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Original Article

DESIGN AND STATISTICAL OPTIMIZATION OF ANTACID ANALGESIC EFFERVESCENT TABLETS BY USING 2^3 FACTORIAL DESIGN

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ABSTRACT

Objective: The present research work was undertaken with an aim to formulate a combination dosage form constituting an antacid and analgesic which may be useful in case of hyperacidity associated headache.

Methods: In this formulation, a mixture of magnesium and aluminium hydroxide was used as the antacid. Ibuprofen was used as analgesic drug while, citric acid and tartaric acid along with sodium bicarbonate were used as effervescent mixture. The prepared tablets of all the formulations were evaluated for physical characterization.

Results: The infra red spectra revealed that there was no chemical interaction between the drug and excipients which showed their compatibility. The results of these studies were found to be within the standard Pharmacopoeial limits. The release character was studied using the disintegration and dissolution studies conducted. The results of 2^3 factorial design revealed that the amounts of crosspovidone, tartaric acid and citric acid used in effervescent formulation significantly affected the dependent variables i. e. Hardness, friability and disintegration time etc. The stability studies of the tablet formulation showed that the tablets remained stable even after exposing to stress condition of temperatures.

Conclusion: It was thus concluded that by adopting a systematic formulation approach, optimized release mechanism can be reached in the shortest time with minimum efforts.

Keywords: Ibuprofen, Hyperacidity, Effervescence, Palatability, Factorial Design.

INTRODUCTION

The oral dosage forms are the most popular way of administering medication despite having some disadvantages like slow absorption and thus onset of action is prolonged. This can be overcome by administrating the drug in liquid from but, many APIs have limited level of stability in liquid form. So, effervescent tablets acts as an alternative dosage form.

These tablets are added into a glass of water just before administration and the drug solution or dispersion to be administered immediately. The manufacturing is done under controlled climatic condition to avoid effervescent reaction. Different carbonates, acids and buffers are usually used to attain good effervescence in a short time and to obtain a clear solution and to give maximum therapeutic effect in a short span of time when taken orally. [1,2] The manufacturing shall be done under controlled climatic condition to avoid effervescent reaction.

The packaging should be done under 25% RH at 25°C. Antacids either directly neutralize acidity, increasing the pH, or reversibly reduce or block the secretion of acid by gastric cells to reduce acidity in the stomach. When gastric hydrochloric acid reaches the nerves in the gastrointestinal mucosa, they signal pain to the central nervous system. This happens when these nerves are exposed. [3] In addition to the reduction of gastric acidity, antacids also alter the profile of prostaglandins produced by gastro duodenal mucosa and this may promote mucosal healing and be related to its therapeutic effect.

Large doses of medication can be easily delivered by effervescent tablets, because the patient just needs to drink one glass of fluid. [4] People who have trouble swallowing pills often appreciate medicine that is available in the form of effervescent tablets, because it usually is easy to swallow the solution. In light of this, the present investigation involving the formulation and statistical optimization of antacid analgesic effervescent tablets consisting magnesium and aluminium hydroxide as antacid and Ibuprofen as analgesic, was carried out by using 2^3 factorial design where citric acid and tartaric acid along with sodium bicarbonate were used as effervescent mixtures. [5]

Mechanism of CaCO3, Mg (OH)2, Al(OH)3 as an antacid

These are used as an antacid for rapid acid neutralization. Each compound in solution dissociates into a metal ion (Na, Ca, Mg, Al) and an acid binding group. The pancreas secretes bicarbonate in the duodenum; which can precipitate Ca and Al so that they are largely excreted in the faeces. Many antacids combine both Al and Mg, ions which counteract each other's action to prevent unwanted constipation or diarrhoea. Al by itself produces constipation due to an astringent action, and $Mg(OH)_2$ produces dinar be taken between meals (Fig. 1). [6]

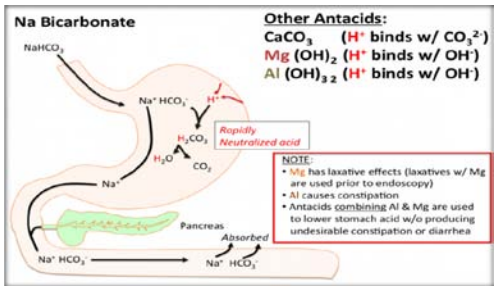

Fig. 1: Mechanism Of $CaCO_3$, Mg $(OH)_2$, Al$(OH)_3$ as an antacid

MATERIALS AND METHODS

Materials

Ibuprofen, Aluminium Hydroxide, Magnesium Hydroxide, Citric Acid, Tartaric Acid, Sodium Hydroxide, and all the other chemical reagents used were of pharmaceutical grade.

