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Formulation, Optimization and Evaluation of Immediate Release Tablet of Apixaban

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Abstract : Apixabanis anticoagulant drug is an anticoagulant for the treatment of venous thromboembolic events. It is taken by mouth. It is direct factor Xa inhibitor. Apixaban has half-life 9-14 hrs. In Artial fibrillation the intial dose 5mg once daily. Apixban is poorly soluble in water hence the basic objective of this study was to produce immediate release apixaban tablets containing super disintigrants via direct compression, to improve disintegration, dissolution and to get faster onset of action. Super disintigrants used in this formulation are microcrystalline cellulose and cross carmellose sodium, sodium starch glycolate. The drug-excipients interaction was investigated by FT- IR. Tablets were subjected to physicochemical characterization such as thickness, weight uniformity, drug content, in vitro drug release, and stability studies. Tablets were found to be satisfactory when evaluated for thickness, weight uniformity, *invitro* drug release, drug content and disintegration time. The in vitro drug release for optimized formulation $N_5$was found to be 96 % in 2.45 min. The optimized formulation N_5 (8% CCS) also showed satisfactory drug content (99.68%) and satisfactory stability. The optimized formulation $N_5$is further selected and compared with the *in-vitro* release profile of the innovator product.

Keywords: Apixaban, venous thromboembolic events, super disintigrants, Cross carmellose sodium.

Introduction

Introduction to immediate release tablets.

Immediate release tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques.[1] IR tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities.[2] Immediate release tablets generally release the drug in less than one hour with the help of Super disintigrants like cross carmellose sodium, sodium starch glycolate and PVP. [3]

Apixaban is chemically 1-(4-methoxyphenyl) -7-oxo-6- [4- (2-oxopiperidin-1 yl)phenyl]-1H,4H, 5H,6H,7H-pyrazolo[3,4-c]pyridine-3-carboxamide. Apixaban is to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It has also been used to lower the risk of developing venous thrombosis post-orthopedic surgical procedures.[6]

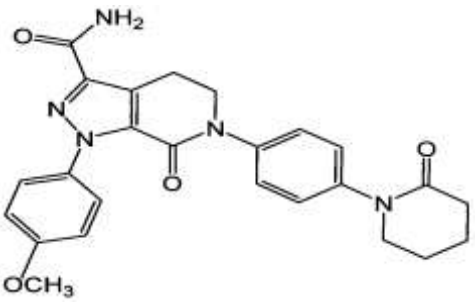

Figure 1: Structure of apixaban

Experimental

Materials and Methods

Apixaban was received from MSN laboratory as gift sample, lactose anhydrous purchased from DMV fronttera, microcrystalline cellulose, crosscarmellose sodium, sodium starch glycolate, crospovidone were purchased from FMC biopolymer, sodium stearate,poloxamer 188, sodium lauryl sulphatewere purchased from DAKSH, magnesium stearate was purchased from peter greven.

Preperation of apixaban immediate release tablet by direct compression[6,7]manufacturing process:

Apixaban, sodium lauryl sulphate and microcrystalline cellulose part-I were co-sifted through # 40 ASTM (premix-I); premix-I was co-sifted along with microcrystalline cellulose part-II (premix-II); premix-II was co-sifted along with microcrystalline cellulose part-III (premix-III) ; premix-III was co-sifted along with microcrystalline cellulose part-IV (Premix-III); lactose anhydrous (supertab 21 AN) and croscarmellose sodium were co-sifted through # 40 ASTM; In double cone blender half quantity of premix-IV was loaded followed by premix-III followed by remaining quantity of premix-IV was loaded into blender and blended for 12 min at 24 rpm; magnesium stearate was sifted through # 60 sieve placed in double cone blender (2L) and lubrication was done at 24 rpm for 3 minutes.

