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Investigation of the Stability with Bracketing Design in Tablet Form

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Abstract

EMA, FDA and ICH guidelines provide guidance to manufacturers of pharmaceutical products for planning and evaluating the stability tests. A full study design is discribed as a model in which samples for every combination of all design factors are tested at all time points. On the other hand matrix and bracket desings are known as a reduced design which can be a suitable alternative to a full design when certain design factors are involved. The bracketing design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Reducing number of stability test with bracketing design is considered as an alternative to the full factorial design to avoid costly and time consuming.

In this study, an application of the survey of 4 different forms of glimepiride tablet by bracket design method is given. Among the four doses of the medicine, the extreme amounts of active pharmaceutical ingredient are chosen and several quality parameters such as content uniformity, weight variation, tablet crushing strength, disintegration and friability, tablet dissolution rate, disintegration time, active substance ingredient amount, diameter and thickness of tablets are determined in accelerated and long-term stability conditions. Using these results, the properties of tablets with intermediate amounts are calculated with the help of statistical modeling. For four of six examined quality control parameters the r^2 values are close to 1 and all found F values are greater than the tabulated values. These results show that the correlations used in the modeling part are accurate.

Keywords: Stability design; Bracketing design; Matrixing design; Quality control methods on tablets; Glimepride

Introduction

Stability of the active substance and the product is defined as the most important factor to consider at pharmaceutical product design and development. It must be demonstrated that pharmaceutical product characteristics from the production have not changed until the patient's use. Therefore, the stability is the most important quality indicator [1,2].

Stability study includes testing which provides evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light. The aim of a stability study is not only to characterize the degradation of an active substance or pharmaceutical product but also to establish a shelf life applicable to all future batches manufactured and packaged under similar circumstances. By running stability tests, degree of maintenance of the physical, microbiological, therapeutic, and toxicological stability of an active substance or pharmaceutical product can be determined.

Tablets, which are obtained by compressing uniform volumes of particles, are solid preparations each containing a single dose of one or more active substance. Most of them are intended for oral administration. Some of them are swallowed whole, some after being chewed, some are dissolved or dispersed in the water before administration and some are retained in the mouth where the active ingredient is liberated [3].

The exception of the general stability properties of solid pharmaceutical forms within the scope of this study, the effect of temperature, humidity, light and oxygen can be seen depending on active or minor substances and manufacturing techniques. There can be caused degradation of the active substance or pharmaceutical form, reduction in activity, and microbial contamination. Due to these factors, significant differences can be observed in bioavailability by changing the resistance to tablets breakage, disintegration and dissolution characteristics [1]. Important parameters for the determination of stability of tablets are; organoleptic properties, mechanical durability, moisture content, disintegration property, dissolution rate, drying loss, weight variation and determination the amount of active ingredient [4,5].

Many designs are available in stability studies. An appropriate stability design can help to achieve the accurate shelf life of the pharmaceutical product. The ICH, FDA and EMA stability guidelines recommends full or reduced designs [6,7].

A full study design is one in which samples for every combination of all design factors are tested at all time points. A reduced design is one in which samples for every factor combination are not all tested at all time points. Bracketing and matrixing which are commonly used reduced designs are based on different principles. Reduced designs are prefered to avoid the cost and time consuming. Bracketing is the design of a stability schedule such that only the extremes of certain design factors are tested al all time points. According to bracketing design, the samples on the extremes of ordered levels of an appropriate factor are tested. The bracketing design assumes that the stability of the intermediate condition samples is included in those at the extremes [7].

Design factors of the bracketing are strength, container size and/or fill. If capsules of different strengths with different plug size are used in same powder blend, and tablets of different strengths are compressed

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with varying amounts of same granulation, and oral solutions of different strengths are with formulations that differ only in minor excipients (e.g., colourants, flavourings), they can be examined with bracketing design.