Method

The tablets were prepared by simple wet granulation technique. All the ingredients were weighed and passed via sieve no. 20 to get free flowing powder the powders were geometrically mixed and then dough prepared with 10% PVA in IPA solution and passed through a sieve. no.8 and dried for not more than 5 mins. Then the granules were passed via sieve. no.14 and retained on a sieve. no.20. The granules along with the post granulating substances are ready for compression. The tablets were compressed with 12 mm diameter punches. [7]

Preformulation

Description

The drug sample of Ibuprofen was analyzed for physical appearance, color, odor, solubility and test. [8]

Melting point determination

Melting point was measured with the use of Thiele's Tube apparatus by paraffin oil, thermometer, thread and burner. [9]

Uv visible spectrophotometric method for Ibuprofen

Standard calibration curve: The spectrum of ibuprofen was determined using Shimadzu UV-1800 instrument Standard stock solution of ibuprofen (100ug/ml) was prepared by dissolving 10 mg of methanol then volume was made up to 100 ml with distilled water.1 ml of stock was diluted to 10 ml with water to get concentration of 10ug/ml. Then resultant solution was scanned from 400 to 200 nm and the spectrum was recorded to obtain the value of λmax.[10]

Infra-red spectrophotometer (IR)

Infrared (IR) spectroscopy was conducted and the spectrum was recorded in the wavelength region of 4000 to 400 cm−1. [11]

Solubility studies

The solubility of the drug in the gastric content is an important criterion for the dissolution and absorption. To understand the solubility profile of saturation solubility studies were carried out in various media with varying PH range. The solubility was determined in 0.1N HCl, phosphate buffer 6.8 and 7.8. [12]

Pre-Compression Parameters

Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane. The angle of repose is designated by θ and given by equation:

Tan θ = r/h or θ = Tan-1 r/h

Where; h = height of the pile, cm, r = radius of the base of the pile, cm.

The lower the angle of repose, better the flow properties, when powder is placed in the hopper and allowed to slide down into the die for compression. It forms a pile. The angle of repose was calculated by measuring the height (h) of the pile and the radius of the base (r) with the ruler. [13]

Bulk Density and tapped density

The Bulk density denotes the total density of the materials as it exists. Bulk volume includes the true volume. Volume of interparticle spaces and intraparticle pores. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

Method

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 gm of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at second intervals. The tapping was continued until no further change in volume was noted.

TBD = wt. of powder/Tapped volume of packing

LBD = wt. of powder/ volume of packing

Application: Bulk density property is used in-

- Checking the uniformity of bulk chemicals.
- Selecting the size of container, mixing apparatus for the production.
- Determining the proper size of the packing material. [13]

Compressibility Index

Whether the powder is porous or non porous, the total porosity expression for the calculation remains the same. [14]

Carr's index (%) = TBD – LBD/TBD × 100

Hausner ratio

It is another parameter to check compressibility of powder. Tap bulk density was subtracted from law bulk density. Different ranges of flow ability in terms of the Hausner ratio are given in Table 1.

Table 1: Evaluation of Flow ability (Hausner ratio)

Ratio	Interpretation	Equivalent to carr's index
1.25	Good flow	20%
>1.25	Poor flow	33%

Applications

Compressibility index provide information about hardness, disintegration, tablet porosity etc., there dissolution and release of drugs. [14]

Post-compression parameters

General Appearance of Tablets

Tablets were examined under a lens for the shape and color of the tablet, its overall elegance, uniformity, consistency, surface texture, odor, taste, etc. [15]

Thickness and Diameter Test

Thickness and diameter test permits accurate measurement and provides information on the variation between tablets. Ten tablets were taken and the thickness and diameter was measured using a Vernier caliper. The tablet thickness and diameter should be controlled within a ± 5% variation of a standard value. [15]

Weight variation test:

The IP weight variation test is run by weighing 20 tablets individually. Calculating the average weight and comparing the individual tablet weight to the average. The tablet meet the IP test, if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. [16]

Hardness Test

Hardness indicates the ability of a tablet to with stand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto Hardness Tester. The force needed to disrupt them by crushing in kg/cm^2 expresses it. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. [16]

