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EMPLOYMENT OF SEQUENTIAL SIMPLEX METHOD OF OPTIMIZATION IN THE DEVELOPMENT OF FAST DISSOLVING TABLETS OF CLOZAPINE

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ABSTRACT

Among the various optimization techniques used, one of the simplest is the sequential simplex design. This approach has the in-built advantage of adjusting the levels of the factors to achieve the desired target. This method of optimization uses the results of previous experiments in a mathematically rigorous fashion to define the parameters (i.e. independent variables) for the next experiment in the search for optimum response. The present work aims at employing this technique to develop fast dissolving tablets of clozapine. The tablets were prepared by direct compression which has the advantage of simplicity and efficiency. Microcrystalline cellulose and polyplasdone were selected as the two variables and the formulations were evaluated for responses such as disintegration time, hardness and friability. The success of the formulations was evaluated in terms of a total response equation generated in accordance with the priority of the response parameters. Based on the ranking, the sequence was continued by different approaches such as reflection, expansion or contraction. The sequence was continued until a desirable disintegration time of less than 10 second with adequate hardness was achieved.

Keywords: *Optimization; Sequential Simplex; fast dissolving tablets; Clozapine; disintegration.*

INTRODUCTION

A formulation with optimum properties can be obtained by trial and error techniques, but this approach is time consuming, unreliable, costly and may provide only a provisionally acceptable solution rather than an optimum solution. Systematic optimization techniques help in obtaining an optimum formulation. These methods can be divided into sequential methods, simultaneous methods or combinations of both. With sequential methods, a small number of initial experiments are planned and carried out; succeeding experiments are based on the results obtained so far in the direction of increase/decrease of the response. In this way a maximum/minimum is reached. These methods are also called hill-climbing methods. Simultaneous methods, however, plan the complete set of experiments (the experimental design) beforehand.

The sequential simplex technique was developed by Spendley *et al.*[1] The method has been used in chemistry for diverse applications like development of analytical methods, pattern recognition, improving reaction yields and drug design. The simplex procedure derives its name from the geometric figure that is moved along the response surface in search of the optimum. This method approaches the optimum in a stepwise fashion by moving away from the low values of the response function rather than by moving in a line towards the maximum.

Clozapine, an antipsychotic agent has been found to be an ideal candidate for mouth dissolving tablets.[2] Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia and is used to suppress both positive and negative symptoms of schizophrenia and neuroleptic responses.[3] However, in case of uncooperative patients administration of medicine needs to be supervised and fast dissolving dosage forms because of their quicker disintegration property are desirable. The development of FDT is challenging because of the intricate balancing of two contradictory factors i.e. adequate mechanical strength for transportability and rapid disintegration time, which is affected by hardness.[4]

The aim of this study is to develop FDT with a target disintegration time of less than 10 s with an adequate hardness using sequential optimization procedure.

MATERIALS AND METHODS

Clozapine and Polyplasdone XL 10 were procured as a gift sample from Torrent Pharmaceuticals, Ahmedabad and International Speciality Products, Hongkong, respectively. Microcrystalline cellulose,

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lactose and magnesium stearate were obtained from Anglo French Drugs and Industries Limited, Bangalore.

Preparation of tablets

The tablets were prepared by direct compression method. Clozapine, microcrystalline cellulose, lactose and polyplasdone XL 10 were passed through # 20 sieve and mixed for 30 min in a suitable container to obtain a uniform blend. The blend was further lubricated with magnesium stearate (previously passed through # 40 sieve) for 5 minutes and compressed into tablets using a 7.5 mm flat punch in a 10 station RIMEK rotary tablet press.

Evaluation of tablets[5-7]

The tablets were evaluated for *in vitro* disintegration time, friability, hardness, wetting time, drug content and *in vitro* drug release.

In vitro disintegration time

The *in vitro* disintegration time was determined using Electrolab disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus containing simulated saliva pH 5.8 as the immersion liquid; one disk was added to each tube. The time taken for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured in seconds.

Wetting time

The method reported by Yunixia *et al.* was used to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small Petri dish (6.5 cm) containing 5 ml of simulated saliva (pH 6.8). A tablet was placed on the paper and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation determined.