A bracketing design is applicable with justification to studies with multiple strengths where relative amounts of active substance and excipients change in a formulation. Justification means that corresponding supportive data on the product are available, e.g. stability profiles of different strengths of clinical or development batches. Bracketing is not applicable if different excipients are used in formulations.

Material and Methods

Glimepiride was kindly provided from Eczacıbaşı Zentiva, Turkey. Other reagents were of analytical grade. Verifying tablets coded as G1 and G4 with three different parallel (GA,GB, and GC) were obtained from market.

In this study, we proposed and studied the bracketing design model with glimepiride including tablets which have four different doses at the market. Bracketing design assumes that the stability of any intermediate level is represented by the stability of the extremes tested. We developed accelerated and long term stability tests for 6 months with the extreme doses (1 mg and 4 mg). Bracketing design was summarized in Table 1.

We calculated the amount of active ingredient of tablets according to EP 2005 under the title "uniformity of content". Briefly, randomly taken 10 tablets were weighed. They all disintegrated into powder. Powder samples (n:3) were taken randomly as an average weight of a tablet. Samples were dissolved in 1 mL acetonitrile-water (4:1 v/v) solution and completed to 100 mL with phosphate buffer saline (PBS; pH: 7.8). 1 mL of final solution was diluted to 10 mL with PBS and measured at 229 nm spectrophotometrically.

Uniformity of weight

20 tablets were selected randomly and their average weight, standard and relative deviations were determined.

Disintegration

Disintegration test was carried on according to method which was specified in EP 5.3, 2006. This test determines the tablets disintegrating within a prescribed time when placed in an immersion fluid under prescribed experimental conditions. Disintegration is defined as the state in which no residue of the tablet remains on the screen of the basket at the required temperature (37 ± 2°C).

Friability

This test is a method to determine physical strength of uncoated tablets upon exposure to mechanical shock and attrition. Briefly, a number of tablets were weighed and placed in the apparatus where they are exposed to rolling and repeated shocks in each turns (25 min^{-1}) within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets were weighed and the weight was compared with the initial weight. The loss due to abrasion was a measure of the tablet friability. The value was expressed as a percentage.

Diameter and thickness of the tablets

One of the important criteria of the tablet, which is not registered in pharmacopoeia, is determining the thickness and diameter of the tablet. A number of tablets were measured with compass and because of their oblong shape two type of average diameter (d1 and d2) and average thickness were calculated.

Dissolution

Dissolution testing was carried out under conditions that were described in EP 2005 with a paddle method at 75 rpm in PBS. Rapidly dissolving tablets ensure 80% dissolution in 15 minutes. So we did analysis from the samples which were taken at 15 min.

Hardness

The tablet breaking force is measured with Stokes in a reproducible way. Breaking force of 10 tablets were recorded as kgf (kp).

Calculating the intermediate levels (G2 and G3)

Linear regression was used to estimate the stability of the intermediate levels coded as G2 (2 mg) and G3 (3 mg) by SPSS, v9. The relationship with extreme levels were defined with the equation 1.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_5X_5 + b_6X_6 \quad \text{(Eq 1)}$$

Y is a dependent value of the estimated stability of G2 or G3. This value cannot be measured, but could be calculated by linear regression of independent variables, such as the amount of active ingredient (X_1); time (X_2); temperature (X_3); diameter-1 (X_4); diameter-2 (X_4); and thickness (X_5). Program omitted the value of diameters from the equation because they had insignificant effect in our modelling.

As several stability studies, in this study we used the linear regression model, which was using parametric assumptions [8]. ANOVA (ANalysis Of VAriance) was used and the hypothesis was established negatively. The analysis of variance is a collection of statistical models, in which the observed variance in a particular variable is partitioned into components attributable to different sources of variation and one-way, two-way, or two-way repeated can be applied much more versatile [9]. We used repeated two-way analysis of variance and multiple independent variables affecting the dependent variables were investigated.

