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DEVELOPMENT AND OPTIMIZATION OF ITOPRIDE HYDROCHLORIDE FAST DISINTEGRATING TABLETS USING FACTORIAL DESIGN AND RESPONSE SURFACE METHODOLOGY

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Keywords:

Fast disintegrating tablets, itopride hydrochloride, factorial design, response surface methodology, sodium starch glycolate

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ABSTRACT: The objective of this work was to use a full factorial design and response surface methodology to optimize and prepare fast disintegrating tablets of Itopride hydrochloride (ITOHCl). Tablets were prepared by direct compression technique and evaluated for their drug content, weight variation, hardness, friability, wetting, disintegration time, and *in-vitro* release. In addition, the optimum formulation was evaluated for taste, mouth feel and *in-vivo* disintegration time in human volunteers. A 3^2 full factorial design was employed to evaluate different variables affecting ITOHCl tablets. Furthermore, The response surface methodology was used to analyze the effect of the total amounts of superdisintegrant (SD, X_1) and the percentage of sodium starch glycolate (% SSG) in the total amounts of superdisintegrant (SSG, X_2) on the % friability (Y_1), Disintegration time (Y_2) and ITOHCl released after 10 mins (Y_3). The increase in the (SD, X1) led to an increase in the % friability while an increase in % SSG led to a decrease in the % friability. The (SD, X1) were found to have a positive influence on the disintegration time, whereas the % SSG had a non-significant effect on the disintegration time. In addition, the release of ITOHCl from different formulations was affected by both (SD, X1) and the percentage of SSG. The optimized formulation showed *in-vivo* disintegration time comes in accordance with the *in-vitro* data and has a good mouth feel and bitter taste masking character compared with commercial ITOHCl tablets.

INTRODUCTION: Fast disintegrating tablets, FDTs, are considered nowadays one of the most promising formulations for delivery of different drugs and have a lot of advantages [1]. Furthermore, it has been shown effective to replace the conventional tablets and capsules for geriatric patients, who had difficulties in swallowing conventional solid dosage forms [2, 3].

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moreover, FDT are suitable for children because of their underdeveloped muscular and nervous system[4]. The characteristic fast absorption of water and rapid disintegration into the saliva makes them superior in achieving a rapid onset of action [5-8]. FDTs are prepared by different technologies, among them, direct compression technique was still used successfully to produce these formulations.

It can produce tablets with good mechanical properties and short disintegration time compared with lyophilization and moulding techniques which offered a low physical resistance and high friability tablets in spite of rapid disintegration [9]. Furthermore, the

tablets prepared by lyophilization and moulding have a low productivity because they involved the steps of injecting a drug solution into a preformed container, lyophilization/ moulding, and coating with an expensive material [10, 11].

It is also worth noting that traditional experimental methods involves significant amount of time and efforts to get meaningful results from different systems. This is why it is very much desirable to obtain an acceptable formulation using minimum amount of materials in a short time period. Factorial design is an efficient method of finding the relative significance of number of variables and their interaction on the response or outcome of the study [12]. Furthermore, the response surface method is a useful and efficient tool to obtain an appropriate model with minimum experiments. Optimization procedure involving factorial designs and analysis of response surfaces is powerful, efficient and also a systematic tool that has been used in developing different oral dosage formulations[13-15].

ITOHCl is a prokinetic agent and it has anticholinesterease activity as well as dopamine D_2 receptor antagonistic activity. Moreover, it is considered to be the drug of choice in gastrointestinal symptoms caused by reduced gastrointestinal motility e.g., dyspepsia, heartburn, anorexia, bloating and nausea and vomiting. ITOHCl is a freely water soluble drug and has an intense bitter taste which make it a challenging drug candidate for FDT drug delivery system. On the other hand, ITOHCL is not available in the dosage form of FDT in the market world over. So, the objective of this study was to prepare FDT of ITOHCl to give a rapid onset of action especially with certain cases need rapid onset of action e.g., nausea and vomiting, facilitate drug administration to elderly people and children. Moreover, to improve the patient compliance and the quality of treatment through masking of Bitter Taste of ITOHCl, thus, will provide a "Patient- Friendly Dosage Form."

A 32 randomized full factorial design was used to design ITOHCl fast disintegrating tablets. In this design two factors were evaluated, each at three levels and experimental trials were performed at all 9 possible combinations.

The proportion of total superdisintegrant added to the formulation (SD, X1) and the percentage of sodium starch glycolate (ssg, X2) were selected as independent variables. While, the % friability (Y1), disintegration time (Y2) and ITOHCl released after 10mins (Y3) were selected as dependent (response) variable. After optimization, ITOHCl fast disintegrating tablets were prepared by direct compression technique using two superdisintegrants namely; sodium starch glycolate and cros-povidone.

Furthermore, the prepared tablets were evaluated for their; uniformity of drug contents, weight variation, percentage friability, wetting time and water absorption ratio, *in-vitro* disintegration time, *in-vitro* release and evaluation of taste, mouth feel and *in-vivo* disintegration time in human volunteers.

MATERIALS AND METHODS:

ITOHCl was supplied from vasuhda co., India. Anhydrous lactose was supplied from FMCO, Ireland. cros-povidone was obtained from isp technologies, inc (GAF) chemicals. Sodium starch glycolate was obtained from roquette, france. Magnesium stearate was supplied from EL-Nasr pharmaceutical Chemicals Co., egypt. Itopride HCl commercial tablets (ganaton®; in tablet form) were purchased from ABBOT, USA. All other chemicals and solvents were of analytical grades and used as received.

Full Factorial Design:

Full factorial experimental design was employed to statistically optimize the formulation parameters of ITOHCl fast disintegrating tablets. A Factorial Design for two factors at three levels each 3^2 is considered identical to a two factor composite design[16, 17]. A computer aided optimization process

using a 3^2 full factorial design and nine experiment runs were performed. Statistical models with interaction terms were derived to evaluate the influence of two independent variables (factors); total amounts of superdisintegrant added (SD, X_1) and the percentage of sodium starch glycolate in the total superdisintegrant (SSG, X_2). According to this design, nine formulations of ITOHCl fast disintegrating tablets were prepared via direct compression technique.

