2}.Min^{-½}$
Y_{11}(AUC)	Dissolution Efficiency [Area Under Curve]	Percentage

Table (8): Matrix of Correlations of Formulations Granulated With Eudragits Polymers.

	CDI	CPO	DIA	DIB	HRD	FRB	HFR	T50	T80	K 1	K 2	K 3	AUC
CDI	1.000												
CPO	-0.603	1.000											
DIA	-0.521	0.203	1.000										
DIB	0.148	-0.698	0.050	1.000									
HRD	-0.915	0.697	0.340	-0.283	1.000								
FRB	0.941	-0.599	-0.302	0.186	-0.930	1.000							
HFR	-0.778	0.677	0.182	-0.407	0.841	-0.742	1.000						
T50	-0.153	0.560	-0.352	-0.787	0.289	-0.288	0.409	1.000					
T80	-0.396	0.822	0.006	-0.873	0.473	-0.429	0.622	0.867	1.000				
K 1	-0.307	-0.240	0.413	0.422	0.218	-0.191	-0.013	-0.444	-0.454	1.000			
K 2	0.146	-0.615	-0.178	0.856	-0.215	0.069	-0.312	-0.469	-0.668	0.167	1.000		
K 3	0.270	-0.558	-0.036	0.565	-0.321	0.307	-0.424	-0.509	-0.649	0.409	0.385	1.000	
AUC	0.208	-0.705	0.284	0.880	-0.349	0.324	-0.484	-0.937	-0.928	0.563	0.593	0.639	1.000

Table (9):Eigenvalues, Relative Information , and Cumulative Relative Information Associated With Each Component After Diagonalisation of Formulations Granulated with Eudragit Polymers.

Principal Component	Eigen-values (i)	Relative Information, % (100 $i\theta^{-1}$)	Cumulative Relative Information,%
I	6.61	50.8	50.8
II	3.26	25.1	75.9
III	1.18	9.1	85.0
IV	0.71	5.5	90.5
V	0.41	3.2	93.7

Table (10): Matrix of Correlations of Formulations Granulated With Cellulosic Polymers.

	CDI	CPO	HRD	DIS	FRB	HFR	TSO	K 1	K 2	K 3
CDI	1.000									
CPO	-0.517	1.000								
HRD	-0.615	0.514	1.000							
DIS	-0.290	0.310	0.410	1.000						
FRB	0.207	-0.100	-0.505	-0.325	1.000					
HFR	-0.545	0.336	0.818	0.461	-0.754	1.000				
TSO	0.271	-0.267	-0.408	-0.952	0.414	-0.478	1.000			
K 1	0.061	0.158	0.219	0.896	-0.301	0.289	-0.850	1.000		
K 2	-0.405	0.353	0.593	0.891	-0.370	0.638	-0.818	0.783	1.000	
K 3	0.019	0.145	0.247	0.910	-0.305	0.310	-0.865	0.983	0.819	1.000

Table (11): Eigenvalues,.Relative Information and Cumulative Relative Information Associated With Each Compon-ent of formulations Granulated With Cellulosic Polymers.

Principal Axis	Eigen-values (i)	Relative Information % (100 $i^{\theta-1}$)	Cumulative Relative Information %
I	5.57	55.7	55.7
II	2.19	21.9	77.6
III	1.09	10.9	88.5
IV	0.50	5.0	93.5
V	0.33	3.3	96.8