Drug–excipient interaction study. [8]

The drug and excipients must be compatible with one another to produce a product i.e. stable, efficacious, attractive, easy to administer and safe. The compatibility studies provide the frame work for the drugs combination with the excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically API will not undergone any changes, after it has been subjected to processing steps during formulation of tablets. Compatibility studies are carried out by mixing definite properties of drug and excipient and kept in glass vials, which is stored at 55°C for one month. The drug and other formulation ingredients were characterized by IR spectroscopy using a FT-IR 8400S (alpha-T). The spectra were taken by KBr discs method in the range of 4000–500 cm^{-1}.

Evaluation of apixaban tablets

Weight variation test: (uniformity of weight)[9]

This test is for uniformity of weight. In this test randomly 20 tablets are selected and mean of 20 tablets taken. The differnce is taken ±2.

Average weight of tablets[10]

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, according indian pharmacopeia limit

±10% for tablets weighing 130mg or less
±7.5% for tablets weighing 130mg to 324mg
±5% for tablets weighing more than 324mg
Twenty tablets were taken randomly and weighed accurately.

Hardness test[11]

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. By taking the hardness was measured in kg/cm^2 using Erweka hardness tester. In each batch 10 tablets checked and noted.

Friability test[12]

Friability is the loss of weight of tablet in the container package, due to removal of fine particles from the surface. This In-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilitor was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Ten tablets were weighed collectively and placed in the chamber of the Friabilitor. In the friabilitor, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilitor. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilitor and intact tablets were again weighed collectively. Permitted friability limit is 0.5 to 1.0%.

$\%\ \text{Friability} = [(\text{Weight}_i - \text{Weight}_f)/\ \text{Weight initial}] \times 100$

Where, W_i is initial weight of tablet before test.

W_f is final weight of the tablets after test.

Tablet size and thickness[13]

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by VernierCalipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.

Assay: (Drug content)[14]

For determination of drug content 20 tablets from each batch were weighed individually and powdered. The quantity of powder was equivalent to 10 mg. The equivalent weight apixaban HCL was transferred into 100 ml volumetric flask diluted to 100 ml with sufficient amount of buffer (0.01N HCL) and sonicated for 15 mins. Then aliquot of the filtrate was diluted suitably and analysed spectrophotometrically at λ max of 280 nm against blank. The content uniformity should not be less than 90% and not more than 110% of the labeled value.

Standard limits

IP: - Active less than 10mg or 10%,
BP: -Active less than 2 mg or 2%,
USP: -Active less than 25mg or 25%.

Disintegration test[15]

For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. This is one of the important quality control tests for disintegrating type tablets. The test was carried out on 6 tablets using Tablet disintegration tester distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration.

FTIR Spectroscopy

Previously dried sample of TEL in one part was mixed with 100 parts of KBr. The mixture was triturated to form fine powder. Thus formed fine powder mixture was compressed in a hydraulic press under pressure of 10 tons to form thin pellet. Same procedure was done for Pluronic F127. The pellets was scanned over a wave number range of 4000 to 400 cm^{-1} in FTIR instrument (Perkin Elmer, Spectrum Bx) and spectral analysis was done.

Differential Scanning Calorimetric (DSC) study

The DSC thermogram of polymeric micelles was recorded by using a differential scanning calorimeter (PerkinElmer 4000, UK) equipped with a computerized data station. The sample (approx. 1mg) was weighed and heated in a closed pierced aluminum pan at a scanning rate of 10°C/min between 30- 300°C and 20 mL/min of nitrogen flow.

X-ray Diffraction Study

Polymeric micelles were studied for X-ray diffraction. The powder X ray diffraction patterns was recorded using an X-ray diffractometer (Bruker D8 advance) with 2.2 KW copper as an anode material and dermic X-ray tube as a source. The sample was analyzed using the 2θ angle of 3-30° using lynux eye detector and filtered using Ni filter.

