ORIGINAL RESEARCH


# FORMULATION AND STASTICAL OPTIMISATION OF FAST DISSOLVING TABLETS OF AMBROXOL HYDROCHLORIDE

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**ABSTRACT**

The aim of the present study is to formulate and optimize fast dissolving tablets of Ambroxol hydrochloride using a $2^3$ response surface methodology employing Design Expert-10.0. Sodium starch glycolate and Camphor were selected as independent variables while disintegration time (sec) and water absorption ratio (%) were considered as responses. The prepared tablets were evaluated for various evaluation parameters including hardness, thickness, friability, drug content uniformity, wetting time, water absorption ratio and disintegration time. The prepared optimized fast dissolving tablets of Ambroxol hydrochloride having above 2 responses-disintegration time(sec) and water absorption ratio of sec and % .The optimized batch having concentration of sodium starch glycolate and camphor was found within the standard limit of parameters-disintegration time (sec) and water absorption ratio(%).The direct compression method in this study is relatively simple and safe and a stable, effective and pleasant tasting fast dissolving tablets, which has a good balance over disintegration time and water absorption ratio, was formulated.

**Keywords**- Ambroxol Hydrochloride, Sodium starch glycolate, Camphor, Statistical optimization.

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## INTRODUCTION

Recent developments in technology have presented viable dosage alternatives for pediatric, geriatric, bedridden, nauseous or non compliant patients. Traditional tablets and capsules administered with 250 ml of water may be inconvenient or impractical for such patients (1). Hence, fast dissolving tablets/ disintegrating tablets are a perfect dosage alternative for them. Fast dissolving tablets dissolve or more commonly disintegrate rapidly, in the saliva usually within a minute, without the aid of water. Also, this dosage form offers an advantage of convenience of administration while traveling, where there may not be an access to water (2). Fast dissolving tablets (FDTs) can be prepared by different methods, such as direct compression, freeze-drying, spray drying, sublimation, wet granulation method. The basic approach for the development of FDTs is the use of superdisintegrant and camphor (3).

Ambroxol is a metabolite of bromohexine with similar actions and uses ansd is chemically described as Trans-4-[(2-Amino-3, 5-dibromobenzyl) amino]-cyclohexanol (4). Ambroxol hydrochloride is introduced into drug therapy with two main purposes: to an expectoration improver and a mucolytic agent used in reduce the number of single doses per day improving the treatment of acute and chronic disorders characterized patient compliance of treatments and to decrease the by the production of excess of thick mucus(5).There are many hydrochloride as a secretion-releasing expectorant in a controlled-release pharmaceutical systems currently variety of respiratory disorders. Ambroxol hydrochloride has short biological half known, ranging from monolithic matrices, membrane life (3-4 hrs) that calls for frequent daily dosing and the therapeutic use in chronic respiratory diseases(6).

Fast dissolving tablets of Ambroxol hydrochloride prepared using direct compression have been optimized successfully using a face-centered Central Composite Design(7) The fast dissolving tablets were prepared by direct compression and evaluated for various evaluation parameters including hardness, thickness, friability, drug content uniformity, wetting time, water absorption ratio and disintegration time. Based on the principles of design of experiments (DOE), the methodology involves the use of various types of experimental designs, generation of polynomial mathematical relationships and mapping of the response over the experimental domain to select the optimum formulation. Therefore, face-centered Central Composite Design was found to be a very suitable tool for process optimization of fast dissolving tablets in this study(8). The optimized batch having concentration of sodium starch glycolate and camphor was found within the standard limit of parameters-disintegration time (sec) and water absorption ratio (%) as 61 sec and 69.67%.

## MATERIALS AND METHODS

### Materials

Ambroxol Hydrochloride was received as a gift sample from Balaji Drugs, Mumbai, India, Camphor was received from Himedia, Mumbai and Sodium starch glycolate and Micro crystalline cellulose were received from Merck specialist Pvt. Ltd, Mumbai. All other chemical and reagents used in this study were of analytical grade.

### Methods

**Drug-Excipient compatibility studies using Fourier Transform infrared spectroscopy (FTIR)**

The FTIR studies were performed to study drug-excipient interaction in the range 4000 -400 $cm^{-1}$ using an FTIR spectrometer (Bruker Model no-10059736) and data had been collected (9**).**

**DRUG EXCIPIENTS COMPATIBILITY STUDIES USING DSC**

In drug formulation it is essential to evaluate the possible interactions between the active principle and the superdisintegrant. Ambroxol Hydrochloride powder was mixed with different excipients in the ratio of 1:1 and the resulting physical mixture was examined on differential scanning calorimeter (Perkin Elmer 2000). Mixtures have been examined under Nitrogen to eliminate oxidative and pyrolytic effect at a standard heating rate (2, 5 or 100C/minute). Thermogram of pure drug was used as a reference (10).