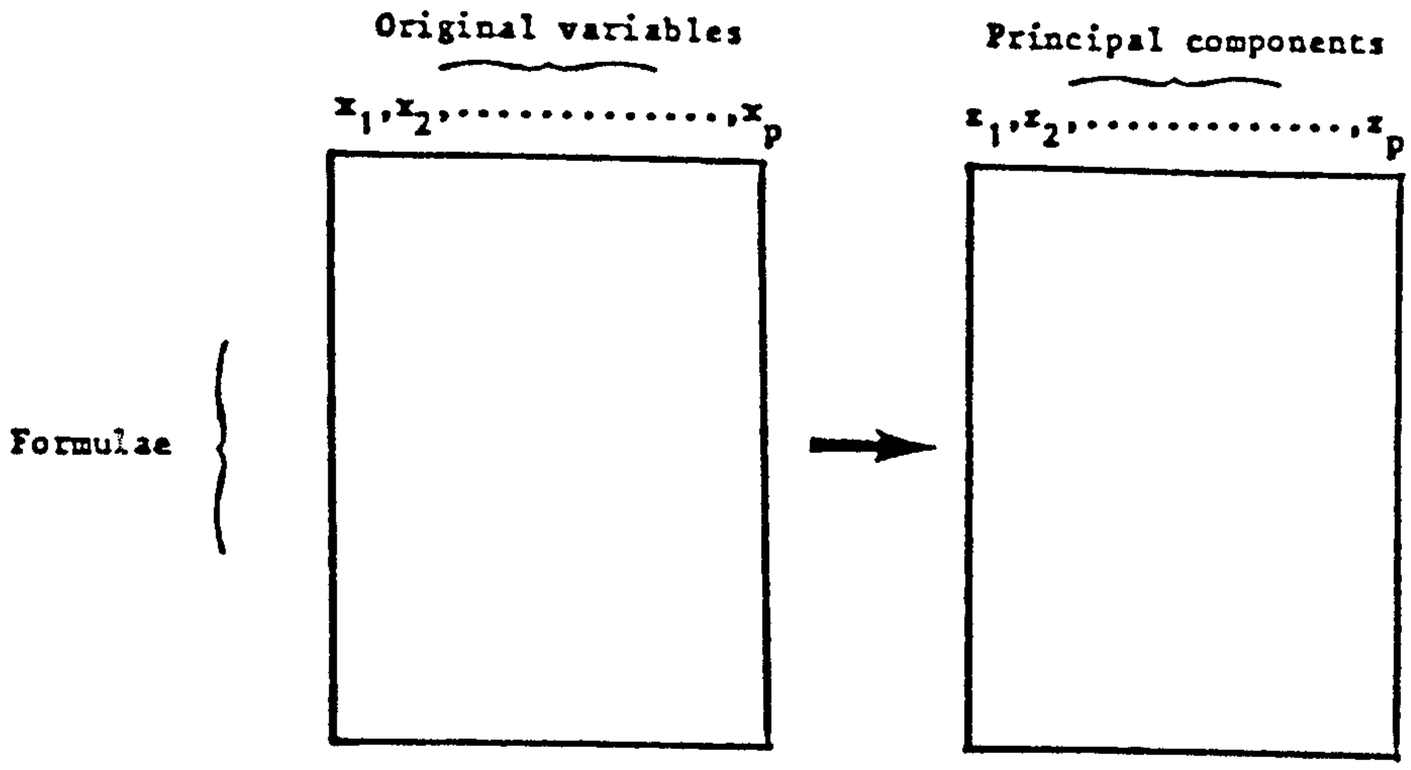

FIGURE (1)
Objective of principal component analysis.

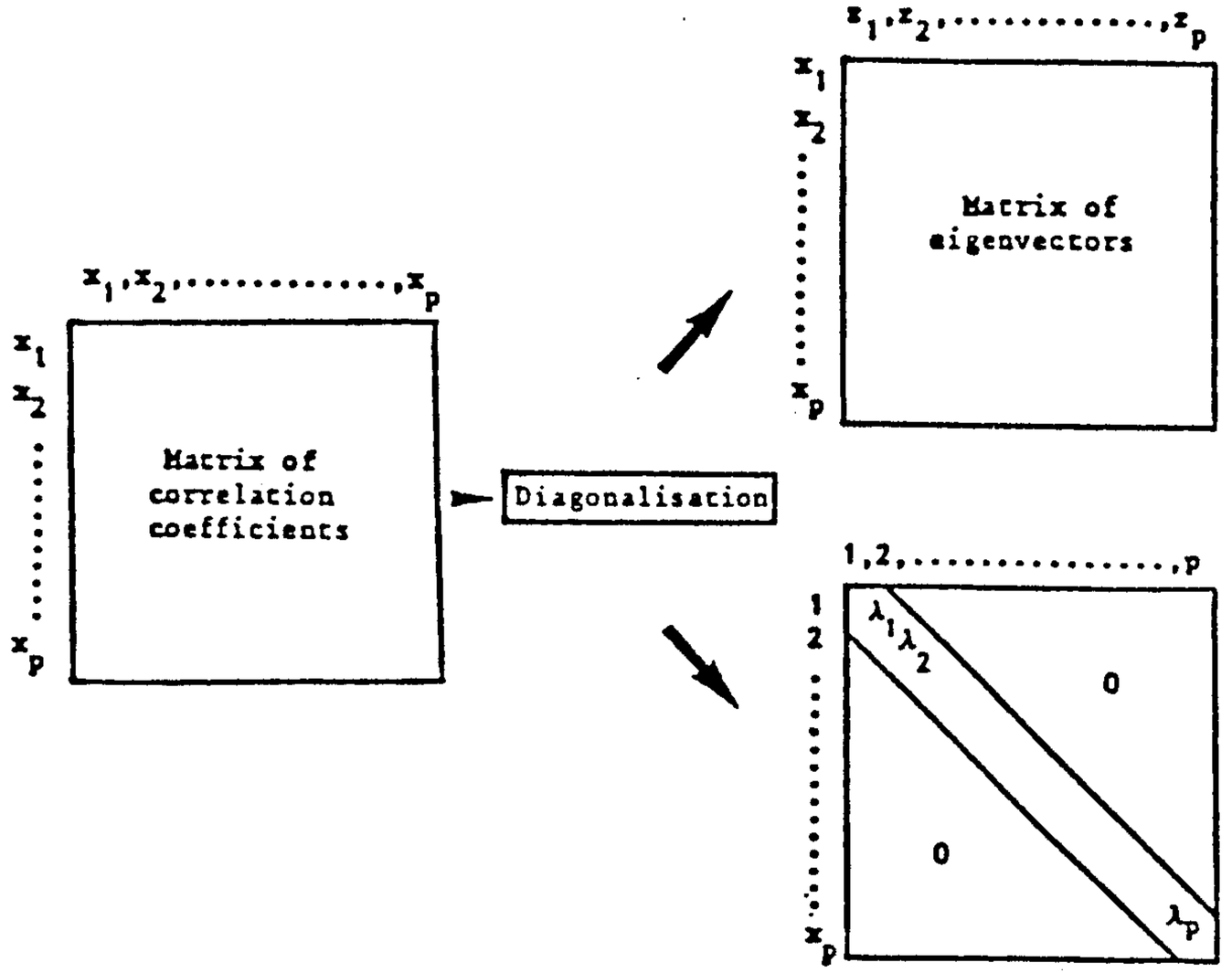

FIGURE (2)
Principle of principal component analysis.