Friability Test for tablets

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was

determined using Electrolab Friabilator. It is expressed in percentage (%). Six tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). % friability of tablets less than 1% are considered acceptable. [16]

Disintegration studies for tablets

This test determines whether tablets disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions. Disintegration is defined as that state in which no residue of the tablet or capsule remains on the screen of the apparatus or, if a residue remains, it consists of fragments of insoluble coating of the tablets or of capsule shells or is a soft mass with no palpable core. One tablet was introduced into each tube and, a disc was added to each tube. The assembly was suspended in the beaker containing distilled water and the apparatus was operated for the specified time. Temperature of the liquid was maintained the at 37° ±1°C. When all five tablets have disintegrated time is measured. [17]

Drug content

The drug content of all formulated batches was determined as per the procedure specified in IP. Twenty tablets were weighed accurately and powdered. Powder is dissolve in methanol and check the absorbance by using UV spectrophotometery. [17]

***In-vitro* Drug Release**

The dissolution test was carried out in distilled water. Aliquots were withdrawn at predetermine time intervals and after suitable dilutions absorbance was measured with the help of UV spectrophotometer at 214 nm. [18]

Stability Studies

According to ICH guidelines, a selected formulation F1 was stored at 40 ± 20C (75 ± 5% RH), 50C and room temperature for a period of 1 month. Formulations were evaluated at periodical intervals of different days for hardness, friability & disintegration time. [19]

Preformulation

Melting point

The melting point of Ibuprofen was found to be 75-76^{0}C.

Drug- excipient IR compatibility study

IR spectra showed the compatibility of drugs with excipients.

To ensure the compatibility of the Ibuprofen with aluminium hydroxide, sodium bicarbonate, citric acid, tartaric acid and povidone preformulation studies were done using IR spectrum recorded on FT-IR by preparing KBr disk. The IR peaks of Ibuprofen with the above excipients resemble almost same structural peaks of pure Ibuprofen indicating the compatibility between the Ibuprofen and aluminium hydroxide, sodium bicarbonate, citric acid, tartaric acid and povidone.

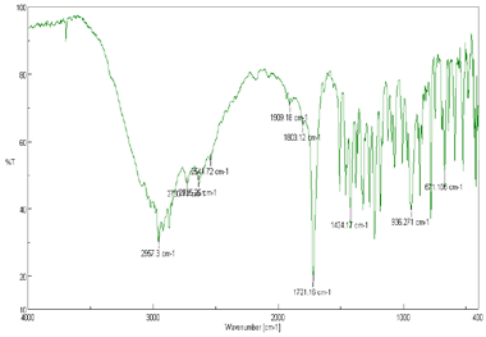

Fig. 2: IR Spectra of Ibuprofen

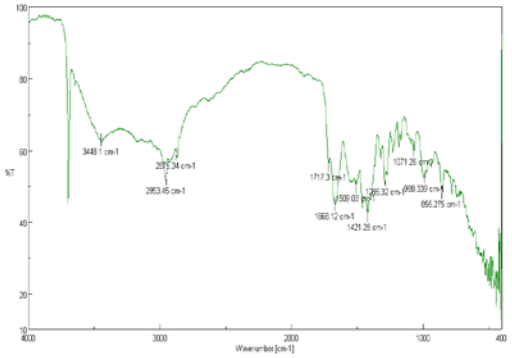

Fig. 3: IR spectra of bland mixture (ibuprofen, aluminium hydroxide, sodium bicarbonate, citric acid, tartaric acid, povidone)

UV visible spectra of ibuprofen

The drug content and release of ibuprofen from the formulation was determined by using UV Spectrophotometer. The UV spectrum of ibuprofen showed λmax at 214 nm.

Calibration curve of ibuprofen in distilled water, acidic buffer pH 1.2 & phosphate buffer pH 7.4

Ibuprofen in water showed absorption at 214 nm and this wavelength was chosen as the analytical wavelength. Beer's law was obeyed between 1to6 µg/ml. Regression analysis was performed on the experimental data. Regression equation for standard curve was y = 0.115x. correlation coefficient for developed method was found to be 0.9987 signifying that the linear relationship existed between absorbance and concentration of the drug. The interference studies with formulation excipients studies were carried and no difference in absorbance was observed at 214 nm.