We established hypothesis negatively, so we expect no relationship between the investigated parameters. Model related results were evaluated by calculating r^2, F and P parameters. Coefficient of determination (r^2) was calculated by regression analysis to explain the degree of linear-correlation between each measured and estimated variable. F is the ratio of the model mean square to the error mean square and used to decide whether the model as a whole has statistically significant predictive capability [9,10]. The P value is the level of the model error, telling us whether a variable has statistically significant predictive capability in the presence of the other variables [9]. The hypothesis was rejected if the F value is higher than the table F, means as there is a relationship between the parameters.

Stability	Drug	1mg			2 mg	3 mg	4 mg		
	Batch	G1A	G1B	G1C			G4A	G4B	G4C
Long term		0. 3. and 6 month	0. 3. and 6 month	0. 3. and 6 month	x	x	0. 3. and 6 month	0. 3. and 6 month	0. 3. and 6 month
Accelerated		0 and 6 month	0 and 6 month	0 and 6 month	x	x	0 and 6 month	0 and 6 month	0 and 6 month

Table 1: Applied bracketing design.

Results

Wavelenght of 229 nm is defined for validation study by using UV spectra of a variety of concentrations those are acquired by Glimepirid's acetonitrile-water (4:1, v/v)/PBS medium (pH 7.8). Method is validated by each validation parameter. Accelerated stability test results of G1 and G4 coded are given in Table 2.

Estimated results of the accelerated stability test of G2 and G3 are given in Table 3, by using the results of extreme points (1 mg (G1) and 4 mg (G4)).

Long term stability (at 25°C and 60 ± 5% relative humidity for 6 months) test results of G1 and G4 coded are given in Table 4. Belong to this data estimated values of G2 and G3 long term stability results are in Table 5.

In our study, the diameter and thickness were also measured. However, there isn't any change in diameter by the effect of time and temperature, so that values of diameter were excluded from the model.

Estimated values which are evaluated from experimental measurements of G1 and G4 were also calculated through modeling for accurate results. The results of estimated and experimental measurements were graphed by regression (Figure 1).

Experimental results of G1 and G4 and estimated results derived from again these results for G2 and G3, and also correlation coefficient of estimation method were given in Table 6. Therein for each series average of experimental results were taken into account.

Discussion

Stability tests are the analyses which defines the shelf life of drug product and they are also important and necessary for observing drug's degradation in the process of time. Extreme samples of factors like vessel size and/or different doses were tested at each time point in Bracket design and it is assumed that extreme samples represents intermediate samples. If the drug has various doses, like in our study, or different vessel sizes are available Bracket design can be used [7].

Two doses (G1 and G4 coded drugs) of the generic drug which has four form in the market was observed in terms of long term and accelerated stability tests on three batches in consideration of quality control tests in the pharmacopoeia and also evaluated with appearance and colour tests in tablet that are not exist in the pharmacopoeia. There was no differencein any samples relating to appearance and colour observations during stability tests.

All the pharmacopoeia criterias were met during disintergation test of drug G1 in each time point both in long term and accelerated tests [3]. Disintegration time of G1/G4 coded drugs were 70/150 seconds respectively at the beginning of the tests but this duration decreased by time. For instance, it was 47/164 seconds after 6 month accelerated stability conditions and 50/162 seconds after 3-6 months long term stability conditions, respectively (Table 2 and 4). Obtained disintegration time datas show that drug G4 meets the pharmacopoeia limits. Because of G4's tablet weight is two times heavier than G1, disintegration time of G4 prolonged compare to G1. Predicted values of G2 is given in the Table 3 and 5. There was no significant difference was found in disintegration time analyses of G2 coded tablet neither at