Three levels of the total amounts of superdisintegrants were used 8, 12 and 16% denoted three values of -1, 0 and +1 in the above design, respectively. Moreover, sodium starch glycolate percent in the total amounts of superdisintegrant was varied to be 0, 25 and 50%, also denoted three values of -1, 0 and +1, respectively. The dependent variables to be tested for the prepared ITOHCl tablets were chosen to be the percentage friability (Y_1), disintegration time (Y_2) and ITOHCl release after 10 mins (Y_3).

Regression Analysis:

The targeted response parameters were statistically analyzed by applying one-way ANOVA test at the level of significance ($p = 0.05$) in Stategraphic plus software (Statpoint Tech., Inc. Warrenton, Virginia). Moreover, the individual parameters were evaluated using the F test and quadratic models of the form:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_3 X_1 X_2 \quad \text{Equation (1)}$$

Where Y is the level of the measured response; β_0 is the intercept β_1 to β_5 are the regression coefficients. X_1 and X_2 stand for the main effects; X_1X_2 is the interaction between the main effects; X_1^2 and X_2^2 are the quadratic terms of the independent variables that were used to simulate the curvature of the designed sample space. Furthermore, a backward elimination procedure was adopted to fit the data into different predictor equations. The quadratic models generated by regression analysis were used to construct the 3-dimensional graphs in which response parameter Y was represented by a curvature surface as a function of X. Moreover, the effect of the independent variables on each response parameters was visualized from the contour plots.

Numerical optimization using desirability approach was employed to locate the optimal settings of the formulation variables to obtain the desired response. Furthermore, an optimized formulation was developed by setting constraints on the dependent and independent variables.

Preparation of ITOHCL Fast Disintegrating Tablets:

ITOHCl fast disintegrating tablets were prepared by direct compression technique. All ingredients were passed through 200 um sieve. Briefly, 50 mg of ITOHCl was mixed in a glass bottle with fast disintegrating excipients at 3 different weight ratios 8, 12 and 16 % w/w from the total tablet weight 150 mg. The efficiency of mixing was verified by determination of ITOHCl content.

Then the obtained powders were mixed intimately by geometrical dilution with aspartame, cherry flavor and lactose. Finally, the formed blend was lubricated with 1% w/w magnesium stearate for another 5 minutes. The produced mixture was compressed into tablets using a single punch tablet machine (Korsch-Berlin, EK/0, Frankfurt, Germany) equipped with a flat faced 8 mm punches. The composition of different ITOHCl fast disintegrating tablet formulations is depicted in **Table 1**.

Evaluation of tablet property:

1- Uniformity of ITOHCl content:

The prepared tablets were tested for their ITOHCl content. Twenty tablets of each formulation were finely powdered and quantities of the powder equivalent to 50 mg of ITOHCl were accurately weighed and transferred to a 100 ml volumetric flask containing 50 ml of methanol and shaken with intermittent sonication (Model 275T, Crest Ultrasonics Corp., Trenton, USA) to ensure complete solubility of the drug. The solution was suitably diluted with 0.1 N HCl and measured spectrophotometrically at λ_{max} of 258 nm with reference to a previously constructed calibration curve in 0.1 N HCl ($R^2 = 0.999$, n=3). The excipients used in the tablet formulations did not interfere with the assay method under these conditions. Each determination has been performed

in triplicate and the mean drug content ± SD was deduced.

Regarding, weight variation test, twenty tablets were selected randomly from each batch formulation and the tablets weight variation and the acceptance value (AV) was calculated for all formulations according the USP 31[18] and using the following equation.

$$AV = \left| M + X^{-} \right| + ks \quad \text{Equation. (2)}$$

Where M is a label claim (100%); X^{-} is a mean of individual contents expressed as a percentage of label claim; K is the acceptability constant, if n = 10, it will be equal 2.4 and S is a sample standard deviation. The thickness of the prepared tablets was assessed using digital caliper (Neiko, U.S.A.).

Hardness:

The hardness of each orally disintegrating tablet was measured using a hardness tester (Erweka; Frankfurt, Germany). The mean hardness of 10 tablets was calculated and reported. The limit for hardness was maintained to be in the average of 3–4 Kg.

Friability:

Twenty tablets pre-weighed (W_0) were rotated for 4 min at 25 rpm using a friability machine (Erweka; Frankfurt, Germany). These tablets were blushed to eliminate the powders on the surface of the tablets and then weighed again (W_f).

The percentage friability was calculated by the following equation.

$$\% \text{ Friability} = (W_f/W_0) \times 100 \quad \text{Equation. (3)}$$

Where; W_0 and W_f are the total weight of the tablets before and after rotation, respectively.

Wetting time and water absorption ratio:

A piece of tissue paper folded twice was placed in a small petri dish (i.d. = 6.5 cm) containing 5mL of water and (0.01%w/v) crystal violet [9]. A tablet was placed on the paper and the time required for complete wetting was measured. Complete wetting can be taken as the time at which colored water covered the entire tablet. Furthermore, wetted tablets are transferred to a tissue paper to wipe off excess water and weighed immediately. The water absorption ratio was determined using following equation.

$$R = (Wa - Wb)/(Wb \times 100) \quad \text{Equation. (4)}$$

Where; Wb is the weight of the tablet before water absorption and *W*a is the weight of the tablet after water absorption [6].

2- *In-vitro* disintegration time:

The test was carried out using USP tablet disintegration test apparatus (Hanson, USA). One tablet was placed in each of six tubes of the basket containing 500 ml distilled water maintained at 37±0.5°C and agitation speed of 30 shakes per min. The tablet was considered disintegrated completely when all the particles passed through the screen. The disintegration time of 6 individual tablets for each formulation was recorded ± S.D.