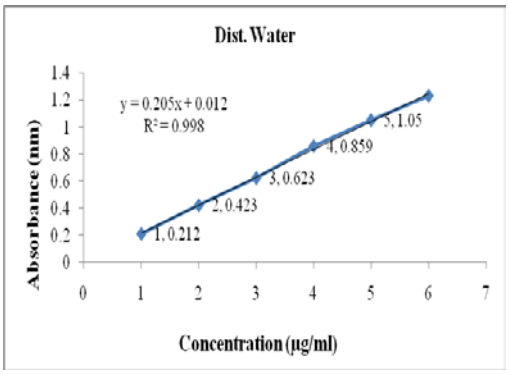

Fig. 4: Calibration plot in distilled water

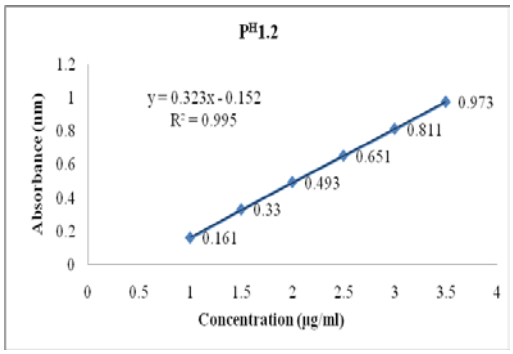

Fig. 5: Calibration plot in acidic buffer of pH 1.2

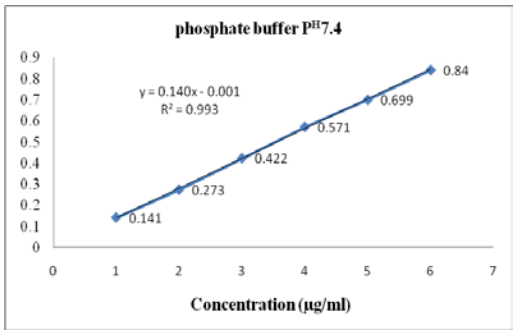

Fig. 6: Calibration plot in phosphate buffer pH 7.4

Table 2: Stability study of ibuprofen

S. No.	Concentration (µg/ml)	Time (hrs.)	Absorbance (nm)
1	5	0	1.05
2	5	1	1.06
3	5	3	1.02
4	5	5	1.07
5	5	12	1.06
6	5	48	1.04

Stability study of Ibuprofen

Stability of a drug has been defined as the ability of a particular formulation, in a specific container to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, retest periods and shelf life to be established.

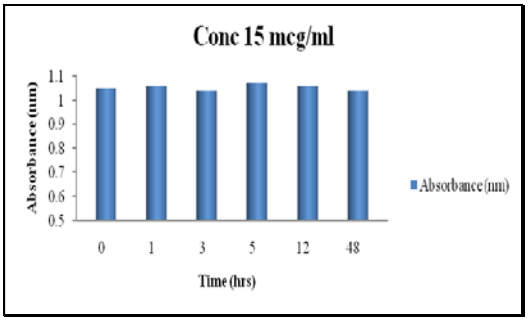

Fig. 7: Stability study of Ibuprofen

Factorial Design

A 2^3 randomized full factorial design was used in the present study. In this design 3factors are evaluated, each at 2 levels, and experimental trials are performed in all 8 possible combinations. The citric acid (X1), and the amount of tartaric acid (X2), crospovidone (X**3**) were selected as independent variables. The hardness, friability and disintegration time were selected as dependent variables. The design matrix and coded levels are mentioned in actual values as shown in table below. Based on the factorial design 8 formulations were devised as shown in Table 3

Table 3: Factorial design of ibuprofen tablet

Ingredients mg/tablet	Batch code							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Ibuprofen (mg)	200	200	200	200	200	200	200	200
Povidone (mg)	16.5	16.5	18.75	18.75	16.5	16.5	18.75	18.75
Citric acid (mg)	40.59	67.98	67.98	40.59	40.59	67.98	67.98	40.59
Tartaric acid (mg)	61.88	101.98	101.98	61.88	101.98	61.88	61.88	101.98
Quantity per tablet (mg)	318.97	386.46	388.71	321.22	359.07	346.36	348.61	361.32

Table 4: Coded Levels

Coded levels	Actual values		
	X1 (mg)	**X2 (mg)**	**X3 (mg)**
-1 (low level)	16.5	40.59	61.88
1(High level)	18.75	67.98	101.98

Table 5: Design matrix of Independent Variables

	Coded levels		
Formulation	**X1 (mg)**	**X2 (mg)**	**X3 (mg)**
F1	-1	-1	+1
F2	-1	-1	+1
F3	-1	+1	-1
F4	-1	-1	+1
F5	-1	+1	+1
F6	+1	+1	+1
F7	+1	-1	_1
F8	+1	-1	-1

Response Surface Analysis (RSA): for Hardness, Friability & Disintegration time

Calculation of Coefficients

The coefficients of the polynomial equations generated using multiple linear regressions analyses (MLRA) for hardness, friability, disintegration time of tablets studied are mentioned below along with the values of r2.

