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Research Article

EXCIPIENT SCREENING AND DEVELOPMENT OF FORMULATION DESIGN SPACE FOR DICLOFENAC SODIUM FAST DISSOLVING TABLETS

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ABSTRACT

The identification of critical aspects of formulation can be achieved by using formulation design space. The application of design of experiments (DOE) to create design space is a part of quality by design (QbD) concept of USFDA. The aim of this research work was to prepare fast dissolving tablets of a model drug, diclofenac sodium by direct compression method that matches commercial reference sample with respect to time for releasing not less than 90% of drug. Preliminary screening was done to characterize the effects of subliming agents (ammonium bicarbonate, camphor and menthol) and lubricants (PEG 4000 and magnesium stearate) on drug release. The design and optimization was done to find the effect of concentration of effervescent agent and superdisintegrant on drug release. The prepared tablets were evaluated for their physicochemical properties and *in vitro* release. The relationship between the independent and dependent variables was found with linear prediction equation. The response and equation data was used to draw the contour plot, response surface diagram and design space. The formulations with 20% of camphor as subliming agent showed least disintegration time of 15-24 sec. The subliming agent, ammonium bicarbonate showed immediate release effect when comparison with other agents, camphor and menthol. The effervescent agent showed fast release effect in comparison with the usage of subliming agents. The increase in sodium starch glycolate concentration showed more predominant fast release effect than increase in effervescent agent concentration. The time taken for 90% of drug release from the formulation with 8% of superdisintegrant and 20% of effervescent agent is 6 min which is same as that marketed reference formulation. In conclusion, the independent variables can be varied within red zone of design space for the achievement of fast drug release.

Keywords: Fast dissolving tablets, Diclofenac sodium, Subliming agents, Effervescent agents, Superdisintegrant, Full factorial design, Response surface, Design space, Quality by design.

INTRODUCTION

The Quality by Design (QbD) is an initiative of US Food and Drug Administration for encouraging the pharmaceutical manufacturers to facilitate high quality of pharmaceutical products. The filing of an abbreviated new drug application (ANDA) under the QbD initiative may result in faster review times. The development design space for formulation and process variables is the prime part of QbD. The design of experiments, DOE is the basic tool to create design space. DOE not only reduces experimental work but also provides valuable information for fast decision making. Sometimes predesign experimentation is required to screen the effects of some parameters to check their suitability.

Many pharmaceutical dosages are administered orally in the form of tablets, capsules granules, powders, and liquids. Generally, a tablet design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. Tablets and capsules are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage forms[1]. These solid preparations are not preferred by pediatric and geriatric patients due to a fear of choking. In recent years, a variety of improved methods have been developed for fast delivery of drugs with the aim of improving performance, convenience and compliance[2]. In order to assist these special patient populations, several fast dissolving drug delivery systems have been developed[3-6]. Fast dissolving tablets disintegrate or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast dissolving tablets. The others termed as fast disintegrating tablets contain agents to enhance the rate of tablet disintegration in the oral cavity and may take up to a minute to completely disintegrate. When these tablets put on the tongue, disintegrate instantaneously and release the drug, which dissolves or disperses in the saliva. As the saliva passes down into the stomach, some drugs are absorbed from the mouth, pharynx and esophagus. In such cases, bioavailability of drugs is significantly greater than those observed from conventional tablet dosage forms. In order to allow fast dissolving tablets to dissolve or disintegrate in the mouth, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable or brittle, which are difficult to handle. Hence often fast dissolving tablets require specialized peel off blister packaging[7]. The slightly water soluble drug diclofenac was used as model drug in present study to select platform technology for further process development. Fast dissolving drug delivery can be achieved by various conventional methods like wet granulation[8,9] or direct compression[10], using freeze drying[5],spray drying[6] or sublimation[8] technologies. The non-complex direct compression process was employed to study specifically the effect of formulation variables such as subliming agents, lubricants types and concentration of superdisintegrant and effervescent agents on drug release.

MATERIALS AND METHODS

Diclofenac sodium was obtained as a gift sample from Nihal Lab, Hyderabad. A gift sample of directly compressible mannitol was obtained from Aurobindo Pharma Ltd, Hyderabad. Sodium starch glycolate was generously gifted by MSN Pharma Pvt. Ltd, Hyderabad. The remaining chemicals/solvents used were of analytical grade.

