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A STUDY ON PROCESS DRIFT OF DIRECTLY COMPRESSIBLE MATRIX TABLETS OF ISONIAZID

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ABSTRACT

Solid oral dosage forms are the preferred route for many drugs and are still the most widely used formulations. Of these, tablets offer the lowest cost approach. Matrix tablets serves as an important tool for oral dosage forms. Pharmaceutical industry engaged in making solid dosage form is facing critical problems in proving their process reproducibility. Even that has reduced profits, especially because of critical deviations which are consequences of continuous process and inadequate research. Up-scaling can be challenging as minor changes in parameters can lead to varying quality results. The main objective of the work was to select critical process parameters (CPP) using retrospective data of a developed product and to establish a design of experiments (DoE) that would improve the robustness of the tableting process. Batches were selected based on the quality results generated during batch release, some of which revealed quality deviations concerning the appearance of the coated tablets. The Minitab 17 software was used for data processing to determine critical process parameters in order to propose new working ranges. This study confirms that it is possible to determine the critical process parameters and create design spaces based on retrospective data of production batches. This type of analysis is thus converted into a tool to optimize the robustness of existing processes. This study will help to determine a design space which can be established with minimum investment in experiments.

KEYWORDS: Direct compression, Formulation variables, Process variables, matrix tablets, Isoniazid.

1. INTRODUCTION

A process drift is an unintended, unexplained or unexpected trend of measured process parameter(s) and/or resulting product attribute(s) away from its intended target value in a time- ordered analysis over the lifetime of a process or product. Process drift is the consequence of variation in a variety of process inputs, including raw materials, manufacturing personnel, and machine (man-machine) interactions or processing conditions. When robust systems are not implemented and capable tools are not used to prevent process drift, resulting manufacturing problems may include: low product yield, batch delays, ingredient and packaging variability, batch failures, product quality-related clinical failures, investigations, recalls, product seizures, injunctions, and consent decrees.[1] The use of tools and approaches such as process analytical technologies (PATs), QbD, in vitro–in vivo correlation (IVIVC), and more thorough excipient characterization should improve the robustness of the finished products and minimize or prevent unintended drift in the quality of the affected commercial drug products.[2]

Many studies on the influence of the powder's mechanical characteristics on the performance of the tablet have been performed in the past.[3-14] Optimization technique is an ideal tool for preparing better quality of dosage forms. This technique is widely used for developing optimal dosage forms and a better process of manufacture.[15]

Optimization was considered as an economical and efficient method which helps understand the relationship between independent and dependent variables. Optimization has been gaining popularity in pharmaceutical research, day by day, since the best results can be obtained in a limited number of experiments.[16]

Direct compression involves simple blending of active pharmaceutical ingredient (API) with other ingredients and direct compaction of the resultant mixture. In contrast to direct compression, wet granulation not only increases the cycle time, but also has certain limits imposed by thermolability and moisture sensitivity of the active ingredient. The unnecessary exposure of any

drug to moisture and heat remains unjustified. Low dilution potential (30%-40% of the drug in the formulation) and the segregation due to the difference in density between API and excipients.[17]

The use of matrix technology has been a commercial success and the pharmaceutical marketplace witnessed a large number of novel drug delivery systems based on them. Matrix polymers help to opportunely modulate and modify the drug release from modified drug delivery systems.[18,19] Isoniazid (INH) is known to be one of the most efficacious anti-TB drugs and is recommended by WHO. It possesses many advantages such as high selectivity towards *Mycobacterium tuberculosis*, excellent bacteriostatic capacity, low price and good patient compliance.[20] Isoniazid here was selected as a model drug in the study.