		Appearance	Disintegration time (sec)	Average weight (mg)	Hardness (kp)	Friability (%)	Dissolution (%)	Amount (mg/tablet)
	Specification limits	oblonged shaped. notched	max. 30'	G1: 85 ± 7.5% G4: 170 ± 7.5%	$\bar{x}$ ± 3.5%	max. 1 %	min. 80% (at 15')	G1: 0.85-1.15 G4: 3.4 – 4.6
G1	**Time**							
G1A	t=0	appropriate	70.00 ± 0.000	84.46 ± 0.001	7.0	0.959	88.889 ± 0.207	0.988 ± 0.010
	6th month	appropriate	47.8 ± 0.408	84.00 ± 0.000	6.5	0.381	62.963 ± 1.480	0.844 ± 0.010
G1B	t=0	appropriate	70.50 ± 0.764	86.27 ± 0.001	7.0	0.939	82.405 ± 0.182	0.823 ± 0.000
	6th month	appropriate	47.25 ± 0.418	86.30 ± 0.000	6.5	0.405	67.593 ± 1.52	0.802 ± 0.000
G1C	t=0	appropriate	70.50 ± 0.836	84.56 ± 0.001	7.0	0.982	82.310 ± 1.263	0.823 ± 0.000
	6th month	appropriate	46.60 ± 0.816	84.00 ± 0.000	6.5	0.595	76.130 ± 0.960	0.761 ± 0.000
G4	**Time**							
G4A	t=0	appropriate	150.5 ± 0.836	167.1 ± 0.002	13	0.276	86.574 ± 0.142	3.868 ± 0.010
	6th month	appropriate	164.6 ± 0.516	168.7 ± 0.001	12	0.551	82.407 ± 0.707	3.745 ± 0.042
G4B	t=0	appropriate	150.5 ± 0.836	167.1 ± 0.001	13	0.143	86.111 ± 0.535	3.909 ± 0.000
	6th month	appropriate	164.1 ± 0.408	166.3 ± 0.001	12	0.343	83.333 ± 0.720	3.642 ± 0.040
G4C	t=0	appropriate	150.0 ± 0.000	167.0 ± 0.001	13	0.096	83.796 ± 0.426	3.868 ± 0.010
	6th month	appropriate	166.0 ± 0.000	166.9 ± 0.000	12	0.372	83.796 ± 0.721	3.683 ± 0.040

Table 2: Accelerated stability test results of G1 and G4 of three different batches.

		Appearance	Disintegration time (sec)	Average weight (mg)	Hardness (kp)	Friability (%)	Dissolution (%)	Amount (mg/tablet)
		oblonged shaped. notched	max. 30'	170 ± 7.5%	$\bar{x}$ ± 3.5%	max. 1 %	min. 80% (at 15')	G2: 1.7-2.3 G3: 2.55-3.45
	G2 t=0	appropriate	109.46	120	8.76	0.28	105.14	1.56
G2	6th month	appropriate	106.37	120	8.22	0.31	96.95	1.43
	G3 t=0	appropriate	141.61	140	10.58	0.18	103.14	2.61
G3	6th month	appropriate	138.52	140	10.03	0.22	94.95	2.49

Table 3: Estimated results of the accelerated stability test of G2 and G3.