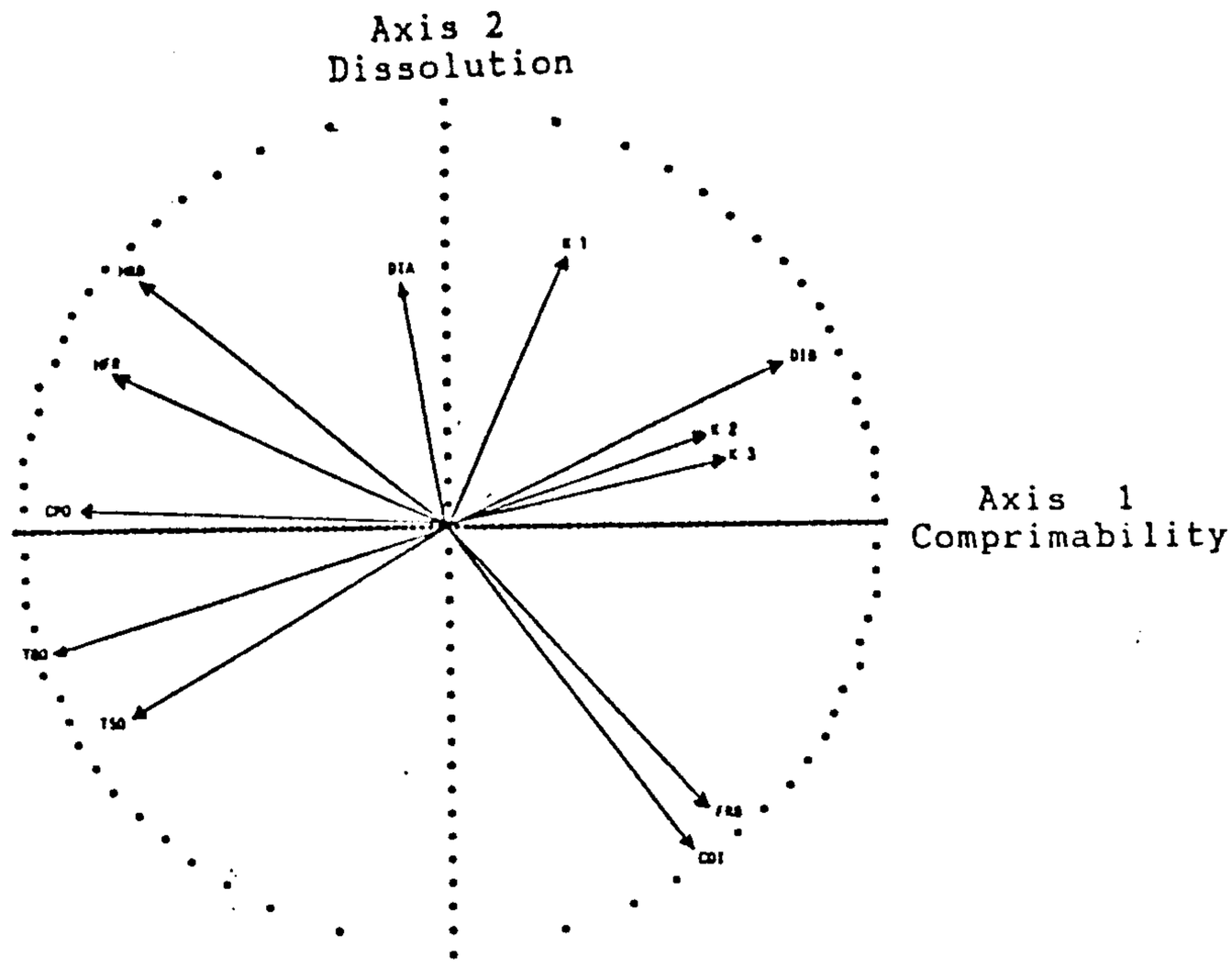

Fig.(3):Circle of Correlations on the Principal Plan 1-2
for Formulations Granulated With Eudragits Matrix