In pharmaceutical industries, manufacturers of generic tablets are usually focused on the optimization of the excipient mixture composition to obtain a product that meet established standards. Several tablet compositions of extended and fast release have been established using statistical design to optimize excipient proportions. However tablet properties do not only depend on the excipient percentage in the solid dosage. Various process variables like compression and granulation i.e., compaction force, compression velocity, tableting temperature, impeller speed and blending time can also have influences.[21,22]

2. MATERIALS AND METHODS

2.1 Formulation of Directly compressed matrix tablets of INH

The matrix tablets of INH were made as per the set specification as mentioned in Table 1. All the ingredients were sifted through # 40 sieve and Physical mixing of Isoniazid and PMC K100M was done geometrically. It was combined with dibasic calcium phosphate and Colloidal silicon oxide (Aerosil). Lubricant Magnesium stearate was mixed and powder blend formed. The blend was compressed by direct compression method using D- tooling (12.5 mm punch size). The tablets were scored.[23,24] Three batches I, II and III of Isoniazid matrix tablets were formulated using varying combinations of the polymer HPMC K100M and Dibasic calcium phosphate as shown in Table 2. The amount of API, Colloidal silicon oxide and magnesium stearate was kept constant.

Three new batches IV, V and VI were formulated keeping the amount of dibasic calcium phosphate constant with 87 mg/ tablet in all three batches as given in Table 2. Variation in the amount of HPMC was made to study the effect of concentration of HPMC polymer on drug release. The concentration of all other excipients was kept constant in all the three batches. Powder blend was analyzed for all the batches prior tablet compression. The Carr's compressibility index and Hausner's ratio was calculated for the powder blend and the evaluation of tablets was performed as per IP 2007.[25]

2.2 Design of Experiment

The DOE trials were carried out to see the influence of different variables on the formulation development. In this study, Concentration of Dibasic calcium phosphate and Compression force were taken as Independent variables and In-vitro drug release and Content uniformity of tablets were considered as dependent variables. The study was designed using Minitab 17 software.[1,26] A 3^2 factorial design was used for the application of DOE. Total nine batches were formulated as given in Table 3.

2.3 Release Studies

Dissolution studies were performed in two dissolution media, 0.1 N hydrochloric acid followed by Phosphate buffer pH 6.8 using Basket type USP Dissolution apparatus at 50 RPM. Dissolution in acidic media was for 2 hrs subsequently for 1 hr by replacing dissolution media with buffer. Five ml aliquot was withdrawn and replaced with fresh media each time. UV readings were taken at 263 nm (λmax of Isoniazid) and concentrations of Isoniazid were calculated in each aliquot. In-vitro drug release study performed for 24 hours.[27,28]

3. RESULTS AND DISCUSSION

3.1 Evaluation of Powder blend and Isoniazid matrix tablets

All batches were first analyzed for powder flow properties as per USP 2016 (NF 37) and tablet evaluation as per IP 2014. Evaluation of powder blend is necessary to understand its flow properties and compressibility which will play a vital role during tablet compression.[29]

Comparison of the obtained values of Carr's index and Hausner's ratio for batches I, II and III to that specified in USP 2016 (NF 37) showed that all three batches had very poor to fair flow properties.[28] Batches IV, V and VI revealed fair flow as shown in the Table 4. All tablets were white in color, showed no chipping or cracking and resulted in good aesthetic appeal with defined content uniformity range and acceptable weight uniformity. In-vitro drug release study was performed on all batches, however batch II showed a consistent drug release for 26 hours and zero burst release as shown in Fig 1. Thus, batch II was chosen for further optimization using DoE trials.

3.2 DOE trials

All batches for DOE trials were evaluated for their powder flow properties before tablet compression. Further tablet evaluation was performed on all the batches and the results are mentioned in Table 5 and 6.

Tablets obtained from all batches had good aesthetic appeal with desired hardness levels. Even though the values of % friability decreased with an increase in

hardness from 7 to 11, all batches passed the friability test. From the above table it can be seen that all the batches confirmed with the uniformity of weight test and had acceptable content uniformity.

Batch VII, VIII and IX showed less than 45% drug release in the first 2 hours. This is attributed to the low amount (69.6 mg/tablet) of DCP in the formulation.

Batch X with DCP concentration 87 mg/tablet showed 48% drug release in first 2 hours followed by 99% at the end on 24 hours. The hardness of batch X was 7 kg/cm2. In contrast to this, batches XI and XII released a total of 89% and 87% of API.