Nine coefficients (ß0 to ß9) were calculated with B0 as the intercept. The coefficients ß0 to ß9 represent various quadratic and interaction terms, but are denoted as such in equation due to their simplicity. The general equation in terms of coded factors is-

Hardness = ß0- ß1X1+ ß2X2- ß3X3+ ß4X1X2+ ß5X1X3+ß6X2X3 - ß7X1- ß8X22- ß9X3

Friability = ß0- ß1X1+ ß2X2- ß3X3- ß4X1X2+ ß5X1X3- ß6X2X3 + ß7X1- ß8X22- ß9X3

Disintegration Time = ß0- ß1X1+ ß2X2+ß3X3+ ß4X1X2+ ß5X1X3 - ß6X2X3 +ß7X12+ ß8X22- ß9X32

Whereas ß0 is intercept and ß1. . . . ß9 is the coefficient of variables which represented various quadratic and interaction terms, but are denoted as such in equation due to their simplicity while X1 X2 X3 are the response variables. The final polynomial equation for Hardness, Friability & Disintegration time generated in terms of coded factors using multiple linear regression analysis is

Hardnes=+2.80-0.074X1+0.028X2-0.046X3+0.086X1X2+0.043X1X3+0.064X2X3-2.500X1-0.03X22-0.087X3

Friability =+0.40-0.018X1+0.060X2-0.095X3-0.11X1X2+ 0.013X1X3-0.11X2X3+1.9X1-0.05 X22-0.19X3

DisintegrationTime=+9.500.71X1+0.35X2+0.35X3+0.60X1X2+1.60X1X3-0.043X2X3+1.25X12+0.50X22+2.50X32

ANOVA for selected factorial model

The statistical evaluation was performed by one-way ANOVA and results showed that p value was less than 0.0001 in all formulations. X1(povidone) factor showed positive effects, X2 (citric acid) factor showed positive effect & X3 (tartaric acid) showed negative effect. While combine effect of X1X2X3 factor showed positive effects; from this data it was cleared that the given model for friability was significant. Therefore it can be derived that the change in p ratio had significant effect on the hardness of the drug while (X2) change in citric acid ratio shows positive effect.

Response surface plots for measured responses.

Fig. 8 & 9 showed that hardness increases with increasing concentrations of povidone & citric acid

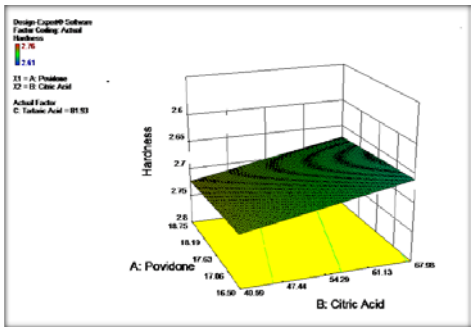

Fig. 8: Response surface plots showing the effect of povidone & citric acid on the hardness from formulation

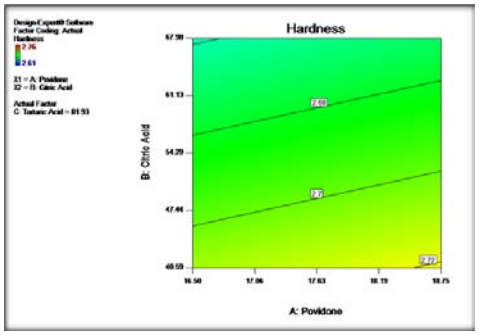

Fig. 9: Counter plots showing the effect povidone & citric acid on the hardness from formulation

ANOVA for selected factorial model

The statistical evaluation was performed by one-way ANOVA and results showed that p value was less than 0.0001 in all formulations. X1 (povidone) factor showed positive effects, X2 (citric acid) factor showed positive effect & X3 (tartaric acid) showed positive effect. While combine effect of X1X2X3 factor shows positive effects from this data it was cleared that the given model for friability was significant. Therefore it can be derived that the change in p ratio had significant effect on the friability of the drug while (X2) change in citric acid ratio shows positive effect.