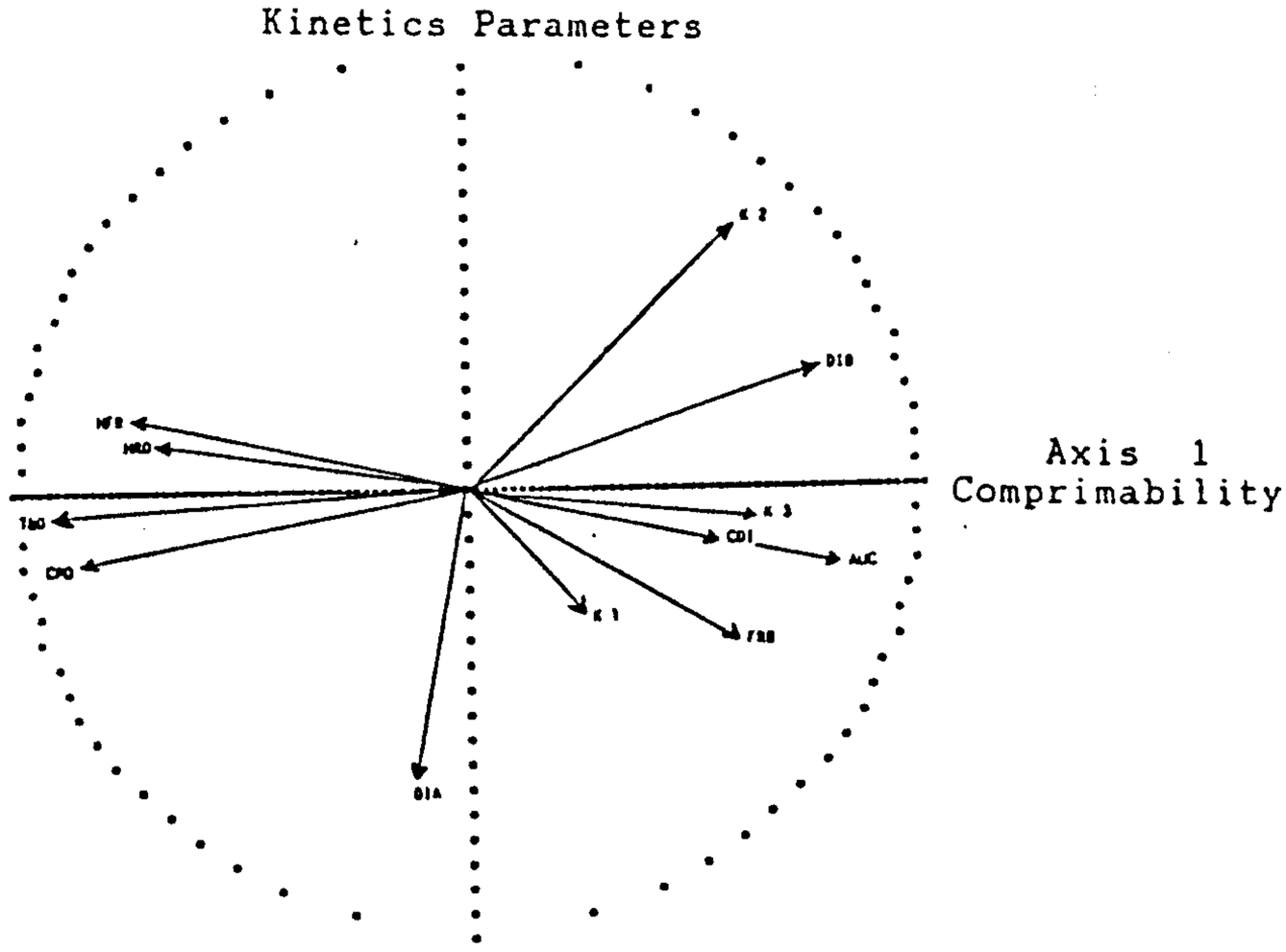

Fig.(4):Circle of Correlations on the Principal Plan 1-3
for Formulations Granulated With Eudragits Matrix