***In-vitro* release study:**

In-vitro release study for fast disintegrating formulations and the commercial ITOHCl tablets (Ganaton®) was performed in USP type II dissolution tester (Erwika, USA). The study was conducted in 500 ml of pH 6.8 as a dissolution medium with paddle speed of 50 rpm at a temperature of 37±0.5°C. Aliquots of dissolution medium (5 ml) were withdrawn at specified intervals, 5, 10, 15 and 30 min and replaced with an equal volume of fresh medium. The concentration of drug in samples was analyzed using UV/Visible spectrophotometer (Jenway, Japan) at a wavelength of 258 nm.

Evaluation of taste, mouth feel and *in-vivo* disintegration time in human volunteers:

The control commercial ITOHCl tablets (F0) and optimized formulation (F9) containing cros-povidone and SSG (1:1 weight ratio) were selected to assess taste, mouth feel and *in-vivo* disintegration time in 12 healthy human volunteers at the age group of 25 to 40 years. Furthermore, a control formulation containing only cheery flavor was prepared and studied to determine its effect on taste masking. The study protocol was approved by the Ethics Committee of Faculty of Medicine, Assiut University and each volunteer gave his written consent to participate in the study. As per the protocol, all volunteers were asked to rinse their mouth with water before placing the tablet on the

tongue and immediately a stopwatch was started. Volunteers were allowed to move the tablet against the upper palate of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting on it or tumbling it from side to side.

The taste and mouth feel were evaluated based on the volunteers' spontaneous verbal judgments immediately after the tablet was placed in their mouth as well as after 3-4 mins. The taste and mouth feel were rated on a scale of 1 through 5. In taste evaluation, '1' was considered to be "good" while a '5' was considered as "awful." In the mouth feel evaluation, '1' was considered to be good" while a '5' was considered as "high grittiness". Time taken for the volunteer to feel that the last noticeable granule or fragment had disintegrated in the oral cavity was considered as the *in-vivo* disintegration time. The volunteers were prohibited swallowing of their saliva during the test and instructed to rinse their mouth after measurement.

TABLE 1: COMPOSITION OF DIFFERENT FORMULATIONS OF ITOHCL FAST DISINTEGRATING TABLETS.

Ingredients(mg/tablet)	Formulation								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
ITO HCl	50	50	50	50	50	50	50	50	50
Cros-povidone	12	18	24	9	13.5	18	6	9	12
Sod.Starch glycolate	0	0	0	3	4.5	6	6	9	12
Aspartame	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Cherry flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Lactose	80.5	74.5	68.5	80.5	74.5	68.5	80.5	74.5	68.5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	150	150	150	150	150	150	150	150	150

RESULTS AND DISCUSSION:

Evaluation of tablet property:

It was found that the prepared ITOHCl FDTs met the criteria for the content uniformity test under the USP 31 specifications. ITOHCl content in all formulations ranged from 96.99±1.87% to 100.45±1.79% of the theoretical label claim. Moreover, the acceptance value (AV) was found to be in the range of 2.60% to 6.01% for all formulations. Furthermore, ITOHCl tablets showed acceptable values for hardness and percentage friability, 3.15±0.14-4.0±0.2 kg and 0.354±0.05-0.659±0.31; respectively. Thus was considered optimum values for FDTs as concluded by other researchers [9, 19]. The wetting time and water absorption ratio are considered the important criteria for determining the capacity of disintegrates to swell in presence of little water. It is also worth noting that the wetting time for all the investigated formulations was less than 1 minute as shown in (**Table 2)**, thus indicates an anticipated more short time for disintegration. Furthermore, formulation F9 showed the lowest water absorption ratio of 37.87±3.72 % and wetting time equal to 22.08±2.78 seconds.

TABLE 2: WATER ABSORPTION RATIO AND WETTING TIME OF ITOHCL FAST DISINTEGRATING TABLETS (N=6±S.D.)

Formulation	Water absorption ratio (%)	Wetting time (s)
F1	17.73±3.64	58.16±3.71
F2	22.21±3.43	48.50±2.22
F3	18.33±4.30	51.78±9.92
F4	12.22±2.38	39.02±4.90
F5	21.87±3.38	35.67±4.57
F6	26.65±3.42	34.33±2.49
F7	29.68±1.94	27.17±3.62
F8	25.53±4.41	25.08±2.32
F9	37.87±3.72	22.08±2.78

Factorial design:

Response data for all 9 experimental runs of factorial design (F1-F9), was performed in accordance to **Table 3** and are presented in (**Fig 1, and 6**). Regarding different combination of factors and factor levels, a significant difference between disintegration time and drug release profiles was obtained.

TABLE 3: A 3^2 FACTORIAL DESIGN LAYOUT SHOWING FACTOR COMBINATIONS AND RESPONSE PARAMETERS OF ITOHCL FAST DISINTEGRATING TABLETS.

Formulation	X_1	X_2	(Y_1)%Friability[a]	(Y_2)Disintegration Time [a]	$(Y_3)Release_{10}$ [a]
1	-1(12)	-1(0)	0.554	87.5	61.14
2	0(18)	-1(0)	0.647	65	71.43
3	1(24)	-1(0)	0.471	60	74.42
4	-1(12)	0(25)	0.414	110.8	68.65
5	0(18)	0(25)	0.432	70.8	73.85
6	1(24)	0(25)	0.659	59.5	80.25
7	-1(12)	1(50)	0.354	107	89.35
8	0(18)	1(50)	0.442	55.8	92.8
9	1(24)	1(50)	0.625	36.8	95.93

The parentheses represent the decoded factor levels. X_1 represents total superdisintegrants; X_2 represents % w/w of sodium starch glycolate in the total amount of superdisintegrants. % Friability, Percentage friability; $Release_{10}$, release after 10 min; [a] The average of three determinations (n = 3).

Full and reduced model of percentage friability:

The percentage friability values for ITOHCl formulations F1 to F9 were ranged from 0.354±0.05 to 0.659±0.31 (**Table 3**). The effect of changing the amount of total superdisintegrants on the percentage friability was investigated using ANOVA test. The output showed the results of fitting a multiple linear regression model to describe the relationship between percentage friability and the independent variables, the amount of superdisintegrant and SSG percentage. For estimation of coefficients in the approximating polynomial function (Eq. 5), applying encoded values of factor levels, the least square regression method was used. A factor is considered to influence the response if the effects significantly differ from zero and the p-value is less than 0.05. A positive sign indicates a synergistic effect, while a negative sign represents an antagonistic effect of the factor on the selected response.