Drug content

Ten tablets were powdered and a quantity equivalent to 25 mg of the drug was taken, dissolved in methanol and sonicated for 30 mins. The drug content was determined by a liquid chromatographic method with a C_{18} column using the mobile phase acetonitrile: 0.05 M phosphate buffer (70:30 v/v) at flow rate 1 ml/min with UV detection at 290 nm.[8]

***In vitro* release studies**

In vitro release studies were carried out using USP XXIII tablet dissolution test apparatus paddle method at 37 ± 1°C, taking 900 ml of pH 4.0 acetate buffer as dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Aliquots of 5 ml were withdrawn after 2, 4, 6, 8, 10, 12 and 45 min and analyzed spectrophotometrically at 290 nm.

Rationale of Optimization process

Formulation design

The initial formulations were designed as per the half factorial design[9] Initial experiments were designed based on the pre-existing knowledge (factors and their levels). Results of these experiments were analyzed with respect to closeness of the target response to obtain the levels of factors for the next experiment in a sequence and the process was continued to obtain the desired formulation. In a 2^n factorial experiment where each factor is studied at 2 levels, the total number of experiments for 2 factors will be 4. In sequential design, the total number of initial experiments is n+1 i.e. 3. In the present work, polyplasdone and microcrystalline cellulose were chosen as the two factors. As in factorial experiment, the high and low levels of each factor were decided taking consideration of the acceptable range. The initial n+1 formulation were designed by keeping each of the factors at high level once while the other factors are at low level as indicated in Table 1.

Table 1: *Levels of factors for the initial set of experiments of the sequence.*

Variables / Expt. No.	X_1 (% Microcrystalline cellulose)	X_2 (% Polyplasdone)
F_1	42.5	2
F_2	35	4
F_3	42.5	4

Conceptual basis of reflection, expansion and contraction

The conceptual basis of designing further experiments with independent variables X_1 and X_2 can be comprehended as in Figure 1.[10] The three points W, B and S representing worst, best and second best formulations define the simplex, which in this case is a triangle. The next point R (the first derived formulation) is found by reflecting across the B-S axis as shown in Figure 1. Further formulae are decided on the basis of response of this derived formulation following the principle of reflection/expansion/contraction. The process continues until a desired optimum is reached.

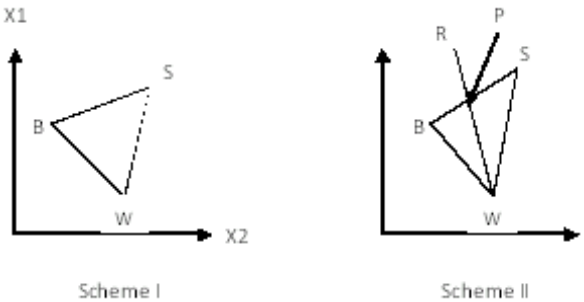

Fig. 1: *Figurative representation of the initial experiments of the simplex and of further sequence formation.*

As indicated in Fig.1, a given simplex is constructed of n+1 vertexes represented as n-dimensional vectors W, S, B. These vertexes are ranked in order of their responses, R_W for worst, Rs for second best and R_B for best. The centroid is P, while W is the eliminated vertex.

$$P = 1/n(S+B) \quad \text{Eq. 1}$$

where n= number of factors
S+B = levels of a particular factor in S and B
The first derived is obtained from the formula

$$R = P + (P - W) \quad \text{(reflection)} \quad \text{Eq. 2}$$

The response R_R at R is evaluated.
If Rs □ R_R □ R_B, then R is retained and the next step is obtained by reflection.
If R_R □ R_B, E is formulated using the formula

$$E = P + 2(P - W) \quad \text{(expansion)} \quad \text{Eq. 3}$$

If R_R □ R_W, then C is formulated using the formula
(contraction) Eq. 4

Normalization of response [10]
The levels of responses used for normalization are indicated in Table 2. This process was done using the equations:

$$N=[(X-M)/(H-M)]x100 \quad \text{Eq. 5}$$

$$N=[(H-X)/(H-M)]x100 \quad \text{Eq. 6}$$

Where N is the normalized factor, X is the original unnormalized value and M and H are the lowest and highest values respectively for the specific factor.

For normalization of hardness parameter equation 5 was used, whereas for disintegration time and friability equation 6 was used. (Table 2)

Table 2: *Levels of responses used for normalization*

Dependent variable (responses)	Low value (M)	High value (H)	Symbol (N)
Disintegration time(s)	2.0	30.0	R_1
Hardness(kg/cm^2)	2.0	05.0	R_2
Friability(%)	0.0	1.0	R_3

Ranking of the responses
Formulations were compared in terms of overall response designated as R_t. For this, a response equation was formed giving due consideration to the desirable parameters in order of priority.

$$R_t = 0.6R_1 + 0.3 R_2 + 0.1 R_3 \quad \text{Eq. 7}$$

where R_1 is the disintegration time, R_2 is hardness and R_3 is friability.