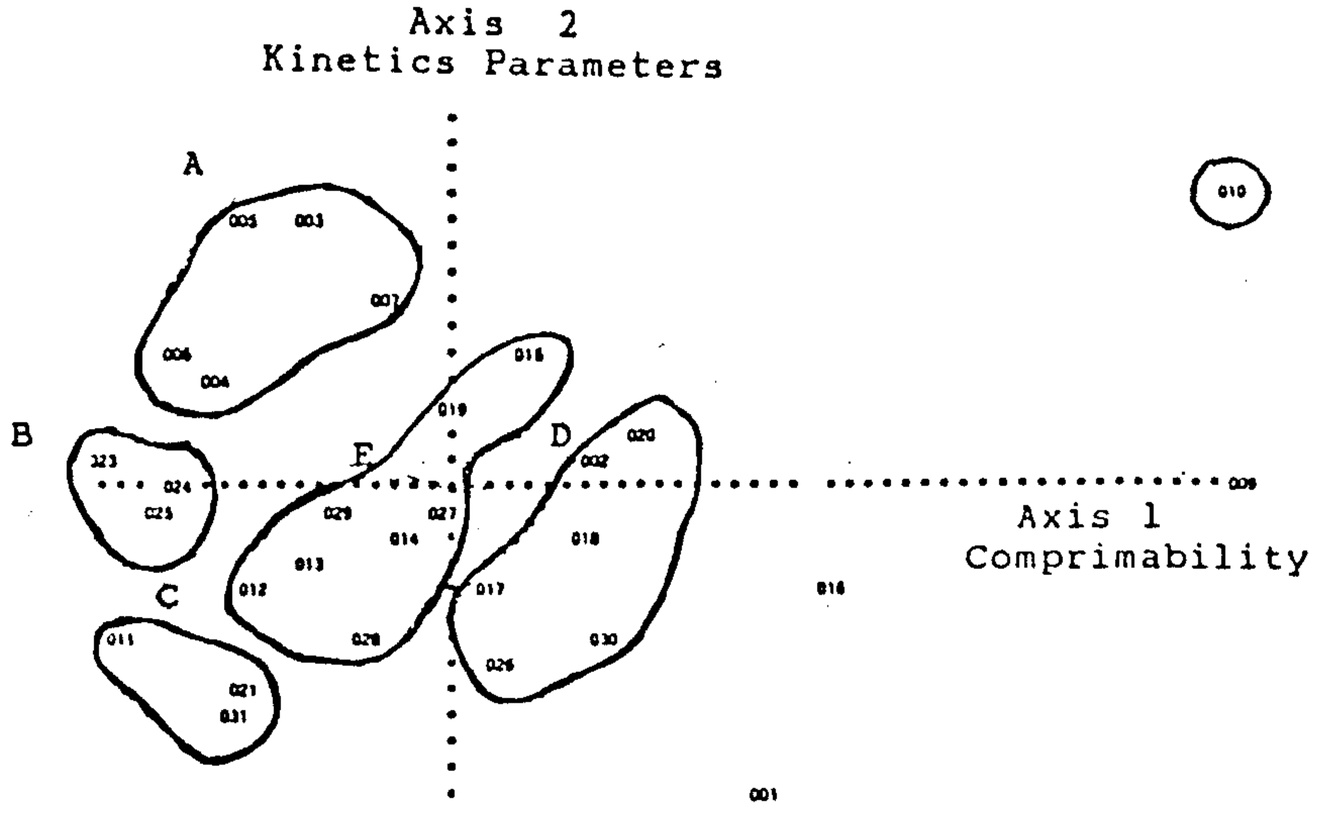

Fig.(5):Representation of the Formulae Granulated With Cellulosic Polymers on the Plan 1-2.

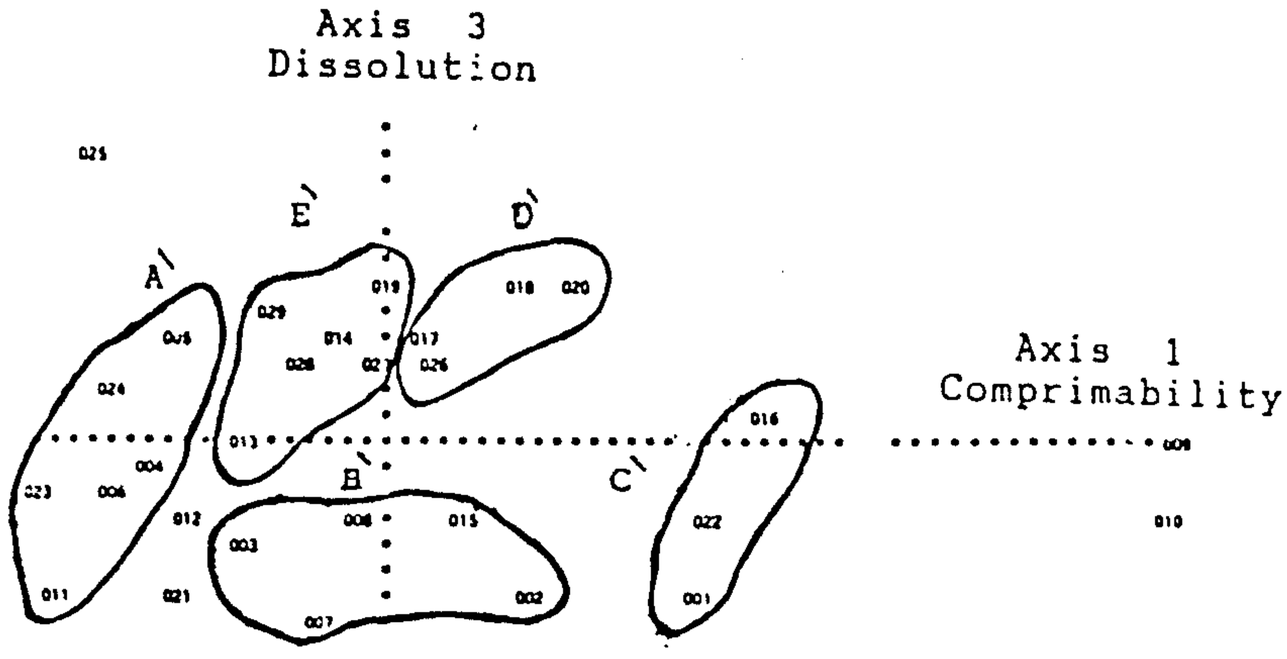

Fig.(6):Representation of the Formulae Granulated With Cellulosic Polymers on the Plan 1-3.