The equation of the fitted model for percentage friability was (Y_1 = 0.542222 + 0.0721667 X_1-0.0751667 X_2-0.0608333 X_1^2+0.0885 X_1 X_2+0.0471667 X_2^2) (Equation 5).

As indicated by positive sign of the coefficient β_1, the increase in the total amounts of SD resulted in increase in the friability. On the other hand, an increase in SSG percentage led to decrease in friability because the coefficient β_2 bears a negative sign. All the tablets showed good mechanical resistance, as indicated by the friability test where it was less than 1 % for all tablet formulations. Both cros-povidone and SSG are known to produce mechanically strong tablets which do not affect tablets friability [20]. The improvement of the tensile strength of the tablet would make it resistant to wear and tear during shipping, storage and administration [21]. Since the P-value calculated using ANOVA test is ≥ 0.10 (**Table 4**), there was not a statistically significant relationship between the percentage friability and the selected independent variables at the 90% or higher confidence level. Furthermore, the R-Squared statistic indicated that the fitted model explained 72.1537% of the variability in the percentage friability.

The standard error of the estimate showed the standard deviation of the residuals was found to be 0.097257. Moreover, the mean absolute error (MAE) has a value of 0.47963 which is the average value of the residuals. The Durbin-Watson (DW) statistic tests the residuals to determine if there is any significant correlation between percentage friability and the selected independent variables. Since the DW value is greater than 1.4, there was not probably any serious autocorrelation in the residuals.

In determining whether the model can be simplified, notice that the highest P-values on the independent variables are 0.1667 and 0.3694, belonging to total Percentage of superdisintegrant and SSG Percentage; respectively (**Table 4**). It was found that the total percentage of superdisintegrant as well as SSG percentage were not statistically significant at 90% or higher confidence level since the P-value is > 0.10. Consequently

total percentage of superdisintegrant and SSG percentage can be removed from the full model to generate a reduced model.

TABLE 4: FACTOR EFFECTS AND ASSOCIATED *P*-VALUES FOR % FRIABILITY (Y1), DISINTEGRATION TIME (Y2) AND *IN-VITRO* RELEASE OF ITOHCL AFTER 10 MINS (Y3).

Factor	Response					
	Y_1		Y_2		Y_3	
	Factor effect	*p*-value	Factor effect	*p*-value	Factor effect	*p*-value
X_1	0.144333	0.1667	-49.6667	0.0002	10.4867	0.0041
X_2	-0.15033	0.3694	-4.3	0.1448	23.6967	0.0004
X_{12}	-0.12166	0.9377	26.1333	0.0063	2.14	0.4167
$X_1 X_2$	0.177	0.1663	21.35	0.0042	3.35	0.1289
X_{22}	0.094333	0.8534	23.3667	0.0087	13.19	0.0102

Fig. 1, shows the 3-D and response surface plots for the effect of total amount of superdisintegrants (X_1), SSG % in total superdisintegrants (X_2) on the response Y_1 (percentage friability). The percentage friability decreased from 0.554±0.19 to 0.354±0.05, while it increased from 0.471±0.09 to 0.625±0.14 at lower and higher levels of SSG percentage with constant amount of total superdisintegrants. On the other hand, the percentage friability decreased from 0.554 to 0.471, while it increased from 0.354 to 0.625 at low and higher levels of the total disintegrants with constant SSG percentage. Hence, the amount of superdisintegrants as well as SSG percentage did not show any significant effect on the percentage friability.

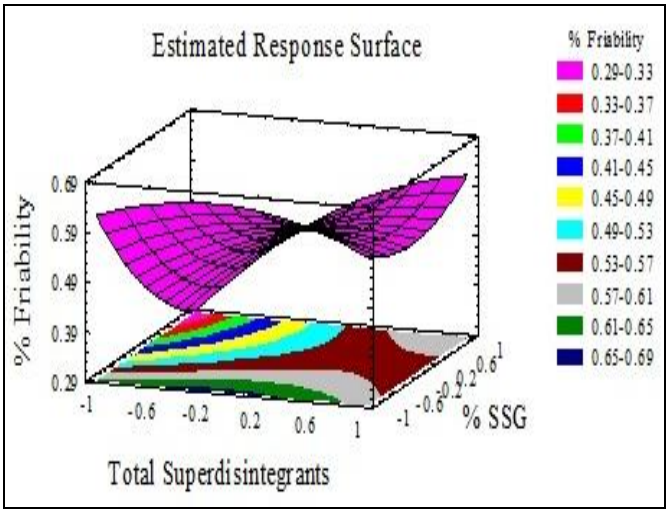

FIG. 1: THREE DIMENSIONAL CONTOUR PLOT FOR THE EFFECT OF TOTAL AMOUNTS OF SUPERDISINTEGRANT (X_1) AND PERCENTAGE OF SODIUM STARCH GLYCOLATE (X_2) ON THE PERCENTAGE FRIABILITY (Y_1).

Full and reduced model of *in-vitro* disintegration time:

The effect of the total amounts of superdisintegrant add to the formulation and the percentage of SSG on the disintegration time can be best described using the following equation,

$$(Y_2 = 71.6556 - 24.8333\ X_1 - 2.15\ X_2 + 13.0667\ X_1^2 - 10.675\ X_1 X_2 - 11.6833\ X_2^2) \quad \text{(Equation 6)}$$

As indicated by a negative sign of the coefficient β_1 and β_2, the increase in the total amounts of SD and SSG percentage resulted in a decrease in the disintegration time. Since the P-value calculated from ANOVA test (**Table 4**) is less than 0.05, there is a statistically significant relationship between disintegration time and the two independent variables at the 95% confidence level. The R-squared statistic indicated that the fitted model explained 77.3447% of the variability in the disintegration time.