Formulation development

Preparation of diclofenac sodium FDT with subliming agents

The studies were carried to find the effect of different subliming agents and different lubricants on drug release. Subliming agents such as ammonium bicarbonate, camphor and menthol were used to increase the porosity of tablets. As the present study was to get the immediate release, the water soluble lubricant PEG 4000 was also explored along with conventional lubricant such as magnesium stearate. The literature showed that subliming agents were used up to the concentration range of 60%[11]. But the subliming agent concentration was restricted to 20% in the present study. The

literature reports showed the concentration of lubricant, magnesium stearate in the range of 0.2 - 2 %[12]. The lubricant level at concentration of 1 % of magnesium stearate and PEG 4000 was used in this study. Sodium starch glycolate, SSG was used as superdisintegrant. The master formulae of the tablets prepared were shown in Table 1.

Table 1: Master formula of diclofenac sodium tablets with sublimation technology, mg

Ingredients (%)	SDA 1	SDCP 2	SDC 3	SDM 4
Diclofenac sodium	50	50	50	50
Ammonium bicarbonate	20	-	-	-
Camphor	-	20	20	-
Menthol	-	-	-	20
Magnesium stearate	1	-	1	1
PEG 4000	-	1	-	-
SSG	2	2	2	2
Aerosil	0.5	0.5	0.5	0.5
Mannitol	26.5	26.5	26.5	26.5
Total weight of tablet	100	100	100	100

Preparation of diclofenac sodium tablets with effervescent agent and superdisintegrant

In this study, the independent variables were the concentrations of effervescent agent and superdisintegrant. The dependent variable was the time taken for 90 % drug release $T_{90\%}$. The independent variables with their levels were mentioned in the Table 2. The effect of these two independent variables was characterized by taking these variables at two levels. The full factorial design with two variables and two levels would require minimum of 4 runs in 2x2 factorial design. The experimental design report was shown in the Table 3.

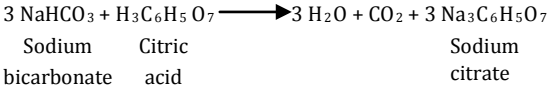
Table 2: Experimental variables with their levels of diclofenac sodium FDT

Variables Level	Lower level, -1	Mid value, 0	Higher level, +1	Experimental unit, e. u
$NaHCO_3$ %	8	14	20	6
SSG %	2	5	8	3

Table 3: Experimental design report of diclofenac sodium FDT

Batch no	$NaHCO_3$ level, X1	SSG level X2
EDF 1	-1	-1
EDF 2	-1	1
EDF 3	1	-1
EDF 4	1	1

The anhydrous form of citric acid alone was used in this study. Citric acid was used in the concentration which is equivalent to neutralize the sodium bicarbonate used in each experimental run. Three moles of sodium bicarbonate reacts with one mole of citric acid and forms three moles of water molecule, one mole of carbon dioxide and three moles of sodium citrate.



One mole of citric acid = 192.14 g

Three moles of sodium bicarbonate = 3*84.01 = 252.03 g

252.03 g sodium bicarbonate = 192.14 g citric acid

8 mg sodium bicarbonate = 8/252.03 * 192.14 = 6.1 mg of citric acid

20 mg sodium bicarbonate = 20/252.03 * 192.14 = 15.25mg of citric acid

Hence, 6.1 mg and 15.25 mg of citric acid was used which was equivalent to react with 8 mg and 20 mg of sodium bicarbonate respectively. The concentrations of the other components were maintained constant and the final composition was adjusted to 100% by adding the diluent, mannitol. The master formulae were shown in the Table 4.

Table 4: Master formula of diclofenac sodium tablets with effervescent and superdisintegrant technology, mg/tablet

Ingredients	EDF1	EDF2	EDF3	EDF4
Diclofenac sodium	50	50	50	50
Sodium bicarbonate	8	8	20	20
SSG	2	8	2	8
Citric acid	6.1	6.1	15.25	15.25
Aerosil	0.5	0. 5	0.5	0.5
PEG 4000	2	2	2	2
Menthol	0.5	0.5	0.5	0.5
Mannitol	30.9	24.9	9.75	3.75
Total weight of tablet	100	100	100	100

All the ingredients were sifted through sieve number 80. The required quantities of sodium bicarbonate and citric acid were accurately weighed, preheated at a temperature of 80°C to remove absorbed /residual moisture in the oven[13] (Biotechnics, Mumbai). The required quantities of diclofenac sodium, sodium bicarbonate, PEG 4000, SSG were weighed and mixed. To the above blend the required quantities of citric acid, aerosil, menthol and finally mannitol were added and the blend was thoroughly mixed. The prepared blend was compressed on 12 station compression machine (CIP machineries, India) to obtain the total tablet weight of 100 mg.