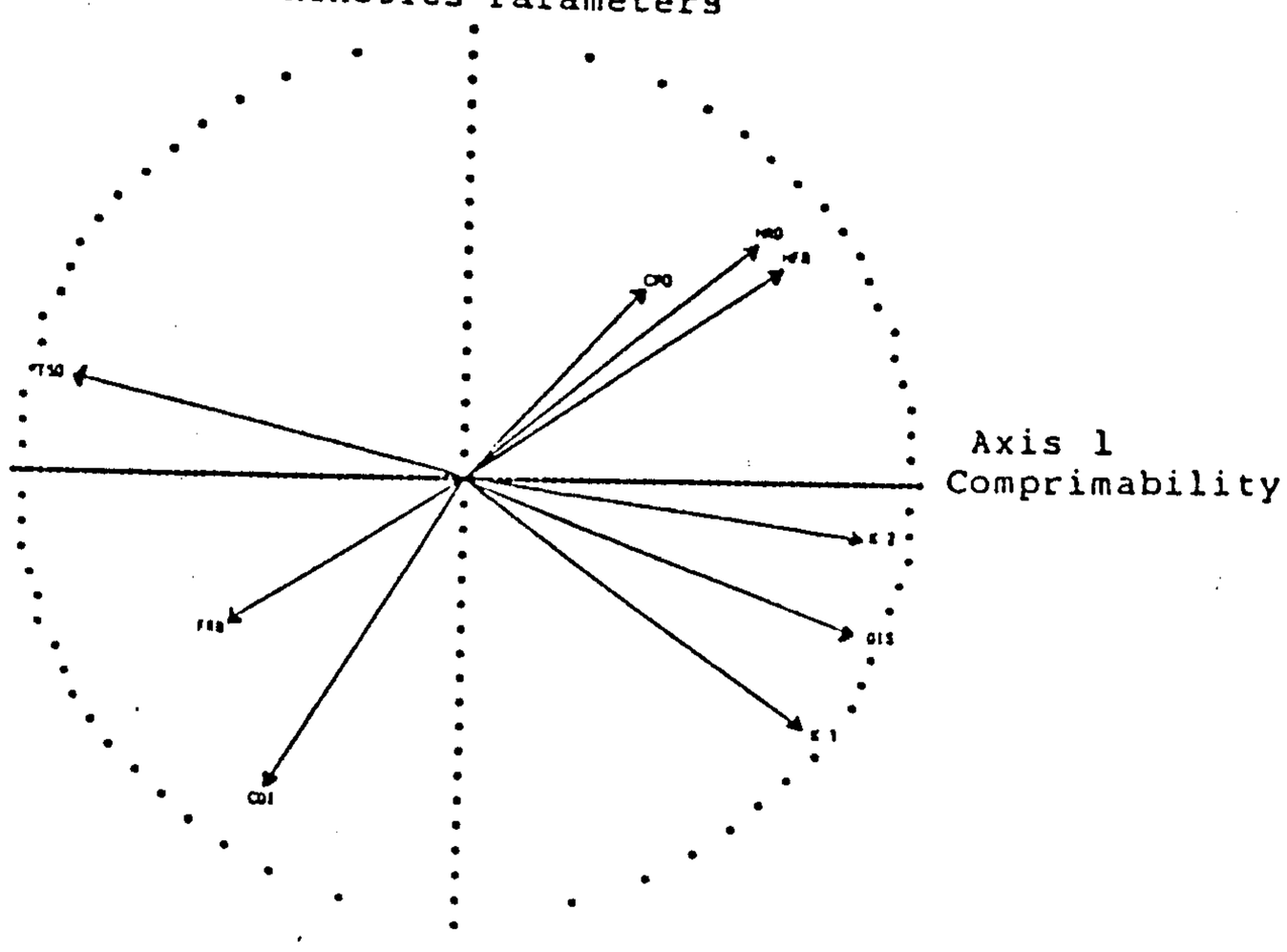

Fig.(7):Circle of Correlations on the Principal Plan 1-2
of Formulations Granulated With Cellulosic Matrix