	Appearance	Disintegration time (sec)	Average weight (mg)	Hardness (kp)	Friability (%)	Dissolution (%)	Amount (mg/tablet)	
	Specification limits	oblonged shaped. notched	max. 30'	G1: 85±7.5% G4: 170 ± 7.5%	$\bar{x}$ ± 3.5%	max. 1%	min. 80% (at 15')	G1: 0.85-1.15 G4: 3.4–4.6
G1	**Time**							
G1A	t=0	appropriate	70.0 ± 0.000	84.46 ± 0.001	7.0	0.959	88.889 ± 0.207	0.988 ± 0.010
		appropriate	49.9 ± 0.000	84.60 ± 0.001	7.0	0.212	77.778 ± 0.200	0.700 ± 0.032
	6th month	appropriate	46.7 ± 0.816	84.56 ± 0.001	6.5	1.361	75.924 ± 0.142	0.761 ± 0.030
G1B	t=0	appropriate	70.5 ± 0.764	86.27 ± 0.001	7.0	0.939	82.407 ± 0.182	0.823 ± 0.000
		appropriate	50.0 ±0.204	86.30 ± 0.001	7.0	0.242	84.259 ± 0.183	0.720 ± 0.028
	6th month	appropriate	48.1 ± 0.480	84.50 ± 0.001	6.5	1.290	80.556 ± 0.150	0.792 ± 0.024
G1C	t=0	appropriate	70.5 ± 0.836	84.56 ± 0.001	7.0	0.982	75.924 ± 1.263	0.823 ± 0.000
		appropriate	50.1 ± 0.204	86.40 ± 0.001	7.0	0.301	90.740 ± 0.192	0.720 ± 0.030
	6th month	appropriate	50.1 ± 0.850	84.50 ± 0.001	6.5	1.112	85.185 ± 0.150	0.823 ± 0.036
G4	**Time**							
G4A	t=0	appropriate	150.5 ± 0.836	167.1 ± 0.002	13.0	0.276	86.574 ± 0.142	3.868 ± 0.010
		appropriate	162.5 ± 0.836	167.3 ± 0.002	11.5	0.335	84.722 ± 0.122	3.868 ± 0.037
	6th month	appropriate	162.5 ± 0.836	166.1 ± 0.001	12.5	0.572	83.333 ± 0.920	3.786 ± 0.025
G4B	t=0	appropriate	150.5 ± 0.836	167.1 ± 0.001	13.0	0.143	86.111 ± 0.535	3.909 ± 0.000
		appropriate	162.5 ± 0.836	167.1 ± 0.001	11.5	0.186	84.722 ± 0.120	3.807 ± 0.021
	6th month	appropriate	162.5 ± 0.836	166.8 ± 0.001	12.5	0.659	84.259 ± 0.800	3.724 ± 0.045
G4C	t = 0	appropriate	150.5 ± 0.000	167.0 ± 0.001	13.0	0.143	83.796 ± 0.426	3.868 ± 0.010
		appropriate	162.0 ± 1.549	167.0 ± 0.001	11.5	0.120	86.574 ± 0.080	3.765 ± 0.040
	6th month	appropriate	162.5 ± 1.549	167.5 ± 0.001	12.5	0.363	85.185 ± 0.860	3.786 ± 0.040

Table 4: Long term stability test results of G1 and G4 of three different batches.