In-vitro dissolution studies[15]

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP - II paddle method and 900 ml of 0.05M sodium phosphate buffer with 0.05% SLS, pH 6.8 as the dissolution medium. The medium was allowed to equilibrate to temperature of 37°c ±0.5°C. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 1 hr in 0.05 M sodium phosphate buffer with 0.05% SLS, pH 6.8 at 75 rpm.

The samples were analysed spectrophotometrically at 280 nm using UV-spectrophotometer. The procedure also repeated by using pH 6.8 buffers as medium.

Limit – Not less than 90% of labelled amount of apixaban was dissolved in 45 min. **Dissolution parameters**
Type of apparatus**:** U.S.P. Type II (paddle)
Medium**:** 0.05M Sodium Phosphate Buffer With 0.05% SLS, pH 6.8
RPM**:** 75
Volume of medium**:** 900 ml
Sampling intervals**:** 5,10, 20, 30 and 45 min.
Sampling volume**:** 5ml,
Wavelength**:** 280 nm.

Table 1: Formulation of apixaban immediate release tablets.

Sr. No.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Apixaban	5	5	5	5	5	5	5	5	5
2	Lactose Anhydrous(Supertab 21 AN)	102.86	102.86	102.86	102.86	102.86	102.86	102.86	102.86	102.86
3	MCC(Avicel PH 112)	78.14	78.14	78.14	78.14	78.14	78.14	78.14	78.14	78.14
4	Crosscarmellose sodium(Ac-Di-Sol)	5	10	15	-	-	-	-	-	-
5	Sodium Starch Glycolate	-	-	-	5	10	15	-	-	-
6	Crospovidone	-	-	-	-	-	-	5	10	15
7	Sodium sterate	1	2	3	-	-	-	-	-	-
8	Poloxamer 188	-	-	-	1	2	3	-	-	-
9	Sodium Lauryl Sulphate	-	-	-	-	-	-	1	2	3
10	Magnesium Stearate	2	2	2	2	2	2	2	2	2

Table. 2 Formulae for preparation of film coating solution for final formulae.

Sr. No.	Ingredients	Quantity
1	Opadry II 32K540053 pink	6.7gm
2	Iso propyl Alcohol	70%
3	Methanol	30%

Table. 3 Coating parameters

Coating parameters						
Coating machine used: GAC–275						
Seal Coating						
Inlet Temp.^{o}C	**Exhaust temp.** ^{o}C	**Atomization (bar)**	**Spray rate(rpm)**	**Pan speed (rpm)**	**Weight gain (%)**	**Curing (Min)**
50–60	45 –50	1 ± 0.2	3–5	10–12	3– 4 %	15

Results and Discussion

The present study of apixaban immediate release tablets were developed with a view to deliver the drug immediately. The formulation development work was initiated with direct compression method and a total of 9 formulations were made. The formulated tablets were evaluated for various pre compression parameters and post compression parameters like thickness, hardness, weight variation, friability, disintegration test, drug content uniformity and in vitro release studies. The formulation N_5showed satisfactory physical parameters, and it was found to be stable among other formulations.

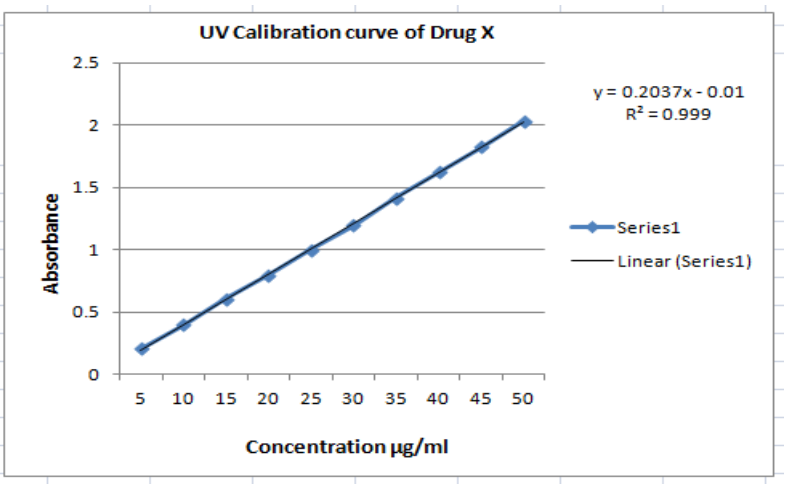

Figure 2: UV calibration curve.

FTIR Spectroscopy

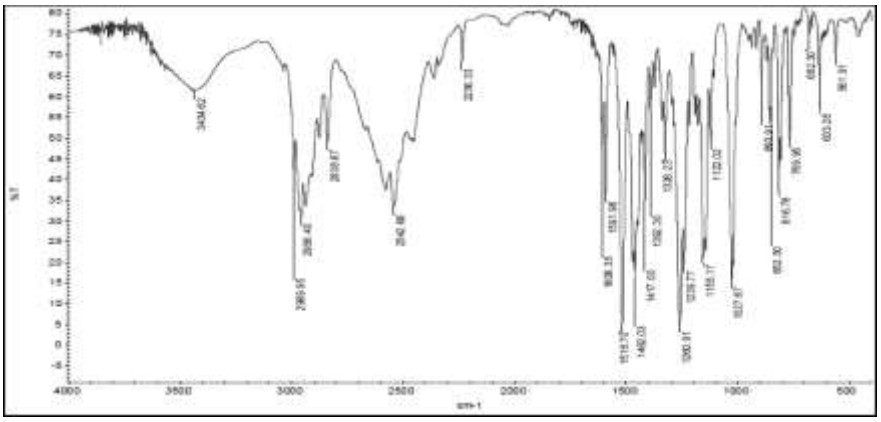

Figure 3: FT-IR spectra of formulation F_5.

Table 4: Interpretation of data of formulation F_5.

IR Values (cm^{-1})	Functional Groups
3325.0	N-H str. of sulphonamido gr.
3250.6	N-H str. of amido gr.
2942.8	CH str. of CH2
2854.2	CH str. of CH2
1688.9	C=O of amide

Drug–excipient interaction study.

IR spectrum of drug and excipients for preformulationstudies.

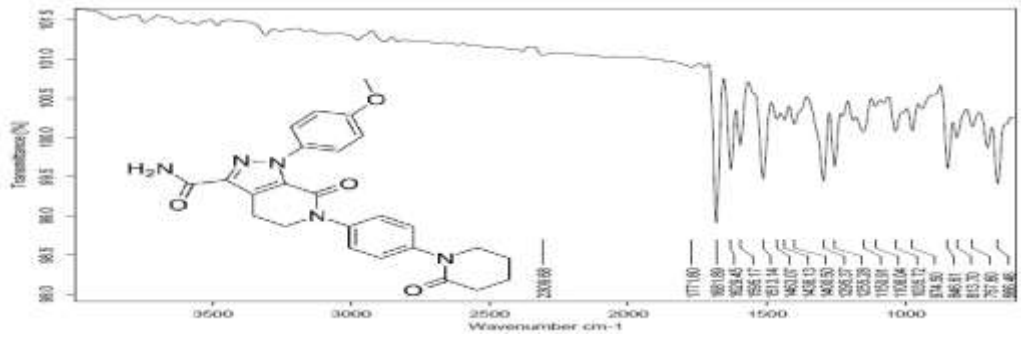

Figure 4: IR spectrum of apixaban

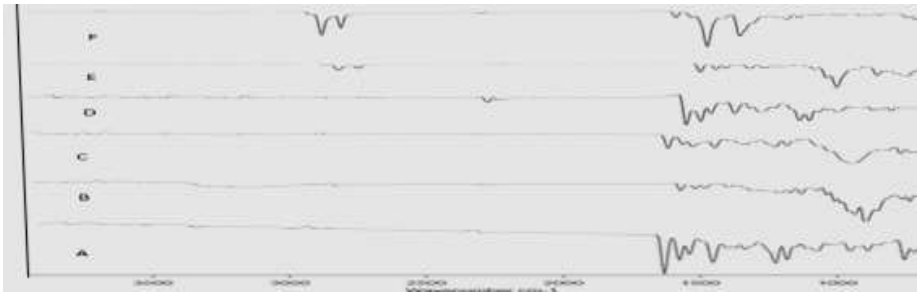

Figure 5: IR spectrum of A) apixaban, B) Drug+lactose, C) Drug + cross carmellose sodium , D) Drug+pvp k30, E) Drug+ sodium lauryl sulphate, F) Drug+ magnesium Stearate

Differential Scanning Calorimetric (DSC) study

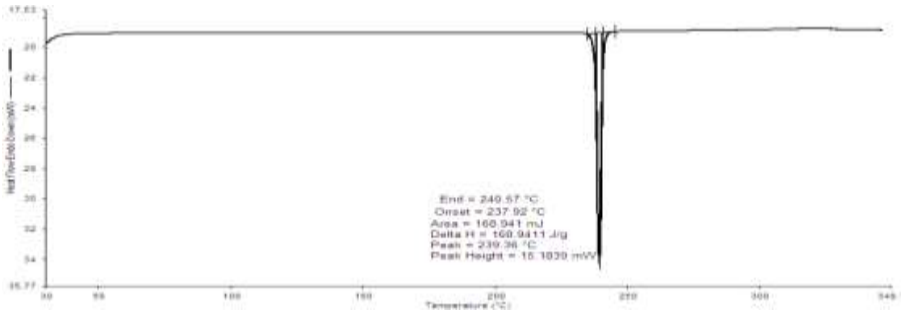

Figure 6:Apixaban DSC thermogram.

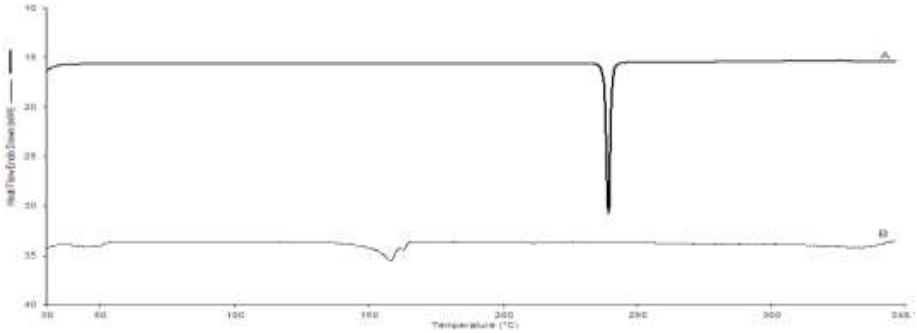

Figure 7: Formulation DSC thermogram.

X-ray Diffraction Study

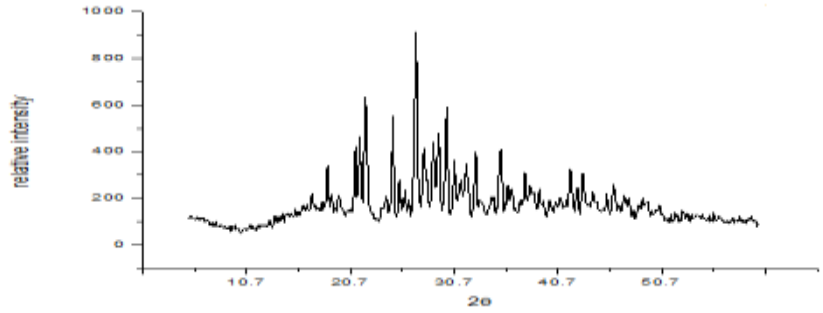

Figure 8:Apixaban XRD spectra.