Response surface plots for measured responses

Fig 10 & 11 showed that friability increases at initial level but later on showed decreasing while concentration of citric acid increases while at initial level when concentration of povidone increases it showed increase in friability but later on showed decreasing friability while concentration of povidone increases.

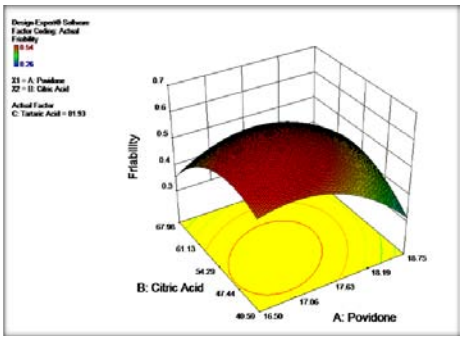

Fig. 10: Response surface plots showing the effect of povidone & citric acid on the friability from formulation

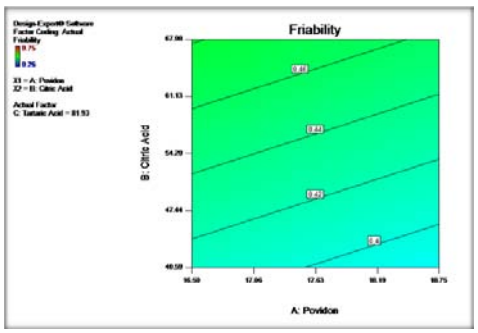

Fig. 11: Counter plots showing the effect povidone & citric acid on the friabilit from formulation

ANOVA for selected factorial model

The statistical evaluation was performed by one-way ANOVA and results were evident that p value was less than 0.0001 in all formulations. X1(povidone) factor showed negative effects, X2 (citric acid) factor showed positive effect & X3 (tartaric acid) showed positive effect. while combine effect of X1X2X3 factor shows positive effects from this data it was cleared that the given model for disintegration time was significant. Therefore it can be derived that the change in p ratio had significant effect on the disintegration time of the drug while (X2) change in citric acid ratio shows positive effect.

Response surface plots for measured responses

Fig. 12 & 13 showed that disintegration time increases when concentration of citric acid increases while at initial level when concentration of povidone increases it showed increase in disintegration time but later on showed decreases disintegration time while concentration of povidone increases.

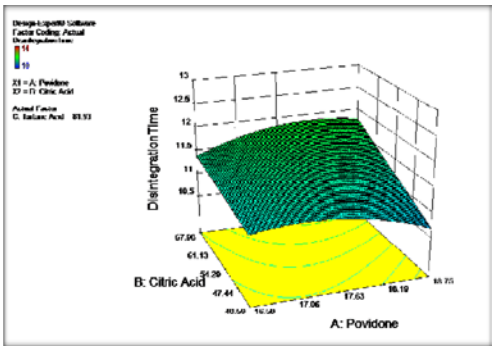

Fig. 12: Response Surface Plots showing the effect of povidone &citric acid on the disintegration time from formulation

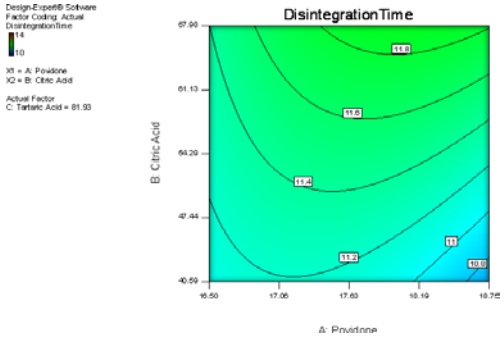

Fig. 13: Counter Plots Showing the Effect of Povidone & Citric Acid on the Disintegration time From Formulation

Table 6: Evaluation of granules

Formulations	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Compressibility index (%)	Hausner's ratio
F1	0.45±0.07	0.714±0.04	27±0.02	10.8±0.31	1.04±0.37
F2	0.57±0.04	0.625±0.05	32±0.03	16.2±0.27	1.38±0.63
F3	0.59±0.05	0.714±0.10	37±0.03	18.5±0.30	1.29±0.62
F4	0.60±0.06	0.714±0.13	36±0.02	17.9±0.26	1.58±0.42
F5	0.76±0.07	0.855±0.32	33±0.09	23.6±0.28	1.31±0.72
F6	0.73±0.12	0.645±0.09	33±0.01	22.4±0.38	1.35±0.53
F7	0.87±0.03	0.745±0.12	40±0.12	23.7±0.42	1.89±0.72
F8	0.91±0.02	0.697±0.32	42±0.08	22.7±0.52	2.01±0.49