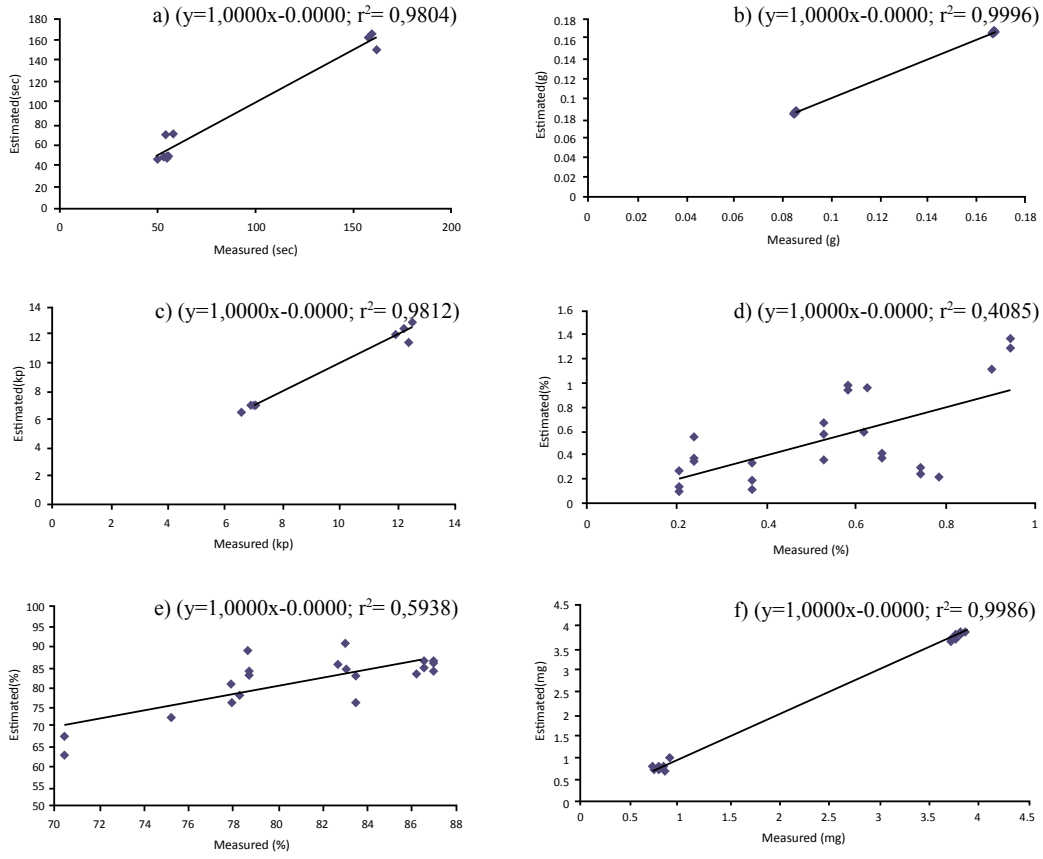

Figure 1: Regression graphs of a) disintegration time, b) average weight, c) hardness, d) friability, e) dissolution rate, and f) content uniformity, measured values correspond to estimated values.

long term nor in accelerated stability tests and results are in the range of pharmacopoeia limits. The predicted values which were obtained for G3, were found in the limitations and there was no big deviations (Table 3 and 5) due to time and temperature for these values.

The results of the long term and accelerated stability tests in terms of bulk uniformity for G1 and G4 coded drugs that have 85 mg and 170 mg tablet weight respectively, were found in EP 5.3.'s limits which specified as maximum deviation has to be 7.5% and no significant change was observed due to temperature end humidity (Table 2 and 4). Predicted tablet weight varioations for G2 and G3 coded tablets is 30% and 17% respectively which are out of pharmacopoeia limits (Table 3 and 5). Because weight of G1 coded tablet is 85 mg, G2, G3 and G4 coded tablets weights are 170 mg and tablet weight doesn't increase proportionally drug dose. Because of that fact it would be more feasible to use measured values instead of predicted values.

Hardness test deviations should be max. 3.5% [4]. There are differences among G1 and G4 coded tablet batches in terms of hardness test results (Table 2 and 4) which are within the limits mentioned before. There is not any deviation values for G2 and G3 coded drugs because of there is only one predicted limit obtained from Bracket design (Table 3 and 5). In addition, because of r^2 value is very close to 1, low standart error value and high F value, no deviation was expected in hardness test results of G2 and G3 coded drugs. From our experimental findings show that upper limit should be 12 kp and all the predicted values is under the limit of 12 kp.

Friability test results of the tablets were given as % loss and the upper limit is indicated as 1% by EP 5.3. During accelerated stabiliity tests of G1 coded drug no value was observed which exceeded the limit but at the 6th month measurements of long term stability studies which are found as 1.361%, 1.290% and 1.12% exceeded the limit of 1%. There

	Appearance	Disintegration time (sec)	Average weight (mg)	Hardness (kp)	Friability (%)	Dissolution (%)	Amount (mg/tablet)
	oblonged shaped. notched	max. 30'	170 ± 7.5%	$\bar{x}$ ± 3.5%	max. 1%	min. 80% (at 15')	G2: 1.7 – 2.3 G3: 2.55-3.45
G2 t =0	appropriate	109.46	120	8.76	0.28	105.14	1.56
G2 3rd month	appropriate	107.27	120	8.64	0.44	104.76	1.5
G2 6th month	appropriate	105.08	110	8.51	0.60	104.38	1.45
G3 t =0	appropriate	141.61	140	10.58	0.18	103.14	2.61
G3 3rd month	appropriate	139.42	140	10.45	0.54	102.76	2.55
G3 6th month	appropriate	137.22	140	10.32	0.30	102.38	2.50

Table 5: Estimated results of the long term stability test of G2 and G3.