Evaluation of fast disintegrating tablets of diclofenac sodium

The diclofenac sodium formulations were evaluated for the following physicochemical parameters and performance characteristics[8].

General appearance

The control of general appearance of tablets involved the measurement of following attributes such as tablet shape, size, color, surface texture.

Weight variation

Ten tablets were selected randomly from each formulation and weighed individually and collectively. The average weight was determined and then individual tablet weights were compared with the average weight.

Thickness

Screw gauge (Dwarakamai, Hyderabad) was used to find the thickness of diclofenac sodium tablets and the average values and the standard deviations were reported.

Hardness

Hardness of the tablet of each formulation was determined by using Monsanto hardness tester (Model: E 30, Dwarakamai, Hyderabad). The average and standard deviation of hardness was reported.

Wetting time

Five circular tissue papers were placed in a petridish of 10 cm diameter. Water containing methyl red indicator was added to the petridish. The tablet was carefully placed on the surface of tissue paper in the petridish at room temperature (25-28°C). The time required for water containing methyl red solution to reach the upper surface and wet the tablet completely was noted as the wetting time[14].

***In vitro* disintegration test**

Three tablets were introduced in each tube of the basket of the disintegration test apparatus (TGR56, Electro Lab, Mumbai) without the disc. The basket was positioned into a beaker containing 900 ml of distilled water maintained at 37 ± 0.5 °C. The stop watch was started and the tablets were observed for disintegration. The stopwatch was stopped when the tablets got disintegrated with no palpable mass remaining in the apparatus and the time was noted as the disintegration time.

Content uniformity of the diclofenac sodium tablets

One tablet was added to 10 ml of simulated saliva fluid (SSF) pH 6.75 and agitated in the cyclomixer (CM 101, Remi Ltd, Mumbai) for 15 min. The solutions were filtered, suitably diluted with SSF pH 6.75 and diclofenac sodium content was determined by using UV Spectrophotometer (UV 1700, Shimadzu) at 276 nm[15].

***In vitro* drug release of diclofenac sodium in SSF pH 6.75**

USP type II apparatus (VDA-D, Veego, India) at 50 rpm was used for *in vitro* drug release study[16]. The dissolution medium consisted of 500 ml of SSF pH 6.75. The temperature of the dissolution medium was maintained at 37 ± 0.5 °C. The sample of 5 ml of dissolution medium was withdrawn at specific time intervals, filtered and suitably diluted prior to analysis. The medium was replenished with 5 ml of dissolution medium maintained at the same temperature. Diclofenac content of these solutions were analyzed by using UV spectrophotometer at 276 nm.

RESULTS AND DISCUSSION

Effect of subliming agents and lubricants

The prepared tablets were having beveled edged flat porous surface in round shape with white color and without any compression defects. The evaluation data of diclofenac sodium FDT by using subliming agents was shown in Table 5.

Table 5: Evaluation data of diclofenac sodium FDT (with subliming agents)

Evaluation parameters	SDA 1 Avg±sd	SDCP 2 Avg±sd	SDC 3 Avg±sd	SDM 4 Avg±sd
Weight variation (mg)[a]	82.78 ± 1.36	81.34 ± 0.42	81.79 ± 1.71	81.54 ± 0.58
Thickness (mm)[a]	2.39 ± 0.01	2.37 ± 0.02	2.38 ± 0.05	2.41 ± 0.01
Hardness (Kg/cm^2)[b]	2.06 ± 0.23	2.15 ± 0.25	2.41 ± 0.05	2.18 ± 0.15
Wetting time (sec) [b]	170 ± 0.57	43 ± 1.15	86 ± 1.52	130 ± 1.54
In vitro D.T (sec)[b]	40 ± 1.15	15 ± 0.57	24 ± 1.00	34 ± 1.15
Content uniformity (%) [a]	100.6 ± 1.88	98.9 ± 0.64	101 ± 1.35	99.3 ± 0.05

[a] Each value is an average of ten determinations ± SD

[b] Each value is an average of three determinations ± SD

The average weight of the tablets was in the range of 81.34 - 82.78 mg and weight variation was found to be less than 3%. This was found to be within acceptable range of weight variation as per I.P 2007 specification limit (not more than 10%). Thickness of the tablets was in the range of 2.37 - 2.41 mm. The hardness of tablets was determined and found in the range of 2.06 - 2.41 Kg/cm^2. Wetting time of the tablets was in the range of 43 - 170 sec**.** Tablets containing camphor as subliming agent exhibited fast disintegration than other subliming agents. *In vitro* disintegration time of the tablets was in the range of 15 - 40 sec**.** All the formulations were subjected for content uniformity test and observed that all the formulations were in the range of 98.9 - 101% meeting I.P.2007 specification limits of diclofenac sodium. The cumulative % drug release plots of diclofenac sodium FDT were shown in Fig. 1.