**Formulation of Fast dissolving tablets of Ambroxol Hydrochloride**

Ambroxol hydrochloride fast dissolving tablets were formulated by using the ingredients Sodium starch

glycolate and Camphor. All the ingredients with drug except Magnesium stearate were taken in the V-blender. The powder blend was mixed well at 20 rpm for 15 minutes, and then mixture was passed through # 40 sieves. Finally Magnesium stearate was added as lubricant and mixed thoroughly. The powder blend was compressed using 8 stations tablet compression machine (Shakti Pharmatech, Ahmadabad, India) to produce tablets of Ambroxol hydrochloride weighing 60mg having diameter of 6mm (11).

## OPTIMIZATION OF AMBROXOL HYDROCHLORIDE FAST DISSOLVING TABLETS

Using Design Expert 10.0, the formulation for Ambroxol Hydrochloride sublingual tablets were prepared with incorporation of Sodium starch glycolate and Camphor. The selection of these super disintegrants was done on the basis of preliminary studies and cost effectiveness.

**Experimental design**

A Central Composite Design using Design Expert Software (Version 10.0, Stat- Ease Inc, and Minneapolis, MN) was used to optimize and evaluate main effects, interaction effects and quadratic effects of the formulation ingredients on the disintegration time, wetting time, water absorption ratio and in vitro release of Ambroxol hydrochloride. A 2-factor, 3-level design was observed to be most suitable for exploring quadratic response surfaces and constructing second-order polynomial models(10,11) The amount of Sodium starch glycolate (X1) and Camphor (X2) were selected as the factors, studied at 3 levels each. The central point (0, 0) was studied in quintuplicate. All other formulation and processing variables were kept invariant throughout the study. The dependent and independent variables selected are also shown along with their low, medium and high levels, which were selected based on the results from preliminary experimentation (10).

The coded levels & actual factor combinations are presented in Table 1.

**Table-1. Factor Combination as per the Chosen Experimental Design**

| Coded Level | X-1 Sodium Starch Glycolate (%) | X-2 Camphor (%) |
|---|---|---|
| -1 | 1.6 | 7.5 |
| 0 | 4.95 | 11.25 |
| 1 | 8.3 | 15 |

**TABLE-2.Formulation of Optimized fast dissolving tablets of Ambroxol Hydrochloride**

| Formulation no | Run | Ambroxol hydrochloride(mg) | Sodium starch glycolate (mg) | Camphor (mg) | Microcrystalline cellulose(mg) | Sodium saccharine (mg) | Talc(mg) | Magnesium stearate(mg) | Mannitol (mg) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 7.5 | 2 | 5 | 2 | 3 | 3 | 5 | 32.5 |
| 2 | 2 | 7.5 | 10 | 5 | 2 | 3 | 3 | 5 | 24.5 |
| 3 | 3 | 7.5 | 2 | 15 | 2 | 3 | 3 | 5 | 22.5 |
| 4 | 4 | 7.5 | 10 | 15 | 2 | 3 | 3 | 5 | 14.5 |
| 5 | 5 | 7.5 | 2 | 7 | 2 | 3 | 3 | 5 | 30.5 |
| 6 | 6 | 7.5 | 10 | 7 | 2 | 3 | 3 | 5 | 22.5 |
| 7 | 7 | 7.5 | 3 | 5 | 2 | 3 | 3 | 5 | 31.5 |
| 8 | 8 | 7.5 | 3 | 15 | 2 | 3 | 3 | 5 | 21.5 |
| 9 | 9 | 7.5 | 3 | 7 | 2 | 3 | 3 | 5 | 29.5 |

**EVALUATION STUDIES OF OPTIMISED FAST DISSOLVING TABLETS OF AMBROXOL HYDROCHLORIDE**

**Pre-Compression Parameter**

Prior to compression, powder was evaluated for flow and compressibility parameters. Flow properties of powder were determined by angle of repose method. Compressibility index of powder was determined by Carr's index and Hausner ratio.

**Bulk density and Tapped density**

Tapped density is the total mass of the powder to the tapped volume of the powder. It is expressed in g/ml.It is expressed in g/ml.