Glimepiride	Type of stability	t (month)	Disintegration time (s)	Avarage weight (mg)	Hardness (kp)	Friability (%)	*Dissolution rate (%)	Amount (mg/ tablet)
G1 (Measured)	Accelerated	0	70.330	85.096	7.000	0.959	84.534	0.878
		6	47.220	84.766	6.500	0.460	68.895	0.802
	Long term	0	70.330	85.096	7.000	0.960	82.406	0.878
		3	50.900	85.766	7.000	0.251	84.259	0.713
		6	48.300	84.520	6.500	1.254	80.555	0.792
G2 (Calculated)	Accelerated	0	109.460	120.000	8.760	0.280	105.140	1.560
		6	106.370	120.000	8.220	0.310	96.950	1.430
	Long term	0	109.460	120.000	8.760	0.280	105.140	1.560
		3	107.270	120.000	8.640	0.440	104.760	1.500
		6	105.080	110.000	8.500	0.600	104.380	1.450
G3 (Calculated)	Accelerated	0	141.610	140.000	10.580	0.180	103.140	2.610
		6	138.520	140.000	10.030	0.220	94.950	2.490
	Long term	0	141.610	140.000	10.580	0.180	103.140	2.610
		3	139.420	140.000	10.450	0.540	102.760	2.550
		6	137.220	140.000	10.320	0.300	102.380	2.500
G4 (Measured)	Accelerated	0	150.330	167.066	13.000	0.172	85.494	3.882
		6	164.900	167.300	12.000	0.422	83.178	3.690
	Long term	0	150.500	167.066	13.000	0.188	85.494	3.910
		3	166.300	167.133	11.500	0.213	85.340	3.813
		6	162.30	166.80	12.5	0.531	84.260	3.765
** correlation coefficiency (r^2)			0.9804	0.9996	0.9832	0.4085	0.5938	0.9986
*** F(calculated)			238.079	12086.627	423.224	3.280	6.943	3288.504
p			0.000	0.000	0.000	0.033	0.001	0.000

*amount of active substance released at 15 minute
**correlation coefficient values of all quality control parameters.
*** F: Degrees of freedom

Table 6: Statistical stability results of bracketing design.

are differences among G4 coded tablet batches in terms of friability test results (Table 2 and 4) which are within the limit. Predicted values of G2 and G3 coded drugs for both stability conditions didn't exceed the pharmacopoeia limit (Table 3 and 5).

Tablet which were used in our study exhibits fast drug release. It is expected that 80 % of drug should be dissolved after 15 minutes [11]. This criteria wasn't met after 6 months of accelerated stabilty study contrary to beginning datas for G1 coded drug. Long term stability studies showed that pharmacopoeia limits were met except some measurements of a batches at 3. and 6. month. Dissolved drug is over 80 % at all the sample points for G4 coded drug after 15 minutes (Table 2 and 4). Initial data for G2 coded is 105.14 after accelerated stability study and all the measurement points after long term stability studies was calculated as 105.14%, 104.765, 104.385 respectively (Table 3 and 5). When the dissolutiun datas of the model were evaluated without dose dependency, high standart deviation could be observed after modelling. Therefore dissoltion datas which exceed 100% have to be evaluated in this way.

Acceptence limit of content uniformity is given in the E.P. as ± % 15. Range of acceptence becomes 0.85–1.15 mg/tablet with that limit for G1 coded drug. These limit is exceeded in two batches of G1 drug after accelerated stability studies and mg drug per tablet was measured as 0.823, 0.802 and 0.761 mg respectively (Table 2). Result of one of these three batches and initial value of G1 were within the limits (Table 4). Range of acceptences are 3.4-4.6 mg/tablet, 1.7-2.3 mg/tablet and 2.55-3.45 mg/tablet respectively for G4 and G2 coded drugs and the results of all batches exceeded the limits after both accelerated and long term stability studies (Table 3 and 5).