Moreover, the standard error of the estimate showed that the standard deviation of the residuals was found to be 13.4905. This value can be used to construct prediction limits for new observations. The MAE of 10.442 was the average value of the residuals. On the other hand, it was not probably any serious autocorrelation in the residuals as the DW value was greater than 1.4. Furthermore, the amount of the superdisintegrant had a significant effect on disintegration time with an F value of 512.6 ($p < 0.001$).

The total amount of the superdisintegrant was found to have a positive influence on the

disintegration time, whereas the percentage of SSG had a non-significant effect on disintegration time. Tablets containing SSG disintegrate due to the rapid uptake of water, followed by rapid and enormous swelling into primary particles. It was clear that increasing the concentration of cros-povidone from 5-15 % w/w, formulations F1-F3, resulted in a significant ($p<0.05$) decrease in the disintegration time. It was reported that increasing the concentration of cros-povidone from 5-15% w/w led to a much more reduction in the disintegration time of sumatriptan succinate orally disintegrating tablets [22]. It was worth noting that, at higher SSG levels in the total amount of superdisintegrant e.g., (F7 and F4, F8 and F5, F9 and F6), an increase in the disintegration time was obtained (**Table 3**).

This possibly was due to the formation of a viscous gel layer around the tablets, which created a barrier for further penetration of the disintegration medium into the tablet. The effect of using higher concentrations of SSG was previously demonstrated to slow down the disintegration and drug release from aspirin tablets due to formation of a viscous barrier around the tablets [23]**.** The effect of cros-povidone on decreasing the time for disintegration compared to SSG might be attributed to the rapid water absorbing nature of cros-povidone, involving both capillary and swelling mechanisms which build up internally pressure leading to the faster disintegration [24]. Furthermore, Cros-povidone has high capillary activity and pronounced hydration but little tendency to gel formation. Therefore, rapid disintegration and, hence, rapid dissolution is expected with increasing cross-povidone concentration in ITO tablets [25].

The response surface contour plots (**Fig. 2)** illustrates that the disintegration time decreased from 87.5±26.78 sec. to 60±12.24 sec. and from 107±23.15 to 36.83±8.47 sec at low and high levels of the total amount of superdisintegrants, respectively as the total amount of superdisintegrants increased. On the other hand, disintegration time increased from 87.5±26.78 sec to 107±23.15 sec. and decreased from 60±12.24 sec. to 36.83±8.47 sec at lower and higher levels of SSG.

In determining whether the model can be simplified and on the finding that the highest P-value on the independent variables was 0.1448, belonging to SSG Percent. It was found that the percentage of SSG was not statistically significant at 90% or higher confidence level, since the P-value is ≥ 0.10. Consequently, the percentage of SSG can be removed from the model. On the other hand, the coefficients of β_1, β_3, β_4 and β_5 were found to be significant at p-value ≤ 0.05, hence they were retained in the reduced models.

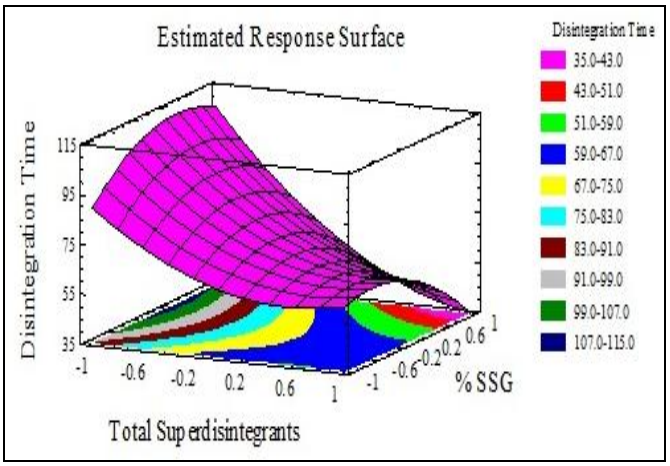

FIG. 2: THREE DIMENSIONAL CONTOUR PLOT FOR THE EFFECT OF TOTAL AMOUNTS OF SUPERDISINTEGRANT (X_1) AND PERCENTAGE OF SODIUM STARCH GLYCOLATE (X_2) ON THE DISINTEGRATION TIME (Y_2).

Full and reduced model of the *in-vitro* release:

Fig. 3 shows the *in-vitro* release of ITOHCl from formulations (F2, F5 and F8) using a constant amount of total superdisintegrants (X_1= 0, 12% of total tablet weight) with variable percentage of SSG, 0%, 25% and 50% for F2, F5 and F8, respectively (X_2). It was found that the highest and the lowest ITOHCL percentage released was found to be 92.8±2.39% and 71.43±2.67% after ten minutes (Y_3); respectively. Hence, after 10 mins, the release of ITOHCl from these formulations can be arranged in the following descending order F8 > F5 > F2.

The effect of using a constant amount of total superdisintegrants (X_1= -1) with variable percentage of SSG, 0%, 25% and 50% for F1, F4 and F7, respectively (X_2) is presented in **(Fig. 4)**. The highest and lowest ITOHCl percentage released was observed to be

89.35±1.09% and 61.14±6.5% after ten minutes (Y_3); respectively. So, these formulations can arranged in the following descending order F7 > F4> F1. Regarding, the effect of constant amount of total superdisintegrants (X_1= +1) with variable percentage of SSG, 0%, 25% and 50% for F3, F6 and F9, respectively, (X_2). It was found that the highest and lowest ITOHCl percentage released was found to be 95.93±1.12% and 74.42±1.14% after ten minutes (Y_3); respectively (**Fig. 5**).

The investigated formulation can be arranged, in the following descending order F9 > F6 > F3. Finally, the release of ITOHCL from fast disintegrating formulations can be arranged in the following order after 10 mins. F9> F8> F7> F6> F3> F5> F2> F4> F1.