Bulk density, $D=M/V_b$, Where M-mass of the powder

$V_b$-bulk volume of the powder

Tapped Density, Dt=M/Vt, Where M-mass of the powder

Vt-tapped volume of the powder (5).

**Compressibility index (I) and Hausner ratio**

Carr's index and Hausner ratio measure the propensity of the powder to be compressed and the flow of granules (6).It is given by formula-

Carr's index, I= (Dt-Db/Dt) X100

Hausner's ratio=tapped density/bulk density

**Angle of repose (□)**

This is the maximum angle between the surface of the pile of a powder and the horizontal plane. Sufficient quantities of granules were passed through a funnel from a particular height onto a flat surface until it formed a heap, which touched the tipped of the funnel. The height of the radius of the heap was measured (7).The angle of repose was calculated as

Angle of repose, tan□=h/r

Where h-height of the pile

R-radius of the pile.

**POST-COMPRESSION PARAMETER**

**Hardness**

The test was done as per the standard methods. The hardness of three randomly selected tablets from each formulation was determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in $kgcm^{-2}$(7).

**Thickness**

The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier caliper (Pico India). The average values were calculated (7)

**Uniformity of weight**

Weight variation test was done as per standard procedure. 20 tablets from each formulation were weighed using an electronic balance, and the average weight was calculated (8).

**Friability**

The friability of tablets was measured using six tablets using a Roche friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were taken out, dedusted, and reweighed. The percentage friability was calculated from the loss in weight as given in equation below (8). The weight loss should not more than 1%.

Friability (%) = ([Initial weight − Final weight]/initial weight) × 100.

**Drug content**

10 tablets were powdered and the powder equivalent to 15 mg was dispersed in phosphate buffer pH 6.8. Volume of the solution made up to 10 mL by media. The mixture was filtered and 1 ml of the filtrate was diluted to 10 mL using phosphate buffer pH 6.8. The absorbance of the sample preparations was measured at 243.0 nm for Ambroxol hydrochloride (8)

**Wetting time**

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of phosphate buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined (7,8)

**Water absorption ratio**

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wet tablet was then weighed (7,8)

Water absorption ratio **(R) = 100 (Wa - Wb)/Wb**

Where Wb and Wa are the weights of tablet before and after water absorption, respectively

**In-vitro disintegration time**

Disintegration time for sublingual tablets was determined using USP tablet disintegration apparatus with phosphate buffer of pH 6.8 as medium. The volume of medium was 900 ml and temperature was 37±0.5°C. The time in seconds taken for complete

disintegration of the tablets with no palatable mass remaining in the apparatus was measured (9)

**Optimization Data Analysis and Numerical Optimization**

Various Response surface methodological techniques in computations for the current optimization study were performed employing Design Expert Software (Version 10.0, Stat- Ease Inc, Minneapolis, MN) (10). Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented below:

$Y = \beta o + \beta 1\ X_1 + \beta 2\ X_2 + \beta 3\ X_1 X_2 + \beta 4\ X^2_1 + \beta 5\ X^2_2 + \beta 6\ X_1 X^2_2 + \beta 7\ X^2_1 X_2$

Where, βo is the intercept representing the arithmetic average of all quantitative outcomes of 10 runs; β1 to β7 are the coefficients computed from the observed experimental values of Y; and X1 and X2 are the coded levels of the independent variable(s).

The terms X1X2 and Xi2 (i = 1 to 2) represent the interaction and quadratic terms, respectively (10). Statistical validation of the polynomial equation was established on the basis of ANOVA provision in the Design Expert Software. Various feasibility and grid searches were conducted to find the composition of optimum formulations. Also, the 3-D response surface graphs and 2-D contour plots were constructed using the output files generated (7).

**RESULT AND DISSCUSSION**

**Drug-Excipient compatibility study using FTIR**

The FTIR studies were carried out as given in the methodology section. The FTIR study showed following interpretation-

- Ketone stretching vibration at(1,4-Quinones) at 1690.25 $cm^{-1}$
- C-H bending at 1690 $cm^{-1}$
- C-N vibration at 1147.44 $cm^{-1}$
- C-Cl stretching at 702.73 $cm^{-1}$.