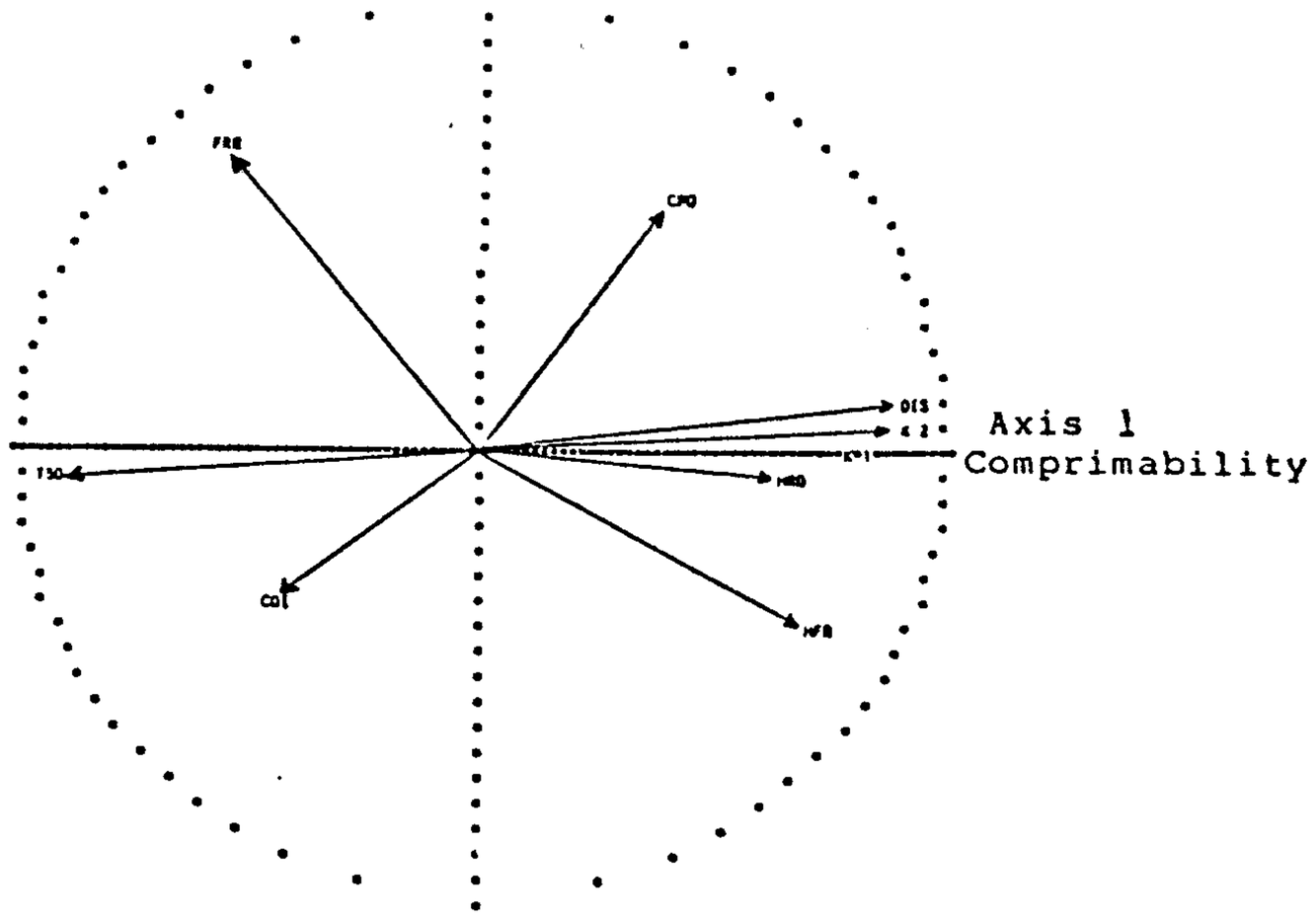

Fig.(8):Circle of Correlations on the Principal Plan 1-3
of Formulations Granulated With Cellulosic Matrix.

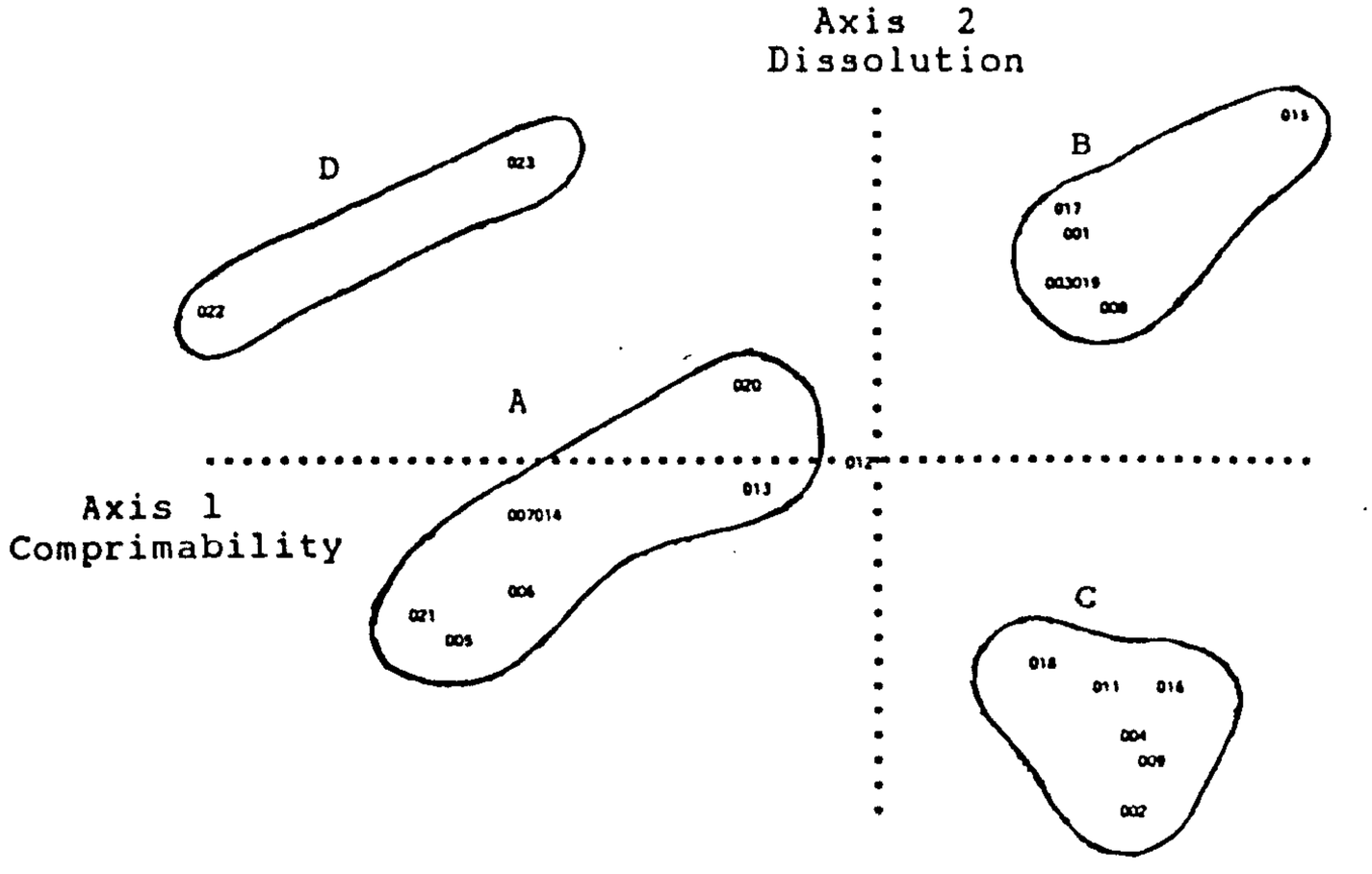

Fig.(9):Representation of Formulae Granulated With Eudragits on the Principal Plan 1-2.