When both experimental and predicted results evaluated it is found that some of the predicted findings are out of the limits. But it can be decided that this is not a problem related with modelling when some of the experimental results also out of the limits is considered If the stability one of the highest or lowest dose were found worse than intermediate doses it would be concluded that there could be a problem related with modelling [7].

Diameter-thickness were evaluated during stability althoug they are not formal pharmacopoeia tests for tablets. There was no difference at diameter-thickness tests during accelerated and long term stability studies for G1-G4 coded drugs. But thickness values are changeable among G1 coded drug's batches. Datas of diameter-thickness depend on tablet production equipments and exhibit a large variation. The main purpose to use diameter-thickness tests in our study is proving the power of Bracket design. But diameter measurements don't have reasonable effect on predicted values in the utilized programme so SPSS programme was automatically ignored.

Each parameter that we hypothesized in our modelling was negative as "there is no relation between values" and acceptabilityof the hypothesis depends on the F value. After all the hypothesis were rejected it was concluded that there is corelation between values by the reason of F values are higher thar table values. Obtained F values calculated as 238.079 for disintegration time, 12086.627 for average tablet weight, 423.224 for hardness, 3.280 for friability, 6.943 for dissolution rate, and 3288.504 for amount of drug quantificaiton. All the datas were found higher than table datas and it means that modelling's corelation power is very high [9]. For this reason it could be concluded that modelling is suitable for Bracket design. Level of error (p) is found lower than 0.05 in all hypothesis (Table 6). Determination coefficient (r^2) of the parameter has to be quiet close to 1 to be able to reach correct result with a high precision [10]. Determination coefficients were calculated very close to 1 for four parameters that we observed and r^2 value for disintegration was found as 0.9804, 0.9996 for average tablet weight, and 0.9832 for hardness. Other parameters' r^2 values can be seen in Table 4 and 6 as 0.4085 for friabilty and dissolution rate's r^2 also can be seen in Table 5 and 6 as 0.5938. These data show that modelling predictions give % 40 correct results in terms of friabilty and % 59 correct results in terms of dissolution rate tests. This result can't be directly related with modelling's estimation power when considering that dissolution rate is rather relavant with drug's characteristics and tablet production technique than its dose. Circumstances are also the same for friability tests. Friability doesn't have a direct corelation with drug dose. Reason of inclusion of these parameters to modelling is F values are higher than table datas although being lower than other F values which are obtained for another parameters.

During our investigation for each formulation of G1 anG4's three batches, 84 measurements carried out for accelerated stability tests and 126 measurements for long term stability tests. Total measurement number is 210. If the full design was used instead of Bracket design, there would be 420 measurements. There is not any necessity for intemiediate storage condition (30°C ± 2 temperature and % 65 ± 5 relative humiditiy) tests [6]) because no significant difference was observed during accelerated 6 months stability studies in G1 and G4 coded drugs [12]. If the full desing was used in the study, sample and investigated parameter number would increase compare to Bracket design.

Conclution

In this study, an application of the survey of Glimeprid Tablet by bracket design method is given. Among the four doses of the medicine, two containing the highest and the lowest amounts of active pharmaceutical ingredient are chosen (G1 and G4) and several quality parameters were determined in accelerated and long-term stability conditions. Using these results, the properties of tablets with intermediate amounts (G2 and G3) are calculated with the help of statistical modeling. For four of six examined quality control parameters the r^2 values are close to 1 and all found F values are greater than the tabulated values. These results show that the correlations used in the modeling part are accurate.

Usability of the reduced methods depends on the kind of medication, type of the factor effecting, the pharmaceutical form of the drug, variation of data and the stability of the drug, in terms of statistical supervision. All characteristics should be known for stability design of a certain medication and a choice according to these data should be made. Therefore, ICH guidelines should be followed and closely examined.

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