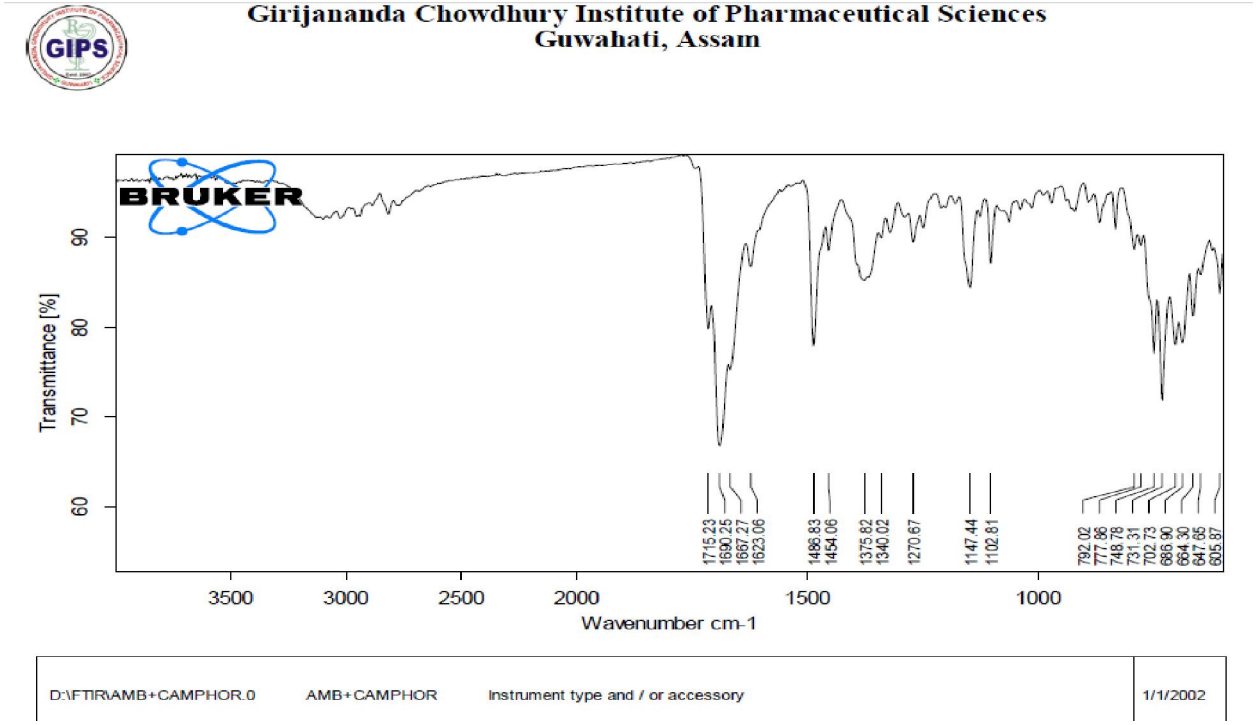


**Fig no-1.FTIR report of Mixture sample(Ambroxol Hydrochloride+Camphor)**

**DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES**

The DSC was carried out by method mentioned in methodology section. The DSC spectra was found in fig no-2.The results obtained with DSC studies showed that there was no interaction between the drug and other excipients used in the mixture sample. The peak point of Ambroxol hydrochloride was 241˚c (240˚c) and for Sodium starch glycolate was 219˚c.