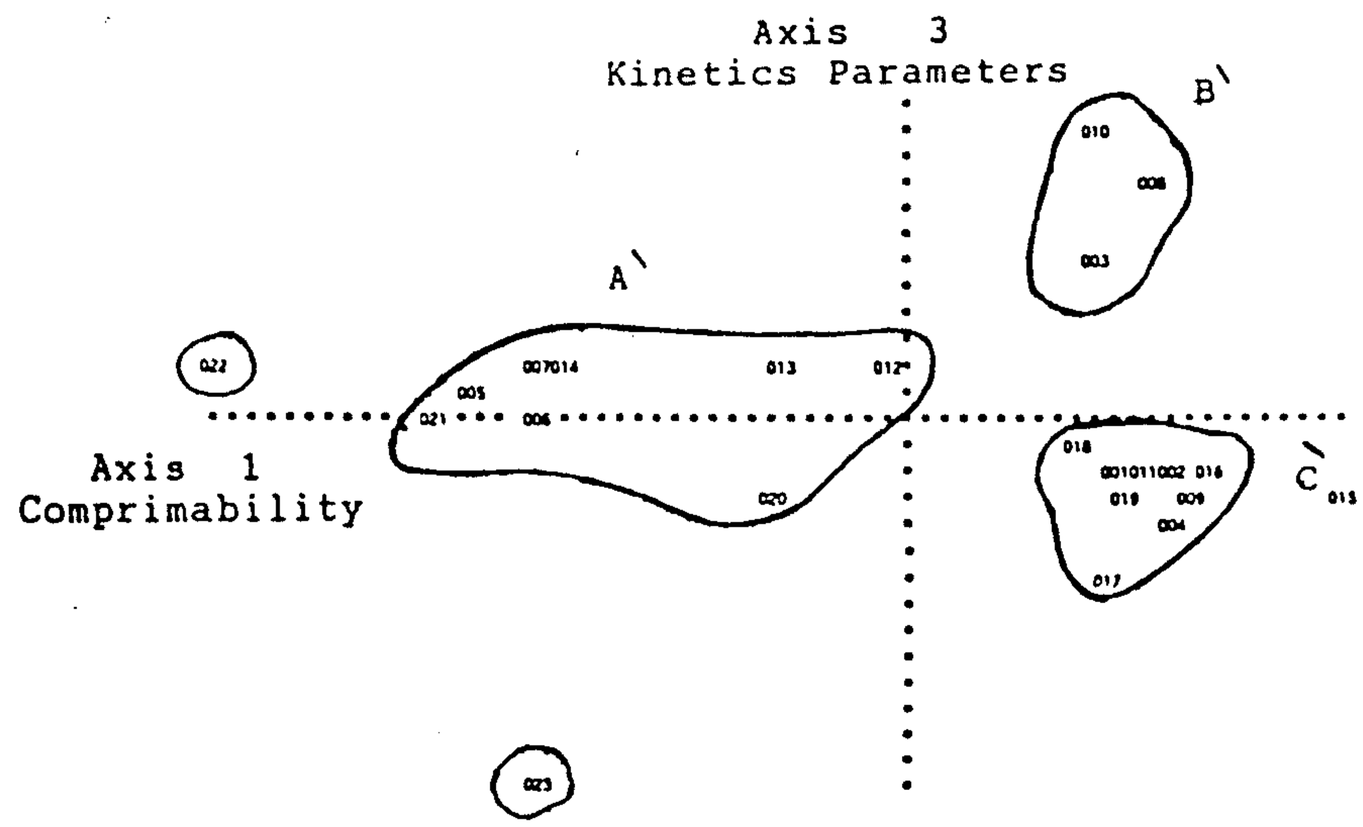

Fig.(10):Representation of Formulae Granulated With Eudragits on the Principal Plan 1-3.

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أختيار الصياغة الأفضل للأقراص المحضرة من صياغات طويلة المفعول من عقار الأيبوبروفين مع بوليمرات الأيدراجيت والسليلوز باستعمال تحليل المكونات الأساسية بواسطة الكمبيوتر

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أستخدمت بوليمرات الأيدراجيت والسليلوز - فى تنظيم انطلاق الايبوبروفين من أقراص المحضرة وذلك بتحضير حبيبات من العقار . ولقد استخدم برنامج كمبيوتر لتحليل المكونات الاساسية للصياغات لاختيار أفضل صياغة من الاقراص المحضرة وقد شملت هذه الصياغات (٥٤ صياغة) احتوت على (٢٣) عاملا مختلفا . ولقد فضل برنامج الكمبيوتر الصياغات طبقا لخاصية الكبس وفاعلية الاتاحة والعوامل الكبسية وكذلك افضل اختيار للبوليمر المستخدم لاطالة المفعول.

ومن هذه الدراسة وجد أن صياغة الايبوبروفين المحبب بواسطة (١٥٪) ايدراجيت رس ب م ويحتوى على ٢٣٪ آفسيل ب هـ ١٠٢ وكذلك صياغة الايبوبروفين المحبب بواسطة ٣٪ ايثيل سليلوز (٢٠) ويحتوى على ٢٣٪ آفسيل ب هـ ١٠٢ هما أفضل الصياغات.

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