As depicted in fig 3, only batches XIII, XIV and XV showed 50 % and more drug release as a consequence of difference in compression force varying from 7, 8 and 9 kg/cm2 respectively with a constant amount of Dibasic calcium phosphate. Increase in tablet hardness resulted in slower drug release from the formulation thus prolonging the duration of release.

Pareto charts as shown in Fig 4 (A & B) revealed that the concentration of dibasic calcium phosphate does not significantly affected both drug release and % friability. Whereas, compression force applied during tablet manufacturing significantly affected the drug release and % friability. There was not much impact of amount of DCP and compression force on drug release and % friability but the amount of DCP had a significant impact on the Content uniformity of the tablets as revealed in Fig 4 (C). Compression force had less significant impact on content uniformity of the tablets. A combination of DCP concentration and compression force had the least role to play in content uniformity of the tablets.

Contour plots display the 3-dimensional relationship in two dimensions, with x- and y- factors (predictors) plotted on the x- and y-scales and response values represented by contours. A contour plot is like a topographical map in which x-, y-, and z-values are plotted instead of longitude, latitude, and elevation. Fig 5 (A) revealed that design space to obtain a 100% drug release for dibasic calcium phosphate was found between 90 to 105 mg/tablet. Design space for Compression force was between 7 to 7.4 kg/cm2. As shown in Fig 5 (B), design space to obtain % friability in permissible limits for dibasic calcium phosphate was found between 90 to 105 mg/tablet. Design space for compression force was between 10 to 11 kg/cm2. As shown in Figure 5 (C), design space to obtain content uniformity in permissible limits for dibasic calcium phosphate was found between 73 to 84 mg/tablet. Design space for Compression force was between 7.2 to 7.5 kg/cm2.

In the present study, HPMC concentration was kept constant considering its suitability with dibasic calcium phosphate in making directly compressible matrix tablets. Dibasic calcium phosphate concentration and compression has significant effect on the friability and release property of the matrix tablets. Design of experiment helped in designing and optimization process and also to understand the process drift. The Critical limits developed through these kind of studies would lead to a robust process for manufacturing directly compressible matrix tablets.[30,31]

Table No 1: Specifications of INH matrix tablets.

S. No:	Elements of INH Tablet	Target
1	Dosage form	Tablet
2	Dosage design	Sustained release matrix tablet
3	Route of administration	Oral
4	Dosage strength	300 mg
5	Therapeutic moiety/ delivery	Swelling, gelling and drug release
6	Appearance	White, scored
7	Weight of the tablet	Average weight ± 5%
8	Diameter of the tablet	12.5 mm ± 0.12 mm
9	Dissolution time	24 hours

Table No 2: Formulation trials of INH tablets (Batches I to VI).

	Quantity (mg/tablet) used per batch					
	Batch I	**Batch II**	**Batch III**	**Batch IV**	**Batch V**	**Batch VI**
Ingredients / Batch size	**100 tablets**	**100 tablets**	**100 tablets**			
Isoniazid (B.No:14344/INH)	300	300	300	300	300	300
HPMC K100M	200	250	300	200	250	300
Dibasic calcium phosphate	137	87	37	87	87	87
Colloidal silicon oxide	6.5	6.5	6.5	6.5	6.5	6.5
Magnesium stearate	6.5	6.5	6.5	6.5	6.5	6.5
Total weight (mg/ tab)	650	650	650	600	650	700

Table No 3: Formulation of DOE trials Batch VII to Batch XV.

	Quantity (mg/tablet) used per batch								
	B-VII	**B-VIII**	**B-IX**	**B- X**	**B-XI**	**B- XII**	**B-XIII**	**B-XIV**	**B- XV**
Ingredients / **Batch size (No. of tablets)**	150	150	150	150	150	150	150	150	150
Isoniazid (B.No:14344/INH)	300	300	300	300	300	300	300	300	300
HPMC K100M	300	300	300	300	300	300	300	300	300
Dibasic calcium phosphate	69.6	69.6	69.6	87	87	87	104.4	104.4	104.4
Colloidal silicon oxide	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Magnesium stearate	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Total weight (mg/ tab)	682.6	682.6	682.6	700	700	700	717.4	717.4	717.4
Compressionforce(kg/cm2)	7	9	11	7	9	11	7	9	11

Table 4: Flow properties of powder blend of INH tablets (Batches I to VI).