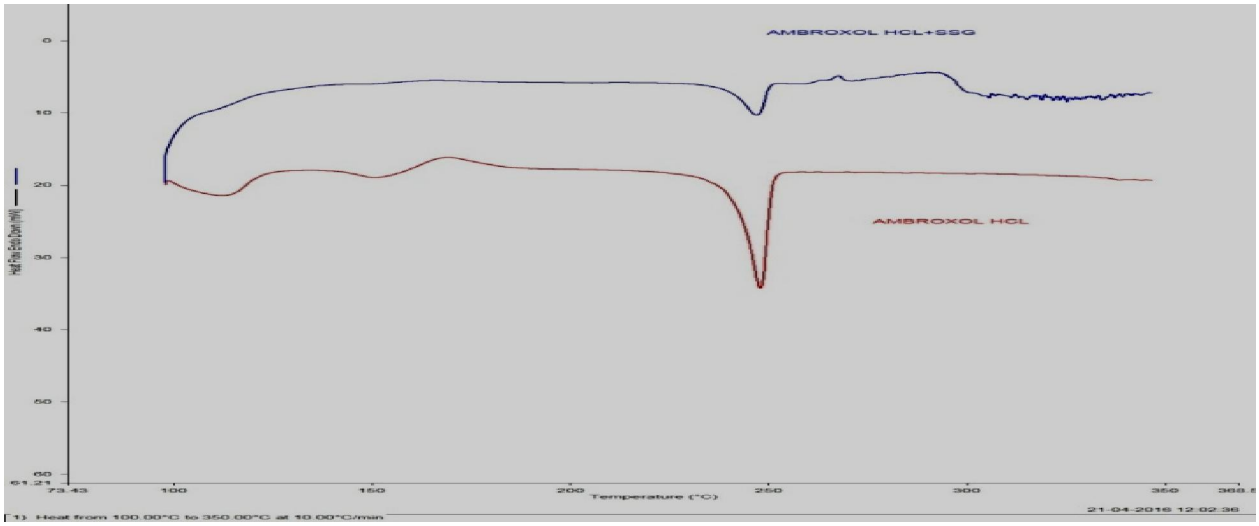


**Fig no-2.DSC study of Mixture sample**

**PRE-FORMULATION PARAMETERS**

The pre-formulation parameters for tablet blend were given in table-3.

## Table 3: Pre-formulation parameters of the tablet blend

| Formulation no | Bulk Density (g/ml) | Tapped Density(g/ml) | Carr's Index (%) | Hausner ratio | Angle of Repose (θ) |
|---|---|---|---|---|---|
| F1 | 0.364 | 0.545 | 10.8 | 1.11 | 31.5 |
| F2 | 0.362 | 0.485 | 10.2 | 1.21 | 30 |
| F3 | 0.379 | 0.530 | 10.2 | 1.13 | 29.6 |
| F4 | 0.375 | 0.493 | 10.5 | 1.57 | 30.2 |
| F5 | 0.360 | 0.477 | 10.8 | 1.06 | 31.5 |
| F6 | 0.419 | 0.471 | 10.9 | 1.20 | 28.6 |
| F7 | 0.417 | 0.456 | 11.1 | 1.07 | 32.1 |
| F8 | 0.416 | 0.458 | 10.0 | 1.09 | 25.6 |
| F9 | 0.428 | 0.428 | 11.2 | 1.99 | 24.3 |

The results of pre-compression studies reveal that the bulk density of powder blend was found between 0.362-0.442 g/cm$^3$ and tapped density was found between 0.428-0.530g/cm$^3$ which is in limit of both bulk density and tapped density. Also in case of Carr's index it was found in between 10-11.2 and Hausner ratio in between 1.06-1.99 which holds the assumption of good compressibility. Lastly angle of repose of the powder blend was found in between 25.6-31.5 which was having property of good flow of the powder blend.

**POST COMPRESSION PARAMETERS OF THE PREPARED AMBROXOL HYDROCHLORIDE FAST DISSOLVING TABLETS**

**Table-4.Post compression parameters of fast dissolving tablets of Ambroxol Hydrochloride**

| Formulation no | Thickness(mm) | Hardness(kg/cm2) | Uniformity of weight | Friability (%) | Drug content (%) | Wetting time(sec) | Water Absorption ratio | In vitro disintegration time(sec) |
|---|---|---|---|---|---|---|---|---|
| F1 | 3 | 3.5 | 60±0.37 | 0.72 | 95.9 | 25 | 44.4 | 34 |
| F2 | 3 | 3.5 | 60±0.89 | 0.68 | 96.8 | 17 | 22.2 | 70 |
| F3 | 3 | 3.5 | 60±0.23 | 0.70 | 93.7 | 20 | 58.9 | 110 |
| F4 | 3 | 3.5 | 60±0.99 | 0.69 | 97.0 | 21 | 72.2 | 107 |
| F5 | 3 | 3.5 | 60±0.45 | 0.81 | 90.9 | 26 | 64.7 | 57 |
| F6 | 3 | 3.5 | 60±0.89 | 0.71 | 92.0 | 21 | 52.9 | 65 |
| F7 | 3 | 3.5 | 60±0.56 | 0.78 | 99.8 | 17 | 50 | 120 |
| F8 | 3 | 3.5 | 60±0.88 | 0.61 | 97.8 | 20 | 61.1 | 130 |
| F9 | 3 | 3.5 | 60±0.90 | 0.88 | 96.9 | 27 | 56.2 | 110 |

The prepared tablets were evaluated for different post-compression parameters like weight variation, hardness, thickness, friability and disintegration time and the results are within the limits which depicted in Table.4. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Disintegration time of various prepared fast dissolving tablets of Ambroxol hydrochloride was found to be within the range of 34 to 130 seconds.