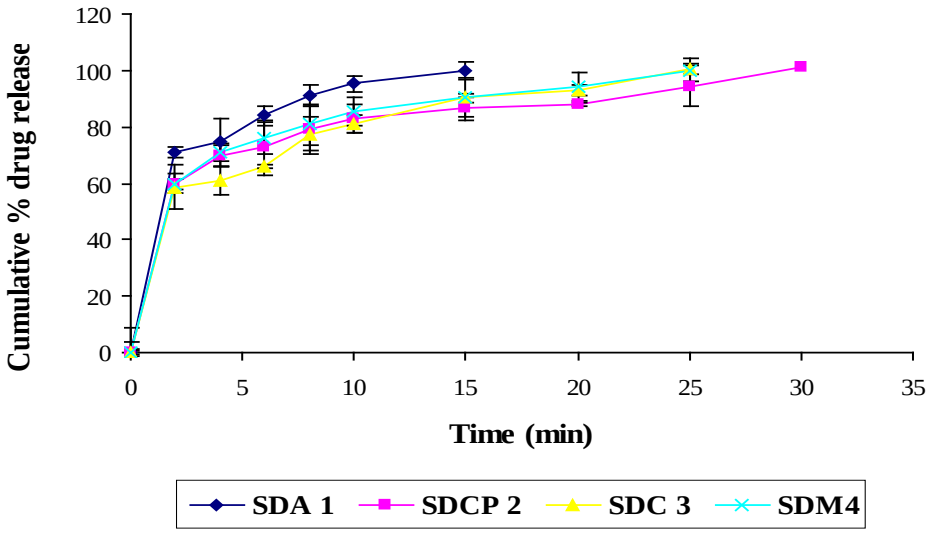


Fig. 1: Cumulative % drug release plots of diclofenac sodium FDT (with subliming agents)

The formulation SDA 1 was showing the least time of 8 min taken for 90 % of drug release. This formulation contains ammonium bicarbonate as subliming agent. This immediate release effect may be due to the water soluble nature of ammonium bicarbonate.

$T_{90\%}$ of formulation containing camphor and 1% of PEG 4000 as lubricant was found to be 25 min, whereas $T_{90\%}$ of 15 min was observed with 1 % magnesium stearate as lubricant. 1% of magnesium stearate was found better than PEG 4000 as a lubricant in spite of its water insoluble nature and hence magnesium stearate was selected as lubricant for subsequent studies. The release kinetic data showed that all the formulations were following first order release kinetics with diffusion mechanism. The correlation coefficient and release rate constant data of diclofenac sodium FDT was shown in Table 6. The first order release kinetic plots were shown in Fig. 2.

Table 7: Drug release kinetics data of diclofenac sodium tablets

Batch no	Parameter	Zero order	First order	Higuchi	Hixson Crowell cube root
SDA 1	R	0.7796	0.9901	0.9346	0.6416
	K	5.2256	-0.1243	3.8043	-0.2108
SDCP 2	R	0.7429	0.9404	0.8975	0.5444
	K	2.0731	-0.0497	5.7353	-0.0740
SDC 3	R	0.8090	0.9669	0.9430	0.5950
	K	2.8631	-0.0665	5.1596	-0.1018
SDM 4	R	0.7394	0.9853	0.8981	0.5441
	K	2.1333	-0.0585	5.7353	-0.0748