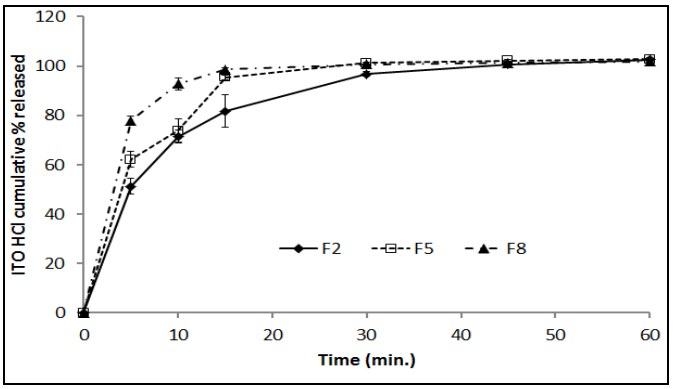

FIG. 3: THE RELEASE PROFILES OF ITOHCL FROM FAST DISINTEGRATING TABLETS, FORMULATIONS F2, F5 AND F8. PREPARED WITH VARIABLE PERCENTAGE OF SODIUM STARCH GLYCOLATE FROM THE TOTAL AMOUNTS OF SUPERDISINTEGRANT, 0% FOR F2; 25% FOR F5 AND 50% FOR F8; (X_2).

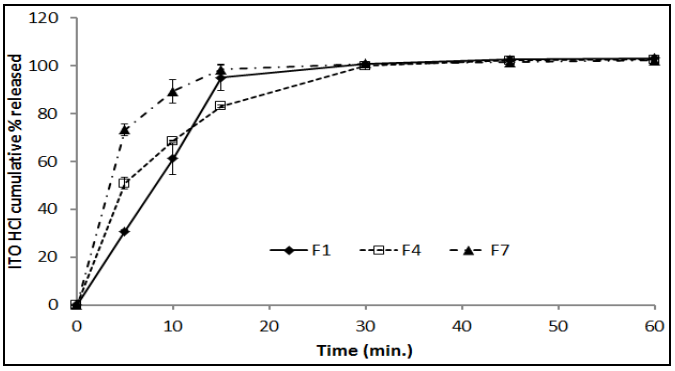

FIG. 4: THE RELEASE PROFILES OF ITOHCL FROM FAST DISINTEGRATING TABLETS, FORMULATIONS F1, F4 AND F7. PREPARED WITH VARIABLE PERCENTAGE OF SODIUM STARCH GLYCOLATE FROM THE TOTAL AMOUNTS OF SUPERDISINTEGRANT, 0% FOR F1; 25% FOR F4 AND 50% FOR F7; (X_2).

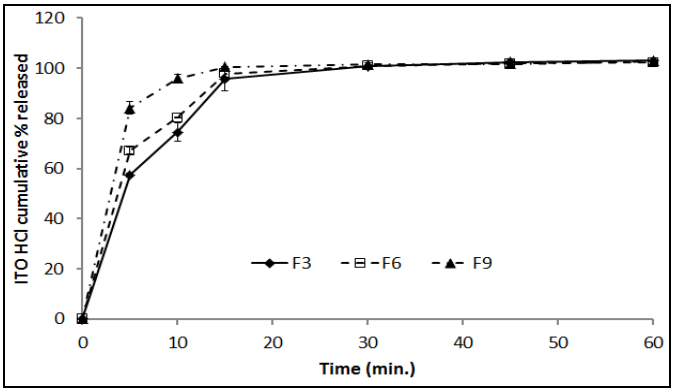

FIG. 5: THE RELEASE PROFILES OF ITOHCL FROM FAST DISINTEGRATING TABLETS, FORMULATIONS F3, F6 AND F9. PREPARED WITH VARIABLE PERCENTAGE OF SODIUM STARCH GLYCOLATE FROM THE TOTAL AMOUNTS OF SUPERDISINTEGRANT, 0% FOR F3; 25% FOR F6 AND 50% FOR F9; (X_2).

The equation of the fitted model which study the effect of the total amount of the superdisintegrant and the percentage of SSG in the total amount of superdisintegrant on ITOHCL released after 10 minutes was (Y_3= 74.9633+ 5.24333 X_1+ 11.8483 X_2-1.07X_1^2-1.675 X_1 X_2+6.595 X_2^2) (Equation. 7). It is worth noting that there was a statistically significant relationship between the variables at the 99% confidence level Since the P-value calculated using ANOVA test was less than 0.01 (**Table 4**).

Furthermore, the R-squared statistic indicated that the fitted model explained 90.2935% of the variability in release after 10 mins. The standard error of the estimate showed the standard deviation of the residuals was equal to 4.24812. Moreover, MAE the average value of the residuals was found to be 3.02333. Since the DW value was less than 1.4, there may be some indication of serial correlation.

In determining whether the model can be simplified, notice that P-values of β_1, β_2 and β_5 were less than 0.05, consequently, these variables cannot be removed from the model. So, we can conclude that both the amount of superdisintegrants as well as percentage of SSG was found to have a positive influence on the ITOHCl release from fast disintegrating tablets. The rapid drug release could be possibly attributed to the easy breakdown of particle as a result of the superdisintegrant action[25, 26]. The Three-dimensional contour plot for the effect of total amount of superdisintegrants (X_1) and percentage of SSG (X_2) on ITOHCl release

after ten minutes (Y_3) is presented in (**Fig. 6**). The response surface plot illustrated that ITOHCl release at the end of 10 mins. increased from 61.14±1.54% to 74.42±1.23% and from 89.35±1.89% to 95.93±1.42% at low and high levels of the total superdisintegrants (X_1); respectively as the superdisintegrant amount increased.

Furthermore, it was found that the levels of SSG in the total amounts of superdisintegrants had a positive influence on the ITOHCl release after ten minutes. It was also evident from the 3-D plot that the ITOHCl released after ten minutes increased from 61.14±1.21% to 89.35±1.32% and from 74.42±1.14% to 95.93±1.12% at low and high percentage of SSG; respectively. A linear relationship between the two independent variables on ITOHCl release after 10 mins was clear from the corresponding contour plots (**Fig. 6**), which also indicated that drug release could be maximized using high levels of total SD at high percentage of SSG.