**STASTICAL OPTIMISATION OF AMBROXOL HYDROCHLORIDE TABLETS**

**ANOVA- Analysis of variance**

Analysis of variance of the responses indicated that response surface models developed for disintegration time and water absorption were significant and adequate, without significant lack of fit. Influences of formulation variables on the response factors are shown.

**Table-5 .ANOVA –Influence of formulation variables on the response factors**

| Response Factor | Model F-value | Prob>F | Lack of fit F-value | Prob>F |
|---|---|---|---|---|
| **Disintegration Time** | 10.80 | 0.0391 | 14.83 | 0.289 |
| $X_1$.Sodium starch glycolate | 10.56 | 0.0475 | do | do |
| $X_2$. Camphor | 10.11 | 0.0501 | do | do |
| **Water Absorption Ratio** | 34.64 | 0.0022 | 0.32 | 0.4866 |
| $X_1$.Sodium starch glycolate | 165.41 | 0.0002 | do | do |
| $X_2$.Camphor | 0.029 | 0.8739 | do | do |

Model summary statistics for the selected significant models are shown in Table 5. It can be observed that R2 is high for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R2 value is in good agreement with the adjusted R2 value, resulting in reliable models.

**Table 6: Model Summary Statistics- Influence of formulation variables on the response factors**

| Response Factor | Std. Deviation | $R^2$ | Adjusted $R^2$ | Predicted R |
|---|---|---|---|---|
| Disintegration Time | 17.46 | 0.9474 | 0.8596 | 0.3668 |
| Water absorption ratio | 7.83 | 0.8157 | 0.7052 | 0.8685 |

**Mathematical equations:** Mathematical relationships generated using multiple regression analysis for the studied response variables are expressed as equations (I and II). The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor.

Disintegration time=113.67– 23.17 $X_1$ +22.67$X_2$ - 16.75 $X_1$ $X_2$ -52.50.27 $X^2_1$ +42.00 $X^2_2$ -973.14$X_1$ $X^2_2$ + 1190.17$X^2_1$ $X_2$- (I)

Water Absorption ratio= 53.67-3.35 $X_1$ +12.67 $X_2$– 42.44 $X_1$ $X_2$ +11.22 $X^2_1$ +160.52 $X^2_2$ -537.74$X_1$ $X^2_2$ + 142.157 $X^2_1$ $X_2$ – (II)

**Response Surface Analysis**

The 3-dimensional response surface plots are shown in Fig and the corresponding contour plots for the studied response properties viz., disintegration time and water absorption ratio are shown in respectively.

**A. Effect of variable in Disintegration Time-** The variables on the present study i.e. the amount of Sodium starch glycolate and Camphor had equal effects in both the responses. These variables effect equally on the disintegration time (sec) as can be seen in the contour (fig-6) as well as 3D- surface plot (fig-7).