R - correlation coefficient, K - release rate constant

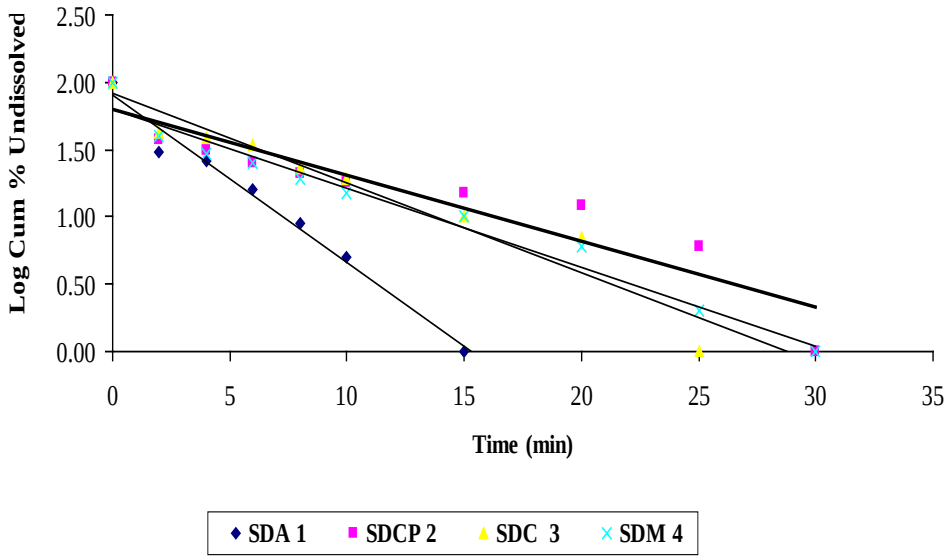


Fig. 2: First order release kinetics plots of diclofenac sodium FDT (with subliming agents)

The increase in porosity of the tablets with further higher levels of subliming agents may result in fast drug release, but produce the tablets that difficult to handle. Hence the further studies were continued by using superdisintegrant and effervescent agents with DOE concept.

Effects of superdisintegrant and effervescent agent concentration

All the tablets were having beveled edged flat smooth surface in round shape with white color without any compression defects. The evaluation data of diclofenac sodium FDT prepared by using effervescent and superdisintegrant agents was shown in the Table 7.

The average weights of the tablets were in the range of 99.1 - 102.3 mg and weight variation was found to be less than 3%. This was found to be within acceptable range of weight variation as per I.P 2007 specification limit. Thickness of the tablets was in the range of 2.37 - 2.43 mm. The hardness of tablets was determined and found in the range of 2.14 - 2.55 Kg/cm^2. The hardness was kept in the lower range to achieve the fast release effect. Wetting time of the tablets was in the range of 63 - 134 sec. *In vitro* disintegration times of the tablets were in the range of 56 - 171 sec. The formulation, EDF 1 showed least *in vitro* D.T of 56 sec. which was containing lower concentrations of effervescent agent and super disintegrant. The low disintegration time might be attributed to the presence of high concentration of water soluble mannitol in EDF-1. All the formulations were showing the content uniformity in the range of 99 - 101 % which was within I.P.2007 specification limits of diclofenac sodium. The percent drug release plots of diclofenac sodium FDT were shown Fig. 3. The formulation EDF4 showed the least time of 6 min for 90 % of drug release which contains highest concentrations of effervescent and super disintegrant agents. The release kinetic data showed that all the formulations were following first order release kinetics with diffusion mechanism. The correlation coefficient and release rate constant data of diclofenac sodium FDT was shown in Table 8. The first order release kinetic plots were shown in Fig. 4.

Table 7: Evaluation data of diclofenac sodium FDT prepared with effervescent and superdisintegrant agents

Evaluation Parameters	EDF1 Avg±sd	EDF2 Avg±sd	EDF3 Avg±sd	EDF4 Avg±sd
Weight variation (mg)[a]	99.1 ± 0.16	101.8 ± 2.47	102.3 ± 0.20	100.9 ± 0.77
Thickness (mm)[a]	2.43 ± 0.06	2.41 ± 0.01	2.37 ± 0.02	2.39 ± 0.01
Hardness (Kg/cm^2)[b]	2.14 ± 0.23	2.55 ± 0.25	2.41 ± 0.05	2.23 ± 0.15
Wetting time (sec)[b]	63 ± 1.15	123 ± 1.73	134 ± 1.15	123 ± 0.57
In vitro D.T (sec)[b]	56 ± 0.57	126 ± 0.57	164 ± 1.73	171 ± 1.15
Content uniformity (%)[a]	99.0 ± 0.32	101 ± 1.30	99.7 ±1.30	99.2 ± 0.26

[a] Each value is an average of ten determinations ± SD

[b] Each value is an average of three determinations ± SD.

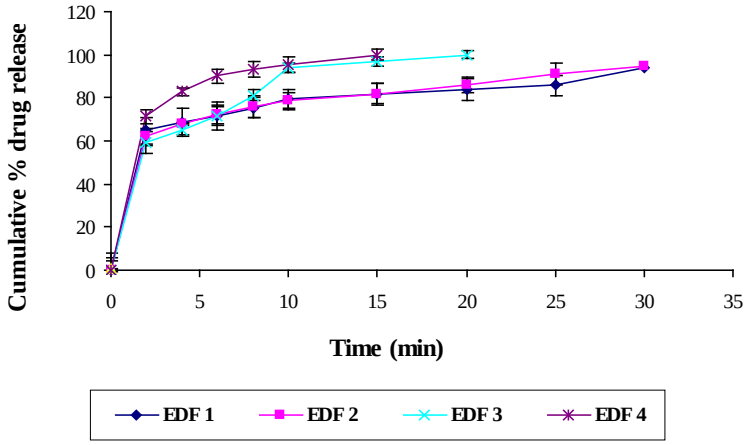


Fig. 3: Cumulative % drug release plot diclofenac sodium FDT (with effervescent)