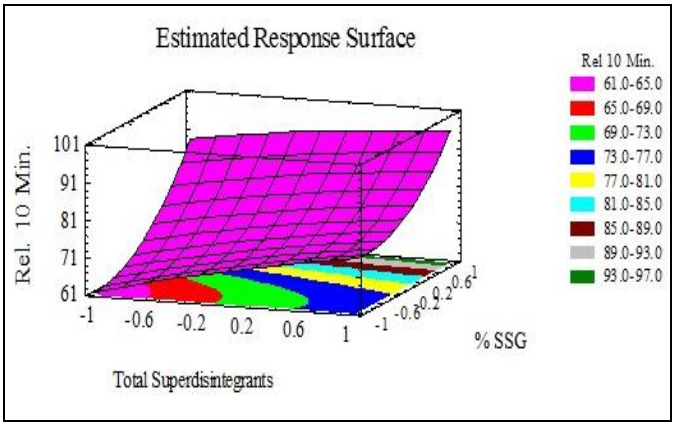

FIG. 6: THREE DIMENSIONAL CONTOUR PLOT FOR THE EFFECT OF TOTAL AMOUNTS OF SUPERDISINTEGRANT (X_1) AND PERCENTAGE OF SSG (X_2) ON ITOHCL RELEASE AFTER TEN MINUTES (Y_3).

Evaluation of taste, mouth feel and *in-vivo* disintegration time in human volunteers:

One of the important parameter in developing the FDTs is to mask the bitter taste of different bitter taste, water soluble drugs. A single blind study was performed to test the optimized formulation in terms of taste masking, mouth feel and *in-vivo* disintegration time. The evaluation was based on the extent to which the subject likes the taste of each tested formulation and ability of the formulation to cause a sense of irritation and/or grittiness when it was placed on the tongue. All the volunteers reported that the control formulation (F0) was very bitter in taste and immediately spitted out the tablet.

Hence, mouth feel and *in vivo* disintegration time of the control formulation was not determined. Among the twelve volunteers, nine volunteers rated formulation (F9) containing 3% aspartame and 1% cherry flavor as '1' indicating a sweet taste, two volunteers rated as '2' indicating that formulation had no taste and one volunteer rated as '3' indicating a slight bitterness of the tablet.

However, the rest of volunteers rated formulation (F9) as '1' suggesting that this formulation was sweet and acceptable. Furthermore, the amount used of aspartame (3% w/w) was also within the limits of United State Food and Drug Administration, USFDA[27]. Additionally, the optimized formulation (F9) had a good mouth feel without any grittiness as proved from ten volunteers rated '1' and rapidly disintegrated in oral cavity in 40.58±1.62 sec (**Table 5**). On the other hand, the presence of flavoring agent alone, cherry flavor, showed no taste masking effect. The pleasant taste and good mouth feeling could be as a result of incorporation of aspartame and cherry flavor in ITOHCl tablet formulation.

Aspartame is known to be 200 time more sweeter than sucrose and beneficial for diabetic patients as well[28, 29]. It was established by many researchers working in the field of FDTs that addition of such additives like aspartame and cherry flavor could impart a good mouth feeling and mask the bitter taste of numerous bitter taste drugs making them a good candidate for FDTs[30, 31]. The mean *in-vivo* disintegration time was in a good agreement with the *in-vitro* data for the optimized formulation (F9), 40.58±1.62 and 36.83±8.47 sec; respectively.

Furthermore, there was no statistically significant difference ($p>0.05$) in the *in-vivo* disintegration time among the different volunteers taking (F9). Thus meaning that the included additives e.g., aspartame, cherry flavor and lactose had no significant effect on the *in-vivo* disintegration time of ITOHCl. Similar results were also recorded for

in-vitro and in-situ disintegration time for donepezil orally disintegrating films[32].

TABLE 5: EVALUATION OF TASTE, MOUTH FEEL AND *IN-VIVO* DISINTEGRATION TIME OF ITOHCL FAST DISINTEGRATING TABLETS IN HUMAN VOLUNTEERS.

Volunteers	Taste		Mouth feel		*In-vivo* disintegration time (seconds)	
	Control	F9	Control	F9	Control	F9
1	5	1	-	1	-	40
2	5	1	-	1	-	42
3	5	1	-	1	-	41
4	4	3	-	2	-	43
5	5	2	-	1	-	38
6	5	1	-	1	-	40
7	5	1	-	1	-	39
8	4	1	-	1	-	41
9	5	1	-	1	-	38
10	5	1	-	1	-	42
11	4	1	-	1	-	43
12	5	2	-	2	-	40
Mean						40.58
S.D.						1.73

n=12. Taste: 1, sweet and good; 2, tasteless; 3, slightly bitter; 4, bitter; 5, awful.
Mouth feel: 1, good; 2, no feeling; 3, slight grittiness; 4, moderate grittiness; 5, high grittiness

CONCLUSION: The results of a 3^2 factorial design and response surface methodology revealed that the total amounts of superdisintegrant and the percentage of SSG significantly affect the dependent variables, percentage friability, disintegration time, and *in-vitro* release of ITOHCl from fast disintegrating tablets. Full factorial design was used successfully to statistically optimize the formulation parameters of ITOHCl fast disintegrating tablets. Furthermore, by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts.

Formulation F9 could be considered to be an optimum formulation since the disintegration time is less than 45 sec when tested either *in-vitro* or *in-vivo* and thus complied with the requirement of fast disintegrating tablets as stipulated by BP. Moreover, this formulation showed a good mouth feel and taste masking as recorded from volunteers and can be adopted for commercialization.