Batch No:	**Parameters**					
	Bulk density (Db)	**Tapped density (Dt)**	**Carr's index [(Dt- Db)/ Dt] *100**	**Flow character**	**Hausner's ratio (Dt/Db)**	**Flow character**
Batch I	0.43	0.640	32.81%	Very poor flow	1.48	Very poor flow
Batch II	0.451	0.549	17.85%	Fair flow	1.21	Fair flow
Batch III	0.453	0.567	20.10%	Fair flow	1.25	Fair flow
Batch IV	0.392	0.491	20.16%	Fair flow	1.252	Fair flow
Batch V	0.405	0.499	18.83%	Fair flow	1.23	Fair flow
Batch VI	0.405	0.499	18.83%	Fair flow	1.23	Fair flow

Table 5: Characterization of INH matrix tablets (Batches I to VI).

S. N.	Parameters	Batch No					
		Batch I	Batch II	Batch III	Batch IV	Batch V	Batch VI
1	Physical appearance	White, smooth, no cracks seen	White, smooth, no cracks seen	White, smooth, no cracks seen	White, smooth, no cracks seen	White, smooth, no cracks seen	White, smooth, no cracks seen
2	Hardness (kg/cm^2)	6	7	6.5	8	7.5	7.5
3	Average diameter	12.59	12.58	12.59	12.56	12.57	12.57
4	Average Thickness	4.33	4.65	4.72	3.85 mm	4.67 mm	4.87 mm
5	Uniformity of weight	650 ±10 mg	650 ±10 mg	650 ±10 mg	600 ±20 mg	650 ± 15 mg	700 ± 15 mg
6	% Friability	0.5%	0.48%	0.77%	0.49%	0.69%	0.48%
7	Content uniformity	99-101%	98-100 %	98.5-100.5 %	98-100 %	99-101 %	98.5-100.5%

Table 6: Characterization of INH matrix tablets (Batches VII - XV).

S. N.	Parameters	Batches								
		B-VII	B-VIII	B-IX	B- X	B-XI	B- XII	B-XIII	B-XIV	B- XV
1	Physical appearance	White	White	White	White	White	White	White	White	White
2	Hardness (kg/cm^2)	7	9	11	7	9	11	7	9	11
3	Average diameter	12.60	12.6	12.58	12.57	12.57	12.56	12.60	12.63	12.61
4	Average thickness	4.96	4.83	4.73	4.88	4.66	4.61	5.32	5.17	4.95
5	Uniformity of weight	682.6 ± 20	682.6 ± 15	682.6 ± 20	700 ± 10	700 ± 12	700 ± 20	717.4 ± 15	717.4 ± 18	717.4 ± 20
6	% Friability	0.71%	0.62%	0.48%	0.69%	0.53%	0.42%	0.66%	0.51%	0.30%
7	Content uniformity	99-101%	98-100%	99.2-100%	98-101%	98-100%	98.2-100%	98-99.8%	99-100%	98-100%