RESULTS AND DISCUSSION
The sequential simplex technique though introduced in the early sixties, formulation design using this technique is few and far between.[1] But compared to other optimization techniques, this method is simple and economical especially for result oriented work.

The numbers of initial experiments are comparatively less and the search can be ended once the desired/ acceptable response is obtained. The first derived formulation is obtained by moving diagonally away from the worst point just like a mirror reflection as given in equation 2.

Once the first derived formulation is included into the simplex sequence, the response of this formulation becomes a determining factor for the sequence formation. There can be three possibilities: The response can be the best or the worst or in between the best and the worst.

If the response is between the worst and the best, the derived formulation is retained and once again we go for reflection. If the response obtained is the best, we try to expand the levels of ingredients which were responsible for the betterment of the response. This is done by expansion as per equation 3. If the response obtained is the worst, then the levels of the factors are contracted i.e. the quantities are less than the average formula by a quantity of half of P-W. This is done using the equation 4. The schematic representation of reflection, expansion and contraction method from the actual experimental data is shown in Figure 2.

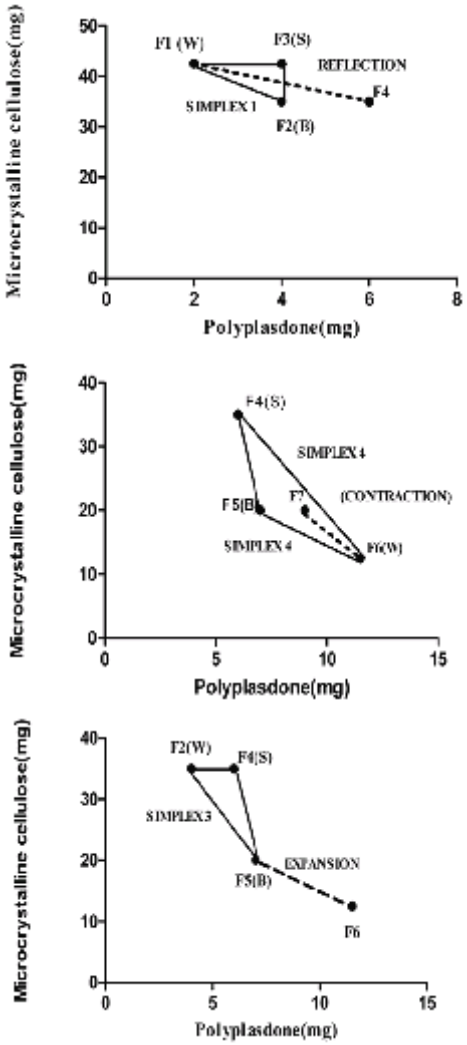

Fig. 2: *Schematic representation of reflection, expansion and contraction method from the actual experimental data as per equations 3, 4 and 5 respectively.*

Reason for selection of independent and dependent variables

The technique chosen for the preparation of FDT was direct compression which bypasses the process of granulation and thereby addition of binders. Hence microcrystalline cellulose was selected as a diluent, which also contributes to the cohesiveness of the tablet.[11,12] Based on the literature, polyplasdone XL 10 was selected as the superdisintegrant.[13,14] Since all the parameters important in FDT i.e disintegration time, hardness and friability can be influenced by the amount of microcrystalline cellulose and polyplasdone XL 10, they were selected as the factors. Since sequential search has an inbuilt flexibility for adjusting the levels of factors, the initial experiments were performed with moderately low levels of these factors.

Rationale for fixing the maximum and minimum levels of responses

An ideal FDT should have very good hardness (5 kg/cm^2), zero friability and dissolve immediately on administration into the mouth (approximately within 2 s). So these were set to be the desirable parameters and constitute one set of limiting values. The other limiting value of the range for each response was constituted from practical considerations. Since most of the FDT have got DT of 30s, the upper limit for DT was 30s. Similarly as the formulations belong to low weight category, a lower hardness is also acceptable. Hence the range chosen was 2 kg/cm^2 and 1% for hardness and friability respectively.

Rationale for normalization of response parameters

Of the three evaluation parameters, a low value for disintegration time and friability is desirable whereas the opposite is true for hardness. Hence while normalizing the data, two equations were used. In the equation 6, a lower value returns a positive result, whereas in equation 5, a higher value returns a positive result.