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REFERENCES:

1. Bhyan B, Jangra S, Kaur M and Singh H: Orally fast dissolving films: Innovations in formulation and technology. Int. J. Pharm. Sci. Rev. Res. 2011; 9:50-75.
2. Goel H, Vora N and Rana V: A novel approach to optimize and formulate fast disintegrating tablets for nausea and vomiting. AAPS Pharm. Sci. Tech. 2008; 9:774-781.
3. Fu Y, Yang S, Jeong SH, Kimura S and Park K: Orally fast disintegrating tablets: development, technologies, taste-masking and clinical studies. Crit. Rev. Ther. Drug Carrier Syst. 2004; 21:433-475.
4. Walid H, Raj K and John H: Fast dissolving drug delivery sytem. Crit. Rev. Ther. Drug Carrier Syst. 2000; 17:61-73.
5. Fu Y, Jeong SH and Park K: Fast-melting tablets based on highly plastic granules. J. Cont. Rel. 2005; 109:203-210.
6. Bi Y, Sunada H, Yonezawa Y, Danjo K, Otsuka A and IIda K: Preparation and evaluation of compressed tablet rapidly disintegrating in the oral cavity. Chem. Pharm. Bull. 1996; 44:2121–2127.
7. Ghenge G, Pande SD, Ahmed A, Jejurker L and Birari T: Development and characterization of fast disintegrating tablets of amlodipine besylate using mucilage of plantago ovate as natural superdisintegrant. Int. J. Pharm. Tech. Res. 2011; 3:938–945.
8. Suresh S, Pandit V and Joshi HP: Preparation and evaluation of mouth dissolving tablets of salbutamol sulphate. Indian J. Pharm. Sci. 2007; 69:467–469.
9. Jung SY, Kim D, Seo YG, Woo JS, Yong CS and Choi H: Development of sildenafil-loaded orally disintegrating tablet with new lactate salt. Drug Dev. Ind. Pharm. 2012; 38:638-641.
10. Mir VG, Heinämäki J, Antikainen O, Sandler N, Revoredo OB, Colarte AI, Nieto OM and Yliruusi J: Application of crustacean chitin as a co-diluent in direct compression of tablets. AAPS Pharm. Sci. Tech. 2010; 11:409–415.
11. Shoukri RA, Ahmed IS and Shamma RN: *In vitro* and *in vivo* evaluation of nimesulide lyophilized orally

disintegrating tablets. Eur. J. Pharm. Biopharm. 2009; 73:162–171.
12. Late SG, Yu YY and Banga AK: Effects of disintegration-promoting agent, lubricants and moisture treatment on optimized fast disintegrating tablets. Int. J. Pharm. 2009; 365:4-11.
13. Sharma V, Philip AK and Pathak K: Modified polysaccharides as fast disintegrating excipients for orodispersible tablets of roxithromycin. AAPS Pharm. Sci. Tech. 2008; 9:87-94.
14. Prajapati BG and Patel DV: Formulation and optimization of domperidone fast dissolving tablets by wet granulation technqiues using factorial design. Int, J. Pharm. Tech. Res.2010; 2:292-299.
15. Late SG and Banga AK: Response surface methodology to optimize novel fast disintegrating tablets using β cyclodextrin as diluent. AAPS Pharm. Sci. Tech. 2010; 11:1627-1635.
16. Pathan IB, Shingare PR and Kurumkar P: Formulation design and optimization of novel mouthdissolving tablets for venlafaxine hydrochloride using sublimation technique. J. Pharm. Res. 2013; 6:593 -598.
17. Singh S and Shah D: Development and Characterization of Mouth Dissolving Tablet of Zolmitriptan. Asian Pacific J. Trop. Disease. 2012; 2:S457-S464.
18. The United States Pharmacopoeial Convention, The United State Pharmacopoeia 31st/National Formulary 26th edition. Vol. 1, the official compendia of standards, Asian edition, Rockville, MD, 2008, pp. 363-368.
19. Late SG, Yu YY and Banga AK: Effect of disintegration-promoting agents, lubricants and moisture treatment on optimized fast disintegrating tablets. Int. J. Pharm. 2009; 365:4-11.
20. Abdelbary A, Elshafeey AH and Zidan G: Comparative effects of different cellulosic-based directly compressed orodispersable tablets on oral bioavailability of famotidine. Carbohydrate Polymers. 2009; 77:799-806.
21. Ali S and Santos C: Crospovidone in development of directly compressible tablets, in: AAPS Annual Meeting and Exposition, Los Angeles, CA, USA, November, 2009.
22. Sheshala R, Khan N and Darwis Y: Formulation and Optimization of Orally Disintegrating Tablets of Sumatriptan Succinate. Chem. Pharm. Bull. 2011; 59:920-928.
23. Zhao N and Augsburger LL: Functionality comparison of 3 classes of superdisintegrants incorporating aspirin tablet disintegration and dissolution. AAPS Pharm. Sci. Tech. 2005; 6:E634-E640.
24. Battu SK, Repka MA, Majumdar S and Madhusudan RY: Formulation and evaluation of rapidly disintegrating fenoverine tablets: effect of superdisintegrants. Drug Dev. Ind. Pharm. 2007; 33:1225-1232.
25. Obaidat A. and Obaidat R. Development and evaluation of fast-dissolving tablets of meloxicam-ß-cyclodextrin complex prepared by direct compression. Acta Pharm. 2011; 61:83–91.
26. Kumar R, Patil S, Patil MB, Patil SR and Paschapur MS: Formulation Evaluation of Mouth Dissolving Tablets of Fenofibrate Using Sublimation Technique. Int. J. Chem. Tech. Res. 2009; 1:840-850.
27. USFDA, "Inactive Ingredient Search for Approved Drug Products," Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Rockville, MD, 2009 (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm)
28. Doe J. Sucralose—Technological Justification. www.food.gov.uk/multimedia/pdfs/sucraconsult2.pdf., Accessed 26 Oct, 2010.
29. Rowe R, Sheskey PJ and Quinn ME: Handbook of Pharmaceutical Excipients. 6th ed., London, UK, Pharmaceutical Press, 2009, p. 48.
30. Saini P, Kumar A, Sharma P and Vishat H: Fast disintegrating oral films: A recent trend in drug delivery. Int. J. Drug. Dev. Res. 2012; 4:80-94.
31. Douroumis D. Orally disintegrating dosage forms and taste masking technologies. Expert Opinion Drug Del. 2011; 8:665-675.
32. Liew KB, Tan YZF and Peh KK: Characterization of Oral Disintegrating Film Containing Donepezil for Alzheimer Disease. AAPS Pharm. Sci. Tech. 2011: 13:134-142.

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