Table 7: Evaluation parameters of tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8
Dimensions (mm)	12.2 ± 0.65	16.2 ± 0.45	17.9 ± 0.37	16.9 ± 0.33	14.7 ± 0.65	16.9 ±0.47	16.3±0.54	18.01±0.95
Hardness (kg/sq. cm)	2.63 ± 0.22	3.49 ± 0.32	2.96 ± 0.21	3.03 ± 0.30	3.28 ± 0.29	3.14 ± 0.24	3.06±0.53	3.17±0.62
Friability (%)	0.66±0.03	1.29±0.27	1.47±0.53	0.89±0.09	0.94±0.73	1.06±0.92	1.64±0.52	1.78±0.03
Disintegration Time(sec.)	9-11	8-10	9-12	8-11	10-14	10-13	14-17	17-20
Weight variation (%)	Pass	Pass	Pass	Pass	Pass	Not Pass	Not Pass	Not Pass

In-vitro Drug Release

Aliquots were withdrawn at predetermined time intervals (up to 5 mins) and after suitable dilutions absorbance was measured with the help of UV spectrophotometer at 214 nm and the Cumulative percentage drug released at various time intervals was calculated by using an equation obtained from a standard curve which is depicted in Fig. 14.

Stability Study

According to ICH guidelines, a selected formulation F1 was stored at 40 ± 20C (75 ± 5% RH), 50C and room temperature for a period of 2 month which is depicted in Table No.8, 9, 10. Formulations were evaluated at periodical intervals of 15 days for hardness, friability & disintegration time. The drug loss was minor. From the stability studies of the optimized batches it was found that the tablet remained stable even after exposing to stress condition of temperature.

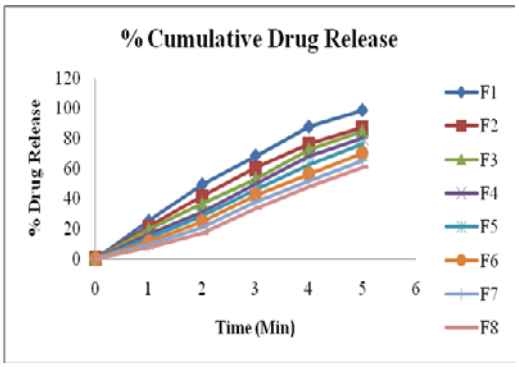

Fig. 14: % Cumulative Drug Release of all formulations

Table 8: Stability data of optimized batch (F1) for temperature at 50C

Evaluation parameters	Storage time (60 days)				
	7	**15**	**30**	**45**	**60**
Hardness (kg/sq. cm)	2.63	2.63	2.65	2.67	2.68
Friability (%)	0.46	0.46	0.46	0.46	0.46
Disintegration time (sec.)	11	11	11	12	12

Table 9: Stability Data of Optimized Batch (F1) At Room Temperature

Evaluation parameters	Storage time (60 days)				
	7	**15**	**30**	**45**	**60**
Hardness (kg/sq. cm)	2.63	2.63	2.65	2.68	2.69
Friability (%)	0.46	0.48	0.48	0.49	0.49
Disintegration time (sec.)	12	12	12	12	12

Table 10: stability data of optimized batch (F1) at temperature 40 ± 20c

Evaluation parameters	Storage time (60 days)				
	7	**15**	**30**	**45**	**60**
Hardness (kg/sq. cm)	2.63	2.63	2.63	2.63	2.63
Friability (%)	0.46	0.46	0.46	0.48	0.48
Disintegration time (sec.)	11	11	11	11	11

CONCLUSION

The study was undertaken with an aim to formulate a combine effervescent tablet of Ibuprofen, Aluminium hydroxide and Magnesium hydroxide. The results of a 2^3 full factorial design revealed that the amounts of crosspovidone and effervescent material significantly affect the dependent variable, *in vitro* dispersion time. It is thus concluded that by adopting a systematic formulation approach, optimized release mechanism can be reached in the shortest time with minimum efforts.

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