Table 8: Drug release kinetics data of diclofenac sodium FDT (with effervescent)

Batch no	Parameter	Zero order	First order	Higuchi	Hixson Crowell cube root
EDF 1	R	0.6811	0.8956	0.8408	0.5129
	K	1.7483	-0.0274	5.7353	-0.0685
EDF 2	R	0.7171	0.9067	0.8776	0.5296
	K	1.9021	-0.0466	5.7353	-0.0712
EDF 3	R	0.8116	0.9868	0.9496	0.6234
	K	3.9136	-0.0979	4.5145	-0.1434
EDF 4	R	0.7405	0.9844	0.9141	0.6258
	K	5.0605	-0.1215	3.8043	-0.2077

R - correlation coefficient, K - release rate constant.

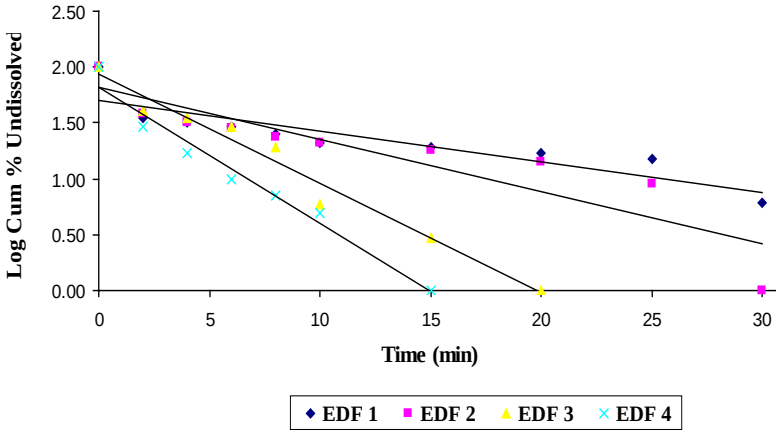


Fig. 4: First order release kinetics plot of diclofenac sodium FDT (with effervescent)

The response data of time taken for 90% of drug release, $T_{90\%}$ was used to draw the contour plot by using DOE wisdom software to find the different levels of independent variables to get similar response as shown in Fig. 5. The same software was used to draw the response surface diagram as shown in Fig. 6 to find the optimum independent variable to get desired response.

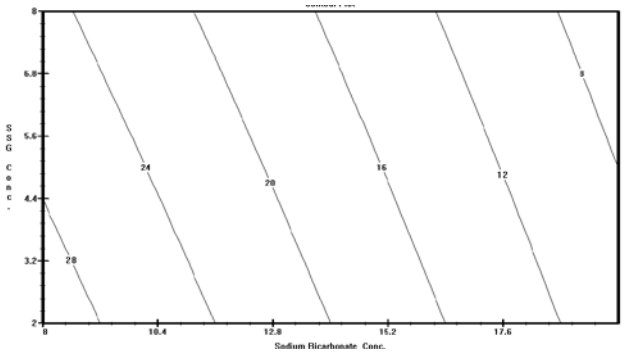


Fig. 5: Contour plot for $T_{90\%}$

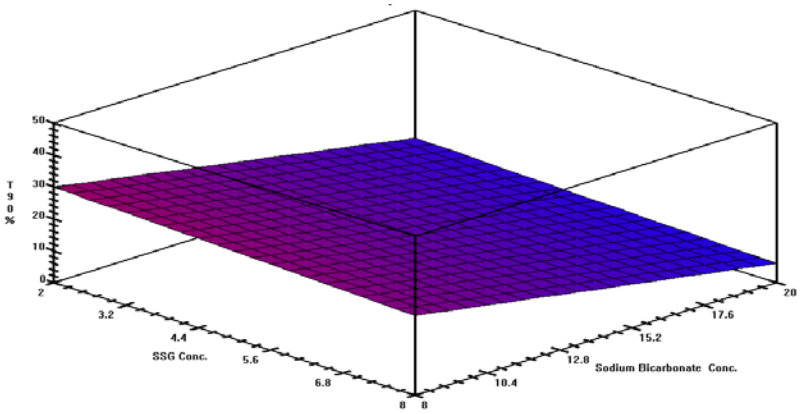


Fig. 6: Response diagram for $T_{90\%}$

The linear equation of the response, $T_{90\%}$ was calculated by using Sigmatech software and the equation was found to be in the form of

Y= bo + b1X1 + b2X 2 + b12X1 X2

Where

Y is the dependent variable

X1 and X2 are the coded values of independent variables

bo is constant and b1, b2, b12 are coefficients,

X1 is the concentration of effervescent agent, sodium bicarbonate

X2 is the concentration of super disintegrant, SSG

Y is the time taken for 90 % of drug release, $T_{90\%}$

With the help of Sigmatech software the constant and coefficient values for the above equation had been determined and shown the Table 11 along with their contributory effect in form of SS ratio (the ratio of square of individual effect to total sum of squares of all effects).

Table 9: Contributory effect of independent variables along with the SS ratio values

Sl. No	Combinations	Coefficient	SS ratio %
1	Bo	19.0	-
2	b1	-1.0	0.813 %
3	b 2	-11.0	98.374 %
4	b12	-1.0	0.813 %

The above coefficient data showed that independent variables, sodium bicarbonate and sodium starch glycolate had the inversely proportional relationship with the dependent variable $T_{90\%}$. The combination was also showing inversely proportional relationship. The predominant main negative effect of sodium starch glycolate would reduce the $T_{90\%}$ in comparison to other individual effect and combined interaction effect. Hence the concentration of sodium starch glycolate can be increased higher level to achieve the immediate release effect when compared to rise in effervescent agent concentration.

This linear equation can be used to predict the $T_{90\%}$ at unknown independent variables. In order to check the accuracy of equation the experimental levels of EDF-4 (Run 4) was substituted in the equation and the response was calculated as follows.

Y= bo + b1X1 + b2X 2 + b12X1 X2

$Y = 19 + (-1)\ X_1 + (-11.0)\ X_2 + (-1.0)\ X_1\ X_2$

$= 19 + (-1)\ (1) + (-11)\ (1) + (-1)\ (1)\ (1)$

$= 19 - 1 - 11 - 1 = 19 - 13 = 6$ min

The above calculated data was matching with the experimental data of EDF-4 indicated that the predicted response by using linear equation was correct.

In order to draw the design space which is used to predict the correct independent variable levels to achieve the desired response, the central composite design would be required. The central composite design for two independent variables at three levels would require 9 runs along with base run at zero levels. Hence the previous design report was modified by changing the +1 and -1 levels into +2 and -2 levels in the central composite design. The central points from extreme 2 levels to midpoint were taken as +1 and -1 level. Accordingly, the experimental unit in central composite design was reduced to half. The design report for central composite design was shown in the Table 12.

Table 10: Modified central composite experimental design for drawing design space

Variables	-2	-1	0	+1	+2	Experimental unit, e. u
$NaHCO_3$ X1	8	11	14	17	20	3

SSG X2	2	3.5	5	6.5	8	1.5

By using the above experimental conditions, the central composite design was planned by using Sigmatech software. The responses for the 9 runs were calculated by using linear equation and $T_{90\%}$ values were reported in the Table 13.

By using the data mentioned in Table 13, the design space was plotted by using Sigmatech software. With the help of design space one can predict the concentration ranges of independent variables for achieving the desired response variable, time taken for 90 % of drug release, $T_{90\%}$.

Table 11: Response report predicted for central composite design with effervescent agent and superdisintegrant

Run No.	Combinations	$NaHCO_3$ level, X1	SSG level, X2	$T_{90\%}$, min
1	1	11	3.5	24.7
2	X1	17	3.5	24.25
3	X2	11	6.5	14.25
4	X12	17	6.5	12.75
5	MID POINT	14.0	5.0	19.0
6	X1 AT -2L	8.0	5.0	20
7	X1 AT +2L	20.0	5.0	18
8	X2 AT -2L	14.0	2.0	30
9	X2 AT +2L	14.0	8.0	8

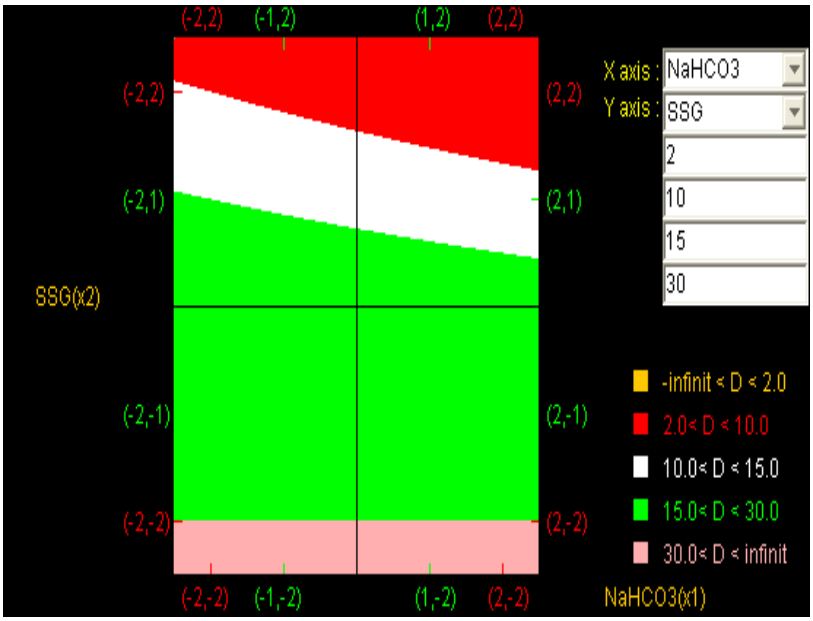


Fig. 6: Design space of diclofenac FDT with formulation variables, effervescent and superdisintegrant for response T90%

In Fig. 6, the levels of sodium bicarbonate were plotted on the X axis and levels of SSG were plotted on Y axis. As there was no yellow zone in design space, $T_{90\ \%}$ would not be achieved within 2 min under the experimental employed. The red zone region can be used to achieve the $T_{90\%}$ within 10 min. The variable levels corresponding to this space can be used to get the fast release of drug.

The white zone indicated the $T_{90\%}$ which can be achieved within 15 min. The green zone indicated the further slow release, where T_{90} % was obtained within 30 min. The pink zone was shown to be not suitable for immediate release with $T_{90\%}$ greater than 30 min.

The design space was indicating that the immediate release can be achieved by selecting the variables in red zone which will produce $T_{90\%}$ less than 10 min. So all the independent variables must be increased to higher level than levels used in the actual runs (20 % of sodium bicarbonate and 8 % sodium starch glycolate) to get $T_{90\%}$ within 2 min.

Comparison with commercial samples

The available marketed formulation of diclofenac sodium dispersible tablet, Voveran D was used as innovator sample for the comparison. The evaluation data of the innovator tablet showed that the thickness of the tablet was in the range of 3.5 ± 0.05 mm, hardness 6 ± 0.52 Kg/cm^2 and *in vitro* disintegration time 15 ± 0.57 sec. The drug release studies showed that the time taken for 90% of drug release, $T_{90\%}$ is 6 min. The prepared formulations SDA-1 with sublimation technology and EDT-4 with effervescent technology showed the better drug release and hence used for the comparison with marketed sample. The drug release plot of innovator was compared with the prepared optimum formulations and shown in Fig. 7.

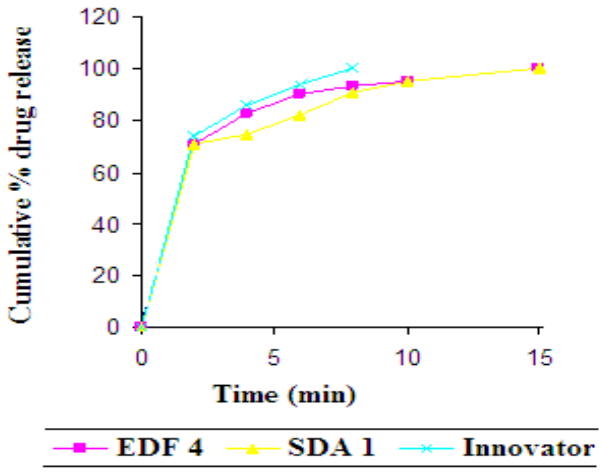


Fig. 7: Comparative drug release plots of innovator and optimum formulations (EDF 4 and SDA 1)

The optimum formulation, EDF 4 of effervescent technology was found to be more comparable to the marketed sample with equivalent $T_{90\%}$ of 6 min chosen as the best formulation. The formulation condition of EDF 4 and formulation design space can be used for further studies of process development.

CONCLUSIONS

The fast dissolving tablets with ammonium bicarbonate as subliming agent showed the fast drug release than camphor and menthol. The usage of magnesium stearate as lubricant showed better drug release than PEG 4000. The increase in superdisintegrant concentration showed predominant fast drug release effect than increase in effervescent concentration. The design space showed that the experimental conditions corresponding to red zone of design space can used to get 90% drug release in 2 to 10 min. In conclusion, the application of DOE and concept of QbD results in the valuable information with least possible experimentation.

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