Response equation

Though the tablets were assessed for individual parameters, the overall success of the formulation was evaluated from a composite parameter that included all the three evaluation parameters in order of assigned priority. Equation 7 shows the highest priority was given for faster disintegration (0.6) as this is the prime objective of the work. Even if the disintegration parameter is met, insufficient hardness can lead to packing and transportation problems. Hence the priority of this factor was kept at a moderate value of 0.3. Since friability comes last in order of priority, a least value (0.1) is assigned.

Discussion about progression of the sequence

The initial three formulations were designed as per Table 1. Among the three initial formulations, F1 and F2 gave the worst and the best overall response of -184.9 and -72.14 respectively. Since the overall response of the first three formulations had negative values, the sequence had to be moved forward. The result of the simplex search is given in Table 3.

Table 3: *Results of simplex search*

Vertex	Simplex	Vertex retained	Method *	Normalized percent desired response			
				R_1	R_2	R_3	R_r
1	1	-	-	-357.0	66.6	93.2	-184.9
2	1	-	-	-160.7	50.0	92.6	-72.14
3	1	-	-	-232.1	83.3	91.5	-105.65
4	2	2,3	R	0.0	62.5	83.6	24.28
5	3	2,4	E	60.0	37.5	65.6	37.91
6	4	4,5	E	-20.0	37.5	55.5	-7.75
7	5	4,5	C	36.0	25.0	100.1	20.62
8	6	5,7	R	92.0	25.0	100.6	69.14
9	7	5,8	E	72.0	40.0	80.8	51.98

** R- Reflection ; E – Expansion ; C – Contraction.*

The next formulation F4 in the sequence was determined by the process of reflection, which showed a positive value (24.28) in simplex 2. The next vector F5 for simplex 3 was determined by expansion which showed a further improvement in the total response (37.91). In an attempt to get closer to the target response, F6 was formulated again by the process of expansion, but this showed a negative response (-7.75) in simplex 4. The next vector F7 was formulated by the process of contraction, which gave a positive response (20.62), which was the second best in simplex 5. As per the rule, the next formulation F8 was determined by reflection which showed an improvement in the total response (69.14) in simplex 6. Expansion of this vector to get a still better response was not successful as the next formulation F9 gave a total response of 51.98 which was less compared to F8. The response improvement during the simplex search is indicated in Fig. 3.

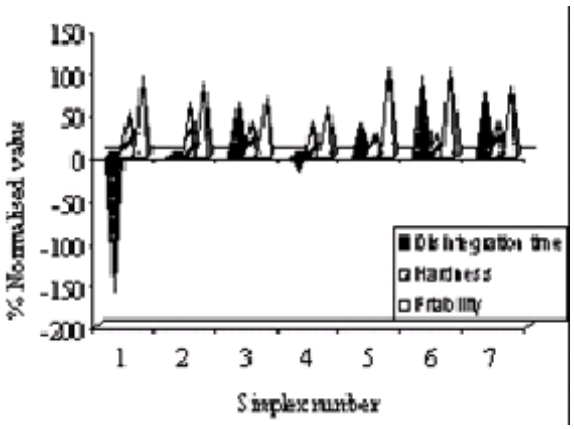

Fig. 3: *Response improvement during the simplex search. The normalized response of the most recent vertex is plotted against the appropriate simplex number.*

The sequential search was stopped at this stage since the formulation F8 was able to meet the target response. The composition of F8 is given in Table 4. The optimized formulation exhibited a good hardness of 3.0 ± 0.2 kg/cm^2. The friability was found to be within

the acceptable limits (0.1% w/w). The disintegration time and wetting time of the tablets was found to be 7 ± 1.3 s and 6 ± 2.5s respectively. *In vitro* drug release studies showed a cumulative percent release of 85.96 % ± 2.5 after a period of 10min. Based on these parameters F8 was considered to be the optimized formulation within the given set of factorial constraints.

Table 4: *Composition of the optimized formulation*

Ingredients	% w/w	Quantity per tablet (mg)
Clozapine	12.5	25
Microcrystalline cellulose	27.5	55
Lactose	55.0	110
Polyplasdone XL 10	4.5	0.45
Magnesium stearate	0.5	1.0

CONCLUSION

We conclude to say that optimization by sequential simplex can be a time saving and economical method for dosage development and result oriented work. In this technique, the numbers of initial experiments are comparatively less and the search can be ended once the desired or acceptable response is obtained. This technique was successfully used to develop fast dissolving tablets of clozapine having a disintegration time of less than 10s and adequate hardness.

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