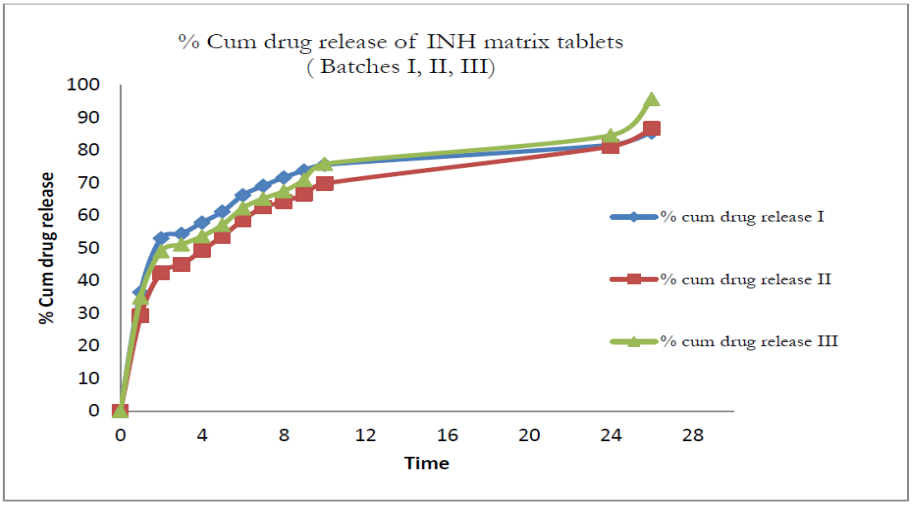

Figure No 1: Drug release profile of INH tablets (Batches I, II, III).

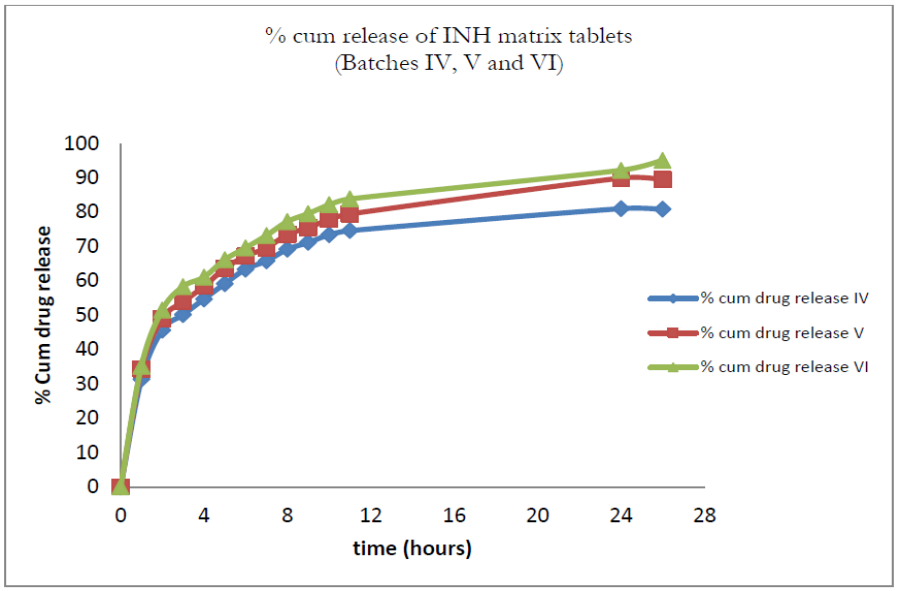

Figure No 2: Drug release profile of INH tablets (Batches IV, V, VI).

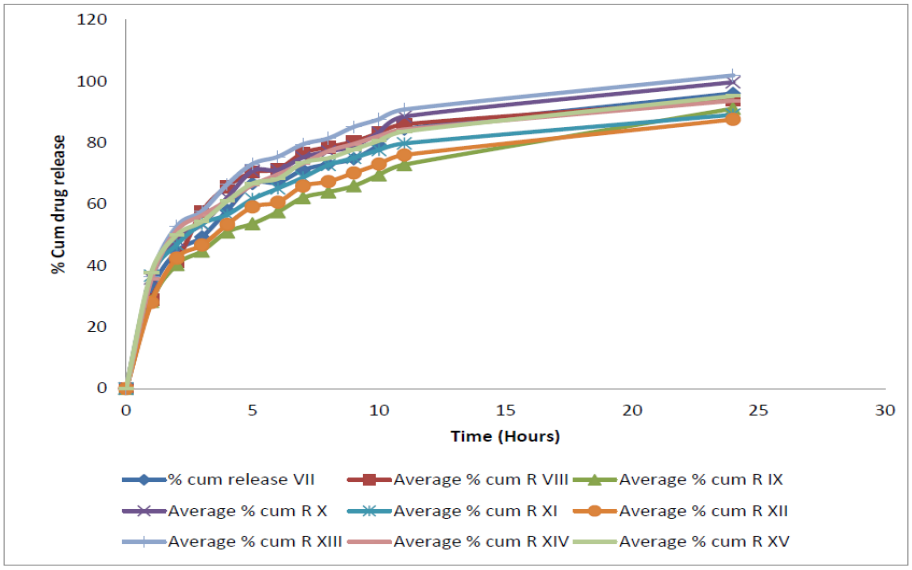

Figure No 3: Drug release profile of INH tablets (Batches VII to XV).

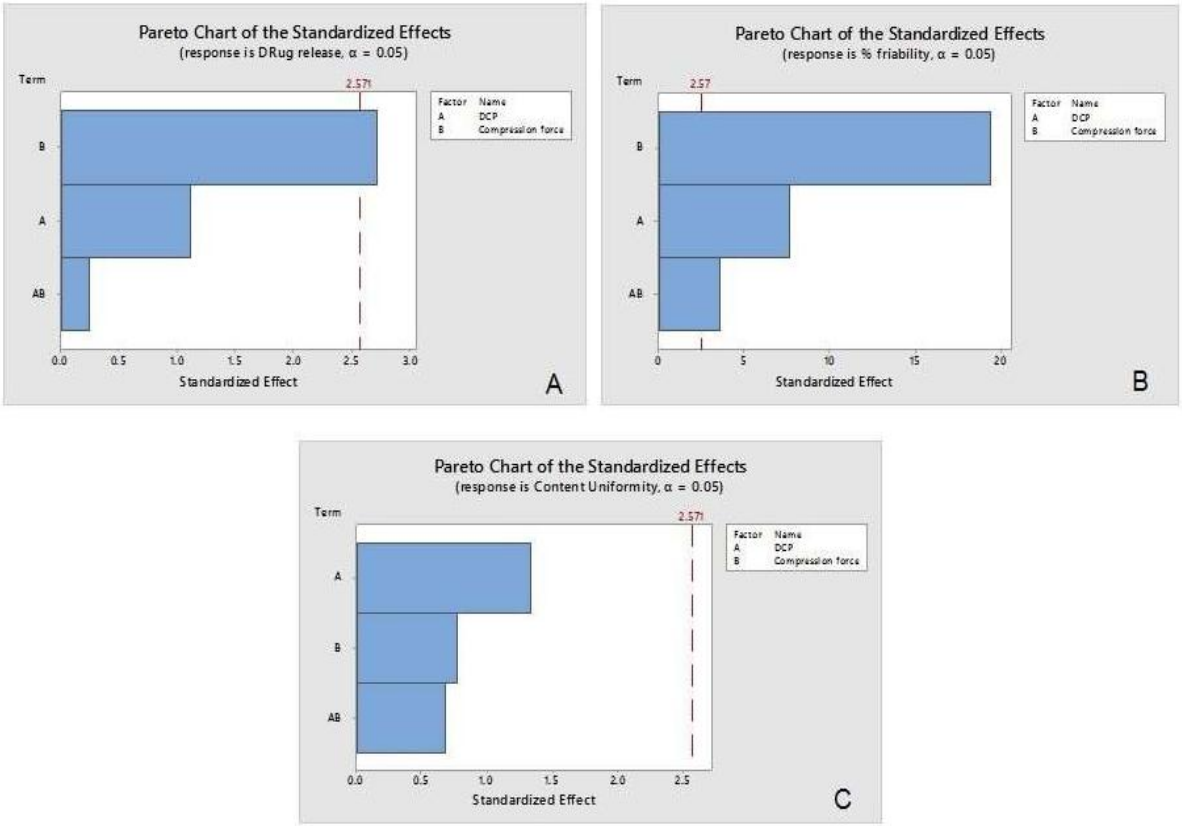

Figure No 4: Pareto Chart A) effect of DCP amount and compression force on Drug release B) effect of DCP amount and compression force on % friability C) effect of DCP amount and compression on Content uniformity.

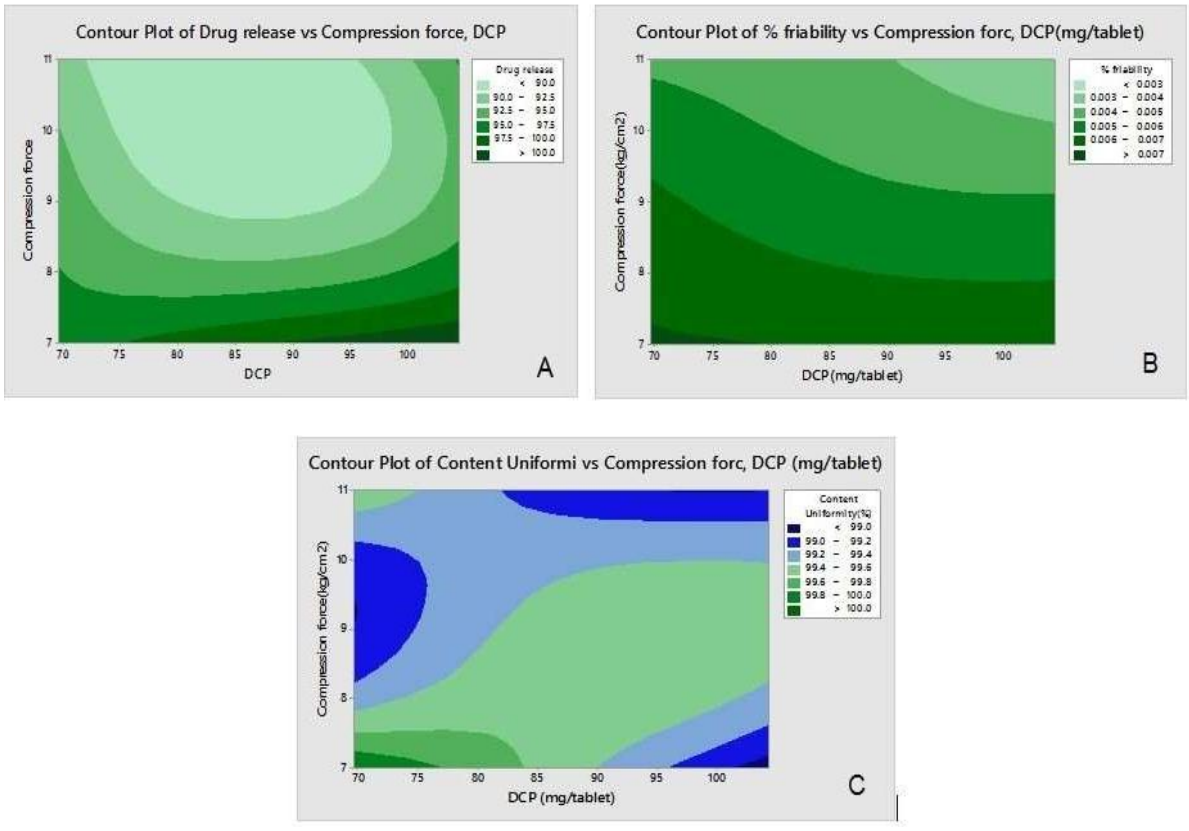

Figure No 5: Contour Plot A) effect of DCP amount and compression on drug release B) effect of DCP amount and compression on % friability C) effect of DCP amount and compression on content uniformity.

4. CONCLUSION

Formulation development encounters hundreds of problems due to process variables and thereby it's a time consuming process. Design of experiment helped formulation development department significantly in overcoming those problems and identifying the causes. This study helped in understanding the correlation between the variables and optimizing a robust formulation. The concept can be applied in developing other formulation.

5. COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human or animal subjects performed by any of the authors.

6. CONFLICT OF INTEREST

No conflict of interest associated with this work.

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