Table 5: Pre compression properties of powdered blend F_1 to F_9

Batch No.	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility Index (%)	Hausner Ratio
F_1	0.400	0.551	37.7	1.377
F_2	0.410	0.538	31.2	1.310
F3	0.412	0.530	28.6	1.280
F_4	0.423	0.528	24.8	1.240
F_5	0.430	0.530	23.2	1.232
F_6	0.432	0.540	25.0	1.250
F^7	0.431	0.539	25.0	1.250
F_8	0.436	0.532	22.0	1.220
F_9	0.442	0.530	19.9	1.199

Table 4: Evaluation data of apixaban immediate release tablets

BatchNo.	Average weight (mg)	Thickness (mm)	Friability (%)	Hardness (N)	Drug content (%)	D T (min.)
F_1	198.3 -203.4	3.90– 3.95	0.021	70 – 82	99.89	2.58
F_2	198.9 -203.3	3.92 – 3.97	0.03	68 – 80	97.14	2.54
F_3	197.3 -203.8	3.88 – 3.94	0.022	69 – 83	99.64	2.52
F_4	197-203	3.90 – 3.95	0.019	72 – 82	100.2	2.50
F_5	198.5 -203.5	3.89 – 3.99	0.025	71 – 83	99.68	2.49
F_6	198.1-203.5	3.93 – 3.96	0.026	65 – 82	98.75	2.50
F_7	197.9 -202.9	3.89 – 3.95	0.03	67– 81	98.49	2.55
F_8	198.5 -203.7	3.93 – 3.98	0.025	69 – 85	100.2	2.52
F_9	198.1-203.5	3.93 – 3.96	0.026	65 – 82	98.77	2.53

Experimental design and response surface analysis[16]

Based on preliminary studies, cross carmellose sodium, sodium laurly sulphate were chosen as superdisintegrant & surfactant respectively. Concentration of superdisintegrant and concentration surfactant was selected as variables while dissolution and disintegration time as response parameters.

A 3^2 full factorial design was selected as it helps in studying effect on response parameters by changing both variables simultaneously with minimum number of experimental runs. The dissolution and disintegration time for the 9 batches (N_1 to N_9) showed a wide variation (94- 96 % and 34-40 sec respectively). The data clearly indicated strong dependence of response variables on the selected independent variables

Table 5: Dissolution and disintegration time of optimized batches

Formulation batch	Dissolution (%)	Disintegration time (sec)
N_1	80	2.59
N_2	84	2.55
N_3	86	2.50
N_4	92	2.49
N_5	96	2.45
N_6	94	2.47
N_7	88	2.56
N_8	85	2.50
N_9	82	2.51

In order to quantify the effect of formulation variables on the response parameters, it was necessary to construct a mathematical model which would help in predicting values of response parameters at any selected values of formulation variables within the boundaries of the design. It may happen that the levels of formulation variables which are intermediate between the selected levels may yield optimum formulation. Design Expert® version 10 software was used to generate a mathematical model for each response parameter and the subsequent statistical analysis.

Mathematical model analysis: dissolution (Y_1)

Statistical analysis was performed using Design Expert® Version 10 and quadratic model was found to be best fit model and polynomial equation is shown below:

Y_1 =+77.79+11.85*A+0.61*B-3.00*AB+0.70*A2+1.72*B2

The results of multiple linear regression analysis showed that both the coefficients 'A' and 'B' bear a positive sign. Therefore, increasing the concentration of superdisintegrant the dissolution rate increases.

ANOVA for response surface Quadratic Model

The analysis of variance (ANOVA) was performed and results are shown in Table . from the data it is evident that P value is less than 0.0500 in all formulations.

Table 6: Analysis of variance table for Y_1 (Dissolution)

Source	Sum of Squares	df	MeanSquare	F Value	p-value Prob> F	
Model	1412.73	5	282.55	777.40	<0.0001	significant
A-Superdisintegrant	1353.90	1	1353.90	3725.16	<0.0001	
B-Surfactant	26.75	1	26.75	73.61	0.0033	
AB	2.22	1	2.22	6.11	0.0899	
A^2	29.82	1	29.82	82.06	0.0028	
B^2	0.023	1	0.023	0.065	0.8158	
Residual	1.09	3	0.36			
Cor Total	1413.82	8				

The Model F-value of 777.40 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant. In this case A, B, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy),model reduction may improve your model. The "Pred R-Squared" of 0.9926 is in reasonable agreement with the "Adj R-Squared" of 0.9979 i.e. the difference is less than 0.2."Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 69.614 indicates an adequate signal. This model can be used to navigate the design space.

Graphical representation:plot for dissolution

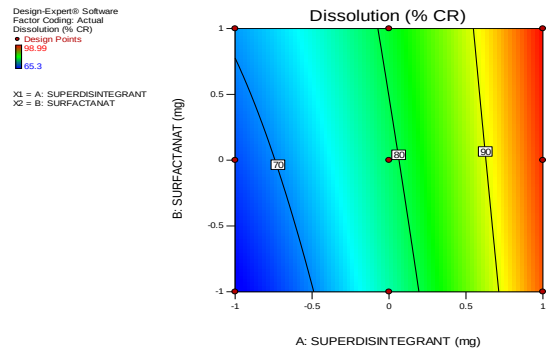

Figure 9: Contour graph for dissolution

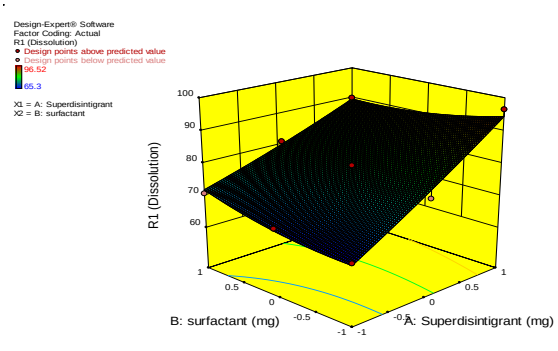

Figure 10: Three dimensional response surface.

The contour plot showing the effect of different proportion of independent variables on the response Y_1 (dissolution) is shown in (figure).

Mathematical model analysis: Disintegration Time (Y_2)

Statistical analysis was performed using Design Expert® Version 10 and quadratic model was found to be best fit model and polynomial equation is shown below:

Y2= +7.21-1.55*A+1.27*B+0.71*AB-0.72*A2+1.03*B2

The results of multiple linear regression analysis showed that both the coefficient 'A' is negative and 'B' bear a positive sign. Therefore, increasing the concentration of surfactant increases the disintegration time.

ANOVA for response surface quadratic model

The analysis of variance (ANOVA) was performed and results are shown in Table. From the data it is evident that P value is less than 0.0500 in all formulations.

Table 7: Analysis of variance table for Y_2 (disintegration time)

Source	Sum of Squares	df	MeanSquare	F Value	p-value Prob> F	
Model	29.16	5	5.83	15.20	0.0243	significant
A- Superdisintegrant	14.42	1	14.42	37.57	0.0087	
B-Surfactant	9.63	1	9.63	25.09	0.0153	
AB	1.96	1	1.96	5.11	0.1089	
A^2	1.03	1	1.03	2.68	0.2003	
B^2	2.14	1	2.14	5.57	0.0995	
Residual	1.15	3	0.38			
Cor Total	30.32	8				

The Model F-value of 15.20 implies the model is significant. There is only a 2.43% chance that an F-value this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant. In this case A, B is significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The "Pred R-Squared" of 0.5414 is not as close to the "Adj R-Squared" of 0.8987 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doin confirmation runs. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 11.138 indicates an adequate signal. This model can be used to navigate the design space. The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

Graphical representation: plot for disintegration time

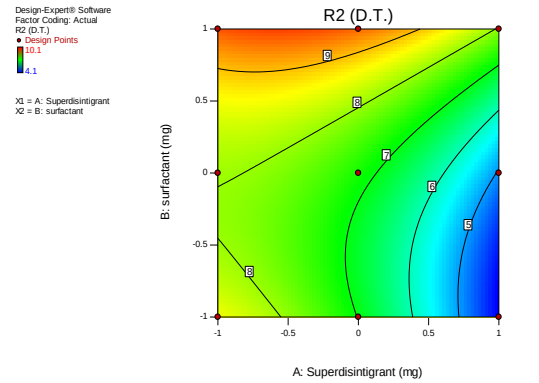

Figure 11: Contour graph for disintegration time

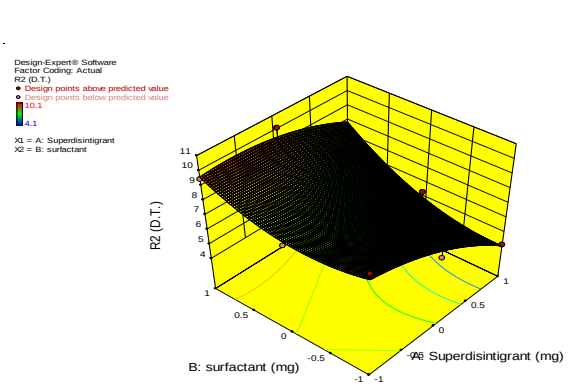

Figure 12:Three dimensional response surface

Dissolution profile of F_5 batch & innovator

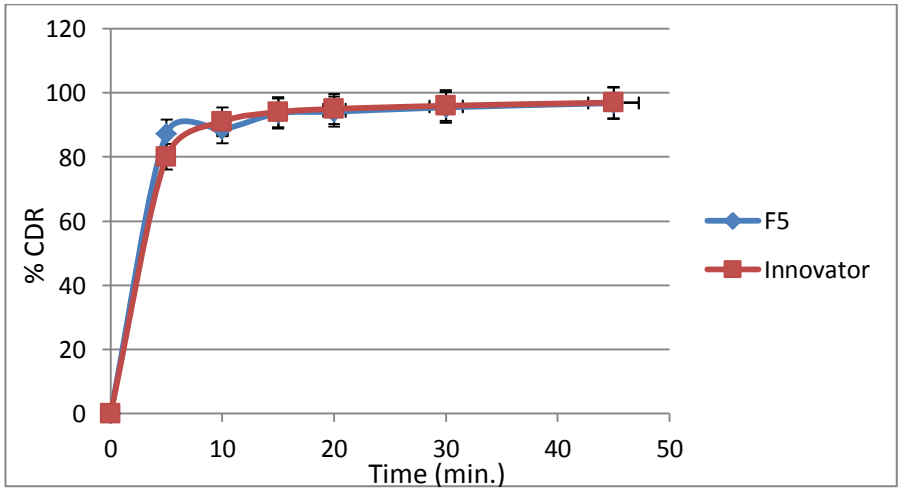

Figure 13: Dissolution profile of F_5 batch & innovator

Conclusion

From the results obtained, following conclusions were drawn:

- ✓ The Drug- excipients compatibility studies showed that the excipients used in thefinal formulation has no interaction with the drug. The excipients werecompatible with API.
- ✓ Evaluation of physicochemical parameters like hardness, friability, dissolutionand assay indicated that the tablet were mechanically stable and complied withnecessary pharmacopoeia specifications and comparable to innovator product.
- ✓ The stability testing of finalized batch at 40 °C /75% RH revealed no significantchange with respect to parameters such as assay, impurities, drug release patternthat indicates the stability of the finished product.
- ✓ The formulation further needs to be evaluated for bioequivalence study in healthyhuman volunteers.
- ✓ Finally, it is concluded that the process adopted for the manufacturing provides a productmeeting all the predetermined specifications and quality characteristics. The processwould imbibe reproducibility and robustness in the formulation.

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