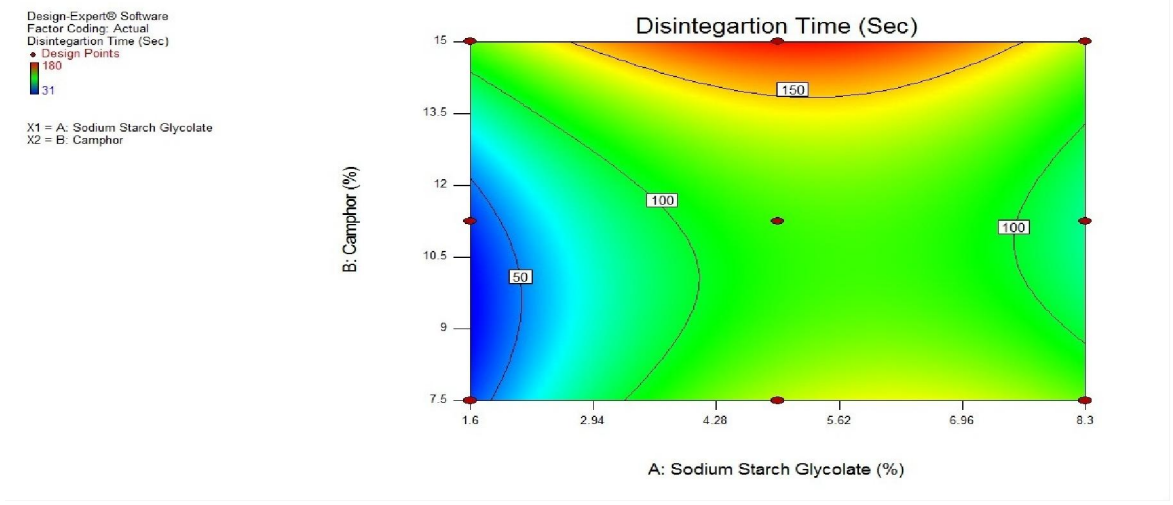


**Fig no-6. Contour plot showing the relationship between various levels of two factors on disintegration time**

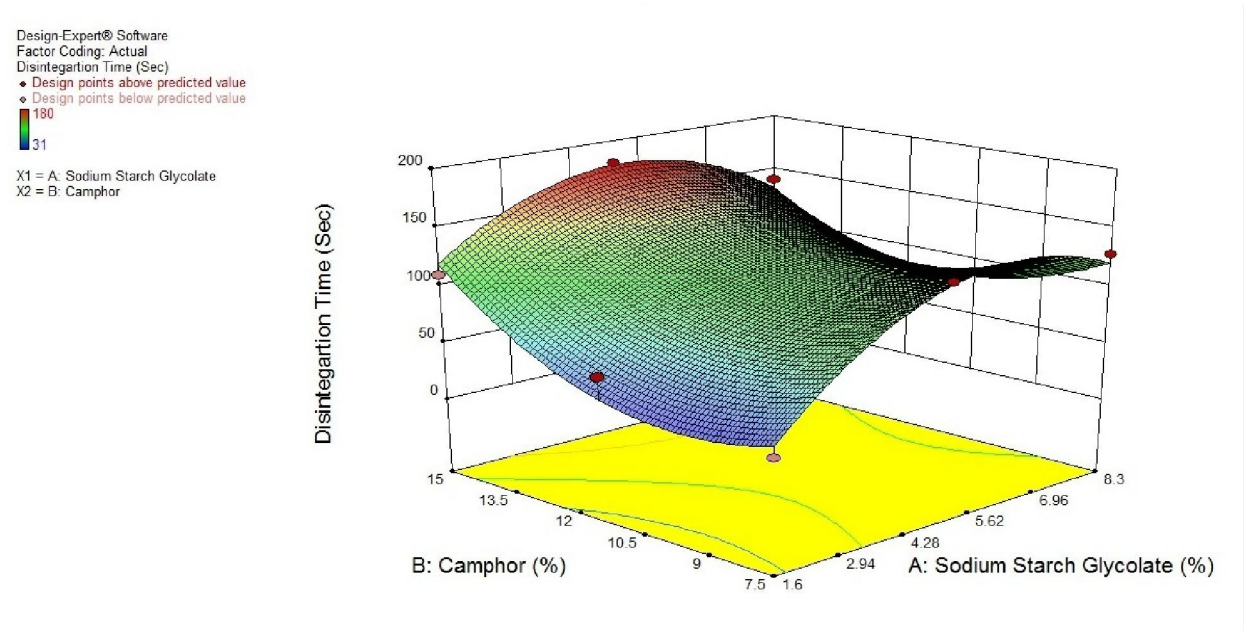


**Fig no-7.3D-Response surface plot showing the influence of two different factors on disintegration time**

**B.Effect of Variables in Water absorption ratio**

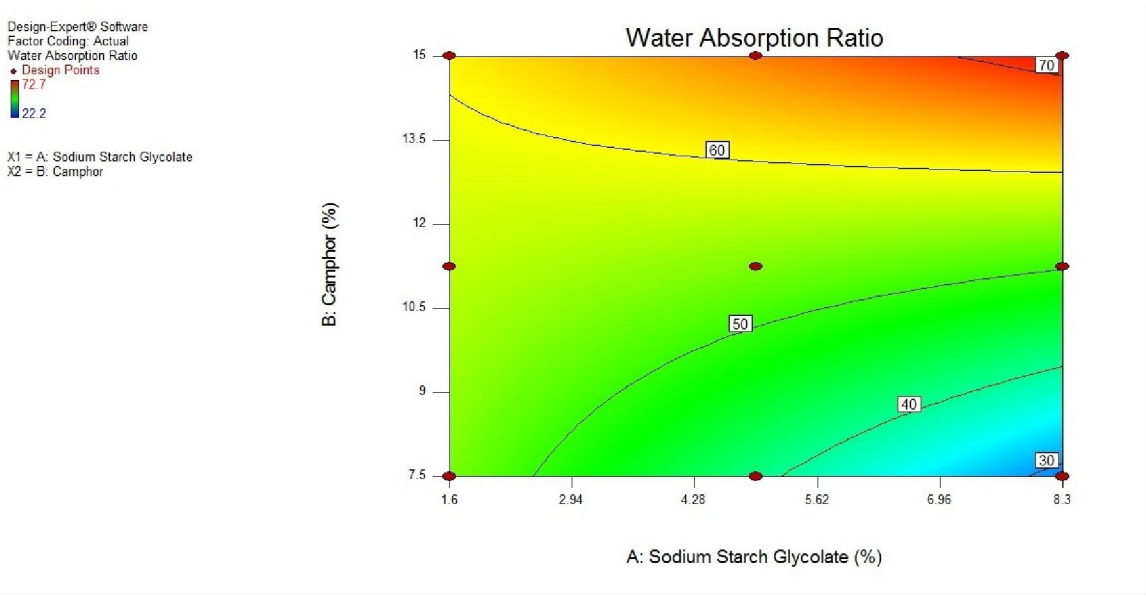


**Fig no-8.Contour plot showing the relationship between various levels of two factors on Water absorption ratio**

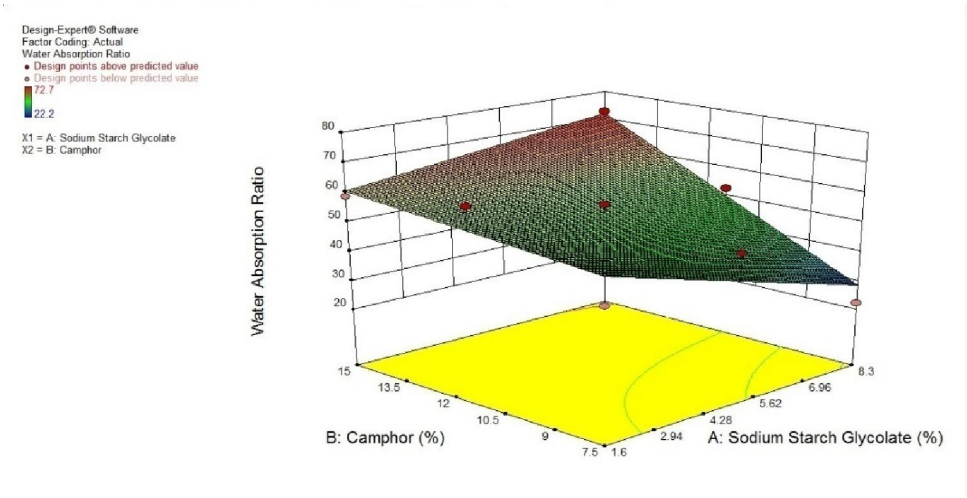


**Fig no-9. 3D-Response surface plot showing the influence of two factors on water absorption ratio**

The variables on the present study i.e. the amount of Sodium starch glycolate and Camphor had equal effects in both the responses. These variables effect equally on the water absorption ratio as can be seen in the contour (fig-8) as well as 3D- surface plot (fig-9).

**Validation of Results**

In order to evaluate the optimization capability of the models generated according to the results of the central composite design, tablets including the optimized formulation were prepared using the optimal process variable settings. All results of the physical evaluation were found to be within limits. Table 7 lists the composition of the final batch, its predicted and experimental values of all the response variables, and the percentage error. From the table, it was cleared that the percentage errors for optimized batch with response variable disintegration time was found to be 3.47 and that of water absorption ratio was found to be 2.36.

**Table-7.Composition of the Optimized Formulation, the Predicted and Experimental values of Response Variables, and Percentage Prediction Error**

| Composition Sodium Starch glycolate: Camphor | Responses variable | Experimental Value | Predicted Value | Percentage Error |
|---|---|---|---|---|
| 4.95:15 | Disintegration Time(sec) | 61 | 45.28 | 3.47 |
| | Water Absorption ratio | 69.67 | 91.21 | 2.36 |

**CONCLUSION**

The response surface methodology (RSM) using Central Composite Design (Design Expert Software ,Version 10.0.Stat- Ease Inc, Minneapolis, MN) with 2-factor, 3-level Central Composite design with super disintegrants sodium starch glycolate and camphor was employed for optimization of fast dissolving tablets of Ambroxol hydrochloride. The quantitative effects of the factors at different levels on the responses could be predicted by using polynomial equations. The observed responses were found to be in close agreement with the predicted values for optimized formulations. The direct compression method in this study is relatively simple and safe and a stable, effective and pleasant tasting fast dissolving tablets, which has a good balance over disintegration time and water absorption ratio, was formulated.

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CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE