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Formulation And Evaluation Of Immediate Release Tablet Of Fimasartan Drug.

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Abstract: Oral delivery is a popular method in the pharmaceutical industry for its safety, convenience, cost-effectiveness, and high patient compliance. Angiotensin II receptor blockers (ARBs), like fimasartan, are used to treat hypertension by relaxing blood vessels and reducing blood pressure. Immediate release tablets are designed to disintegrate quickly, allowing for the swift release of active ingredients. These tablets are preferred due to their ease of self-administration, compactness, and simple manufacturing process. Formulation and evaluation of immediate-release tablets of Fimasartan were successful, demonstrating acceptable physicochemical properties and rapid drug release. These tablets offer convenience and efficacy for managing hypertension, but further studies, including stability testing and clinical trials, are needed to confirm their long-term stability, bioavailability, and clinical effectiveness before they can be introduced into the market and prescribed to patients.

Keywords: Fimasartan, Hypertension, Immediate release, Formulation, Oral delivery

INTRODUCTION:

Oral delivery is widely recognized as the gold standard in the pharmaceutical industry, valued for its safety, convenience, cost-effectiveness, and high patient compliance. The oral bioavailability of a drug largely depends on its solubility and permeability. However, nearly 40% of new chemical entities developed by the pharmaceutical industry are poorly soluble in water, leading to challenges with bioavailability.[1] Due to their poor solubility, these drugs often require higher doses to achieve the desired therapeutic effect, which can increase the risk of toxicity. If these drugs are not fully released in the gastrointestinal tract, their bioavailability remains low. Therefore, enhancing the solubility and/or dissolution rate of these drugs is crucial for improving their bioavailability.[2]

Fimasartan

Angiotensin II receptor blockers (ARBs), such as fimasartan, are mostly used to treat hypertension, or high blood pressure. It helps to relax blood vessels and reduce blood pressure by blocking the effects of the hormone angiotensin II, which constricts blood vessels.[3] This lower blood pressure contributes to a lower risk of heart attacks, strokes, and other cardiovascular problems. By blocking the angiotensin II receptor type 1 (AT1), fimasartan stops angiotensin II from binding and constricting blood vessels. mostly used for the treatment of hypertension. As decided by a doctor, it can also be used to treat heart failure or other cardiovascular diseases.[4]

Immediate release dosage form

Immediate release tablets are designed to disintegrate quickly and dissolve rapidly, allowing for the swift release of the active ingredients. This immediate release is achieved through the use of suitable pharmaceutically acceptable diluents or carriers that do not significantly delay the drug's release or absorption. Immediate release dosage forms have gained popularity as an alternative to conventional oral dosage forms due to their ability to disintegrate quickly after administration, resulting in an enhanced dissolution rate.[5] In current research and development, novel drug delivery systems are being created to target expanding markets, extend product life cycles, and generate new opportunities. Tablets remain the most popular dosage form due to their ease of self-administration, compactness, and simple manufacturing process. In situations where a faster onset of action is necessary compared to conventional therapies, immediate release dosage forms are preferred. These forms disintegrate rapidly after administration, thanks to the use of super disintegrants, which ensure quick tablet breakdown in the stomach.[6]

MATERIALS AND METHODS:

Materials and Instruments: A complimentary Fimasartan sample was obtained. The manufacturer supplied the best pharma grades available, or LR grade, for all components utilized in the experiment.

UV-visible spectrophotometric analysis:[7]

This UV-visible spectrophotometric examination was performed with a Japan V 550 from Jasco Corporation. Software called Spectra Manager and a spectrophotometer were employed in the analysis. To determine λ max, 0.1N hydrochloric acid was utilized as the solvent system. Fimasartan sample (20 µg/ml) was used, and 256 nm was found to be the λ max. The results' spectra were represented in figure

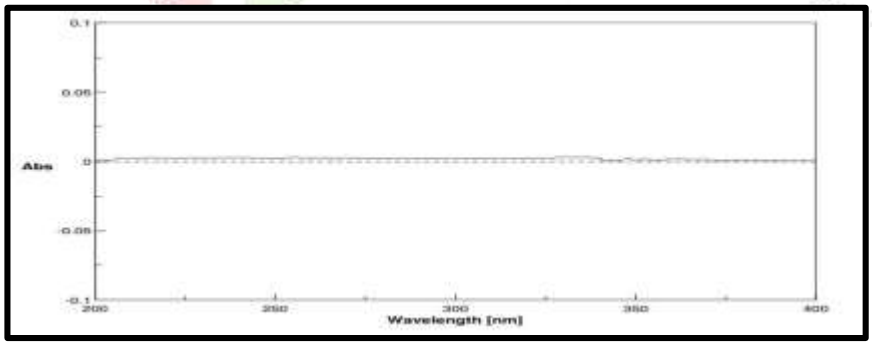

Fig No 1: Blank in 0.1 N HCL

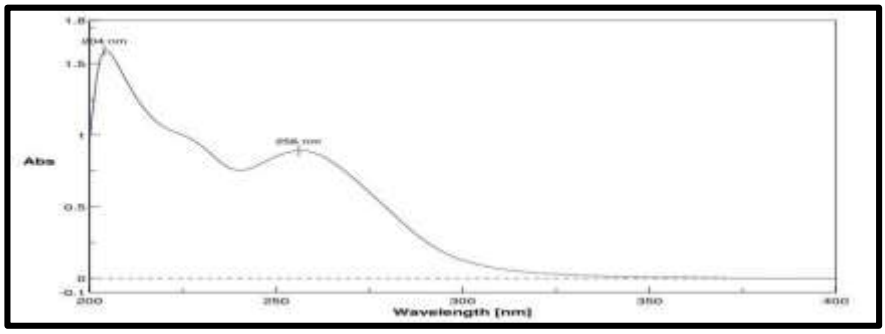

Fig No 2: 20 PPM solution of Fimasartan in 0.1 N HCL

Preparation of Calibration curve for Fimasartan in 0.1 N Hydrochloric acid[8].

The calibration curve of Fimasartan was drawn by measuring the absorbance of different concentrations in 0.1N hydrochloric acid at 256 nm. The calibration curve obtained as shown

Table 1: Calibration curve for Fimasartan

Sr.no.	Concentration (ppm)	Absorbance
1.	5	0.2458
2.	10	0.4855
3.	15	0.6745
4.	20	0..8912
5.	25	1.0254

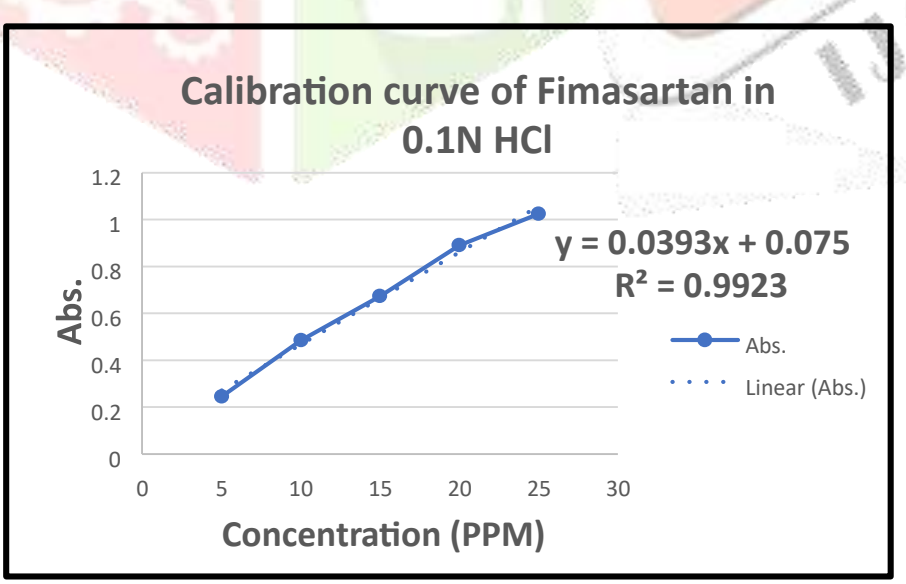

Fig No.3 Calibration curve method

The calibration curves were linear and obeyed Beer-Lambert's law in the concentration range 5-25µg/ml. The correlation coefficient values were 0.9923 indicating excellent linearity of the data.

Formulation of Immediate release tablet:

Table No 2: Formulation ingredients and its roles

Sr.no.	Ingredients	Role
1.	Fimasartan	Anti-hypertension
2.	Cross povidone	Super disintegrating agent
3.	Microcrystalline cellulose(MCC)	Direct compression binder
4.	Mannitol	Swelling agent, Diluent
5.	Magnesium stearate	Lubricant
6.	Talc	Glidant

Formulation strategy:

Table No 3: Formulation strategy

Sr.no.	Ingredients	Quantity (mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Fimasartan	120	120	120	120	120	120	120	120	120
2.	Cross povidone	5.6	5.6	5.6	11.2	11.2	11.2	16.8	16.8	16.8
3.	Microcrystalline cellulose (MCC)	21	31.5	42	21	31.5	42	21	31.5	42
4.	Mannitol	119.4	108.9	98.4	113.8	103.3	92.8	108.2	97.7	87.2
5.	Magnesium stearate	7	7	7	7	7	7	7	7	7
6.	Talc	7	7	7	7	7	7	7	7	7
Total weight of tablet		280mg.								

Evaluation of formulated batches: A. Pre compression parameters:

The powder blend from all the batches were evaluated for density and flow property parameters which includes Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose.

Table No 4: Precompression parameters

Batches	Bulk density	Tapped density	Compressibility index	Hausner's ratio	Angle of repose
F1	0.5589	0.6542	14.57	1.17	25.20
F2	0.5738	0.6821	15.88	1.19	27.24
F3	0.5708	0.6635	13.97	1.16	26.36
F4	0.5578	0.6459	13.65	1.16	25.74
F5	0.5400	0.6195	12.83	1.15	24.34
F6	0.5273	0.6378	17.33	1.21	23.45
F7	0.5432	0.6328	14.16	1.16	25.98
F8	0.5523	0.6542	15.58	1.18	24.34
F9	0.5534	0.6452	14.23	1.17	24.15

The tablets from all trial batches were white round convex shaped beveled edge with having plane upper and lower side.

Thickness and diameter:

Using a Vernier caliper, the diameter and thickness of each tablet were measured after they were chosen at random. Table 5 displayed the mean values. The values in every formulation are essentially the same. The diameter was found to be in the range of 8.7 – 8.9 mm, and the thickness ranged from 4.35 ±0.02 mm to 4.37 ±0.05 mm, respectively. The values' uniformity shows that the formulas were compressed without sticking.

Hardness:

The hardness of each batch was measured using a Monsanto hardness tester, and the findings are shown in Table 5. It was discovered that the hardness ranged from 4 to 6 kg/cm2. Every batch that was developed had a consistent hardness that was both adequate and had good mechanical strength

.

Friability:

Using the Roche Friabilator, tablets from all batches were assessed. The friability of the tablets was found to be within an acceptable range of 0.34 to 0.73 (less than 1%). The outcome was displayed in Table 5.

Table No 5: Post compression parameters

Batches	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)
F1	4.36±0.01	8.7 ±0.01	4	0.70
F2	4.37±0.05	8.9 ±0.03	4.5	0.34
F3	4.36±0.05	8.8 ±0.02	5.5	0.35
F4	4.35±0.02	8.9 ±0.02	4	0.36
F5	4.35±0.01	8.7 ±0.02	5	0.72
F6	4.35±0.05	8.8 ±0.02	6	0.72
F7	4.37±0.05	8.7 ±0.02	4.5	0.34

F8	4.37±0.02	8.8 ±0.02	5.5	0.73
F9	4.37±0.01	8.7 ±0.02	6	0.36

Drug content: Drug content uniformity test was performed for all formulated batches and results were expressed in table 6. The drug content was found to be between 98- 102 % which was under specified limit.

Table No 6: Drug content

Batches	Drug content
F1	100.41
F2	99.99
F3	100.65
F4	101.45
F5	100.50
F6	98.21
F7	99.84
F8	101.55
F9	99.28

Weight Variation:

The direct compression method was utilized to prepare the tablets. Due to the material's unrestricted flow, homogeneous die fill allowed for the production of tablets with consistent weight. According to pharmacopoeia criteria, all manufactured batches of tablets had acceptable weight variations, with differences of less than 5%. Table 7 presented the findings.

Table No 7: Weight variation results

Batches	Weight variation	
	Weight (mg) ± S. D	Weight variation (5%)
F1	282 ± 2	Passes
F2	285 ± 5	Passes
F3	284 ± 7	Passes
F4	289 ± 3	Passes
F5	280 ± 6	Passes
F6	284 ± 5	Passes
F7	284 ± 8	Passes
F8	281 ± 4	Passes
F9	286 ± 6	Passes

Stability Result:

Table No 8: Stability Result

Evaluation parameters	Results
Physical appearance	White round convex shaped
Hardness	4.5 kg/cm^2
Friability	0.34
Disintegration time	2 min 10 sec
Drug content	99.55 %
In vitro dissolution study	99.07 %

Disintegration test:

For every batch that was created, the disintegration time was measured, and the findings are shown in Table 12. The disintegration time was discovered to be between two and four minutes and fifteen seconds. The super disintegrating agent concentration was inversely correlated with the disintegration time, while the binder concentration was directly correlated.

Table No 9: Disintegration time results

Batches	Disintegration time (Min)
F1	3 min 40 sec ± 15 sec
F2	3 min 56 sec ± 15sec
F3	4 min 15 sec ± 10 sec
F4	2 min 40 sec ± 15 sec
F5	2 min 45 sec ± 10 sec
F6	2 min 55 sec ± 10 sec
F7	2 min 10 sec ± 15 sec
F8	2 min 25 sec ± 15 sec
F9	2 min 45 sec ± 15 sec

In vitro dissolution test:

All of the prepared batches were evaluated in vitro for 30 minutes using 0.1N hydrochloric acid as the dissolution medium, and the percentage CDR was calculated using the corresponding equation of line. The results were expressed in table 10

Table No 10: In vitro dissolution study

Time (min) ↓ / Batches →	% Cumulative Drug Release (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	21.55	19.78	19.66	24.69	23.65	21.36	26.65	25.67	24.45
10	42.56	38.66	37.47	44.36	43.23	39.85	46.36	44.78	42.78
15	61.98	58.82	56.99	65.78	57.75	52.37	64.99	62.85	63.56
20	79.41	75.95	68.98	78.88	74.22	74.21	79.32	79.69	76.89
25	91.15	88.86	85.65	90.66	87.78	87.29	88.75	89.65	86.46
30	96.44	95.99	94.48	97.26	97.35	96.77	99.21	98.94	98.25

Table No 11: The layout of the Actual Design of DOE

Runs	Factor1	Factor 2	Response 1	Response 2
	A: % Cross povidone	B: % MCC	Disintegration time (Min)	Hardness (kg/cm^2)
1	4	15	2.55	6
2	2	15	4.15	5.5
3	6	7.5	2.1	4.5
4	4	11.25	2.45	5
5	6	15	2.45	6
6	2	7.5	3.4	4
7	2	11.25	3.56	4.5
8	4	7.5	2.4	4
9	6	11.25	2.25	5.5

Results for the Disintegration time of DOE:

1. **Fit Summary:** After entering the data in Design-Expert software, fit summary applied to the data after which the " Linear vs Mean " was suggested by the software.

Table No 12: Fit summary table for Disintegration time of DOE

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Mean vs Total	71.1773	1	71.1773			
Linear vs Mean	3.3564	2	1.6782	15.20	0.0045	
2FI vs Linear	0.0400	1	0.0400	0.32	0.5953	
Quadratic vs 2FI	0.5529	2	0.2765	11.96	0.0372	Suggested
Cubic vs Quadratic	0.0654	2	0.0327	8.15	0.2404	Aliased
Residual	0.0040	1	0.0040			
Total	75.1961	9	8.3551			

2. **ANOVA for Disintegration time of DOE:** The analysis of variance (ANOVA) was performed to identify significant and insignificant factors. The results of ANOVA for the disintegration time of DOE are as following table 13.

Table No 13: ANOVA table for a disintegration time of DOE

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	3.8938	3.00	1.30	51.92	0.0003	significant
A-Cross povidone	3.0960	1.00	3.10	123.86	0.0001	
B-MCC	0.2604	1.00	0.26	10.42	0.0233	
A^2	0.5373	1.00	0.54	21.50	0.0057	
Residual	0.1250	5.00	0.02			
Cor Total	4.0188	8.00				

The Model F-value of 51.92 implies the model is significant. There is only a 0.03% chance that a "Model 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 and A^2 are significant model terms.

3. **Fit Statistics for disintegration time of DOE**

Table No 14: Fit statistics for disintegration time of DOE

Std. Dev.	0.16	R-Squared	0.9689
Mean	2.81	Adj R-Squared	0.9502
C.V. %	5.62	Pred R-Squared	0.8848
PRESS	0.46	Adeq Precision	17.58

The "Pred R-Squared" of 0.8848 is in reasonable agreement with the "Adj RSquared" of 0.9502. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. ratio of 17.58 indicates an adequate signal.

This model can be used to navigate the design space.

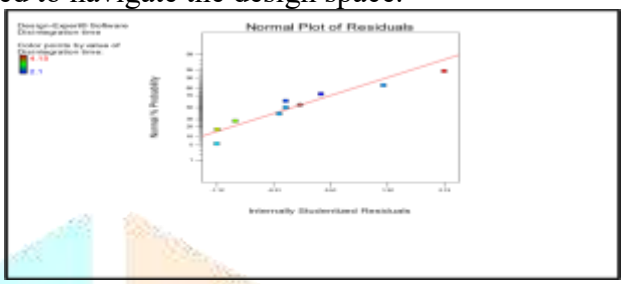

Fig No 4: Normal % Probability for DOE of disintegration time for DOE

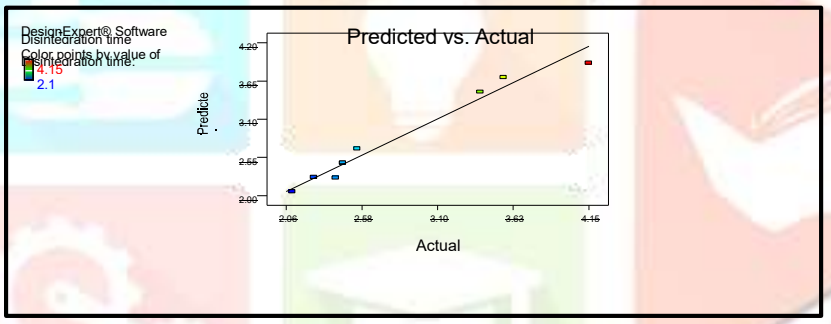

Fig No 5 : Predicted Vs Actual for DOE of disintegration time for DOE

Model Graphs of disintegration time: One-factor Graphs of disintegration time

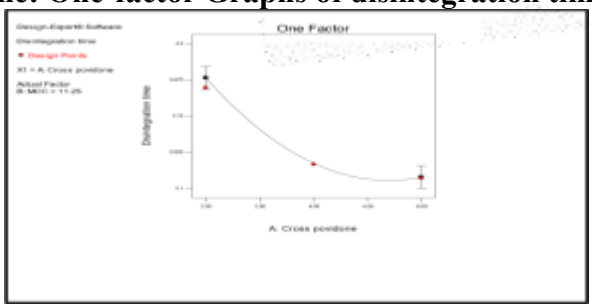

Fig No 6: Effect of % Cross povidone on disintegration time

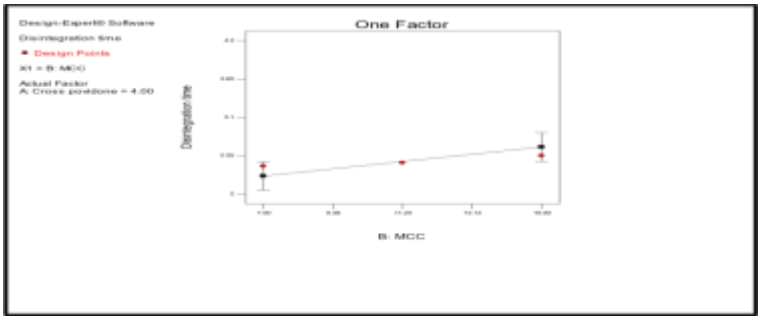

Fig No 7: Effect of % MCC on disintegration time

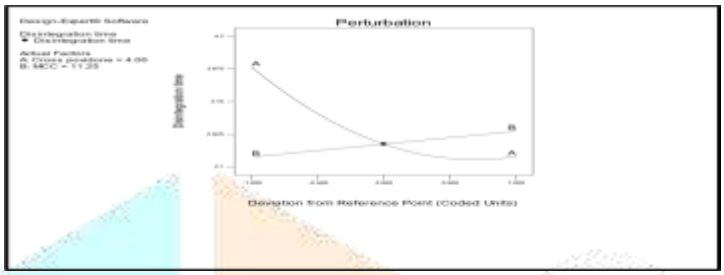

Fig No 8: Effect of All 2 factors on disintegration time

Conclusion: Percentage of cross povidone and MCC in formulation having impact on disintegration time of drug. As % cross povidone increases disintegration time decreases. As % MCC increases in formulation disintegration time also increases.

Cross povidone is having high impact on disintegration time as compare to MCC as its P value is very low as compare to MCC.

Results for the Hardness of DOE:

1. **Fit Summary:** After entering the data in Design-Expert software, fit summary applied to the data after which the "Linear vs Mean" was suggested by the software.

Table No 15: Fit summary table for Hardness of DOE

Source	Sum of Squares	df	Square Mean	F Value	p-value Prob > F	
Mean vs Total	225.00	1.00	225.00			
Linear vs Mean	4.83	2.00	2.42	87	< 0.0001	Suggested
2FI vs Linear	0.00	1.00	0.00	0	1.0000	
Quadratic vs 2FI	0.00	2.00	0.00	0	1.0000	
Cubic vs Quadratic	0.17	2.00	0.08	63660000	< 0.0001	Aliased
Residual	0.00	1.00	0.00			
Total	230.00	9	25.56			

2. **ANOVA for Hardness of DOE:**

The analysis of variance (ANOVA) was performed to identify significant and insignificant factors. The results of ANOVA for the hardness factor of DOE are as following table 16

Table No16: ANOVA table for hardness of DOE as such

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	4.83	2.00	2.42	87.00	< 0.0001	significant
A-Cross povidone	0.67	1.00	0.67	24	0.0027	
B-MCC	4.17	1.00	4.17	150	< 0.0001	
Residual	0.17	6.00	0.03			
Cor Total	5.00	8.00				

The Model F-value of 87.00 implies the model is significant. There is only a 0.01% chance that a "Model 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 and B are significant model terms.

3. Fit Statistics for hardness for DOE

Table No 17: Fit statistics for hardness for DOE

Std. Dev.	0.17	R-Squared	0.9667
Mean	5.00	Adj R-Squared	0.9556
C.V. %	3.33	Pred R-Squared	0.9214
PRESS	0.39	Adeq Precision	24.249

The “Pred R-Squared” of 0.9214 is in reasonable agreement with the “Adj R-Squared” of 0.0.9556

“Adeq Precision” measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 24.249 indicates an adequate signal. This model can be used to navigate the design space.

4. Final Equation in Terms of Coded Factors of hardness for DOE:

Table No 18: Final equation in terms of coded factor of hardness

Hardness	=
+5.00	
+0.33	* A
+0.83	* B

Graphical Presentation: Diagnostics of hardness for DOE:

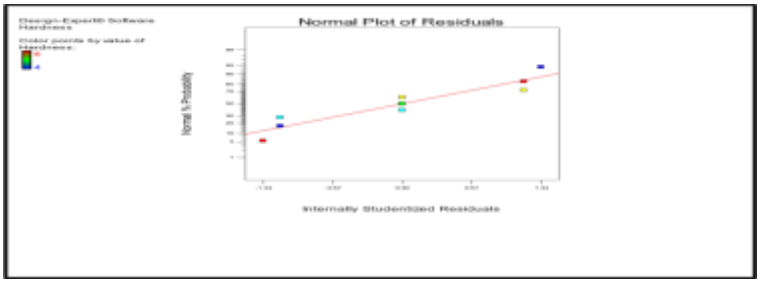

Fig No 9: Normal % Probability for DOE of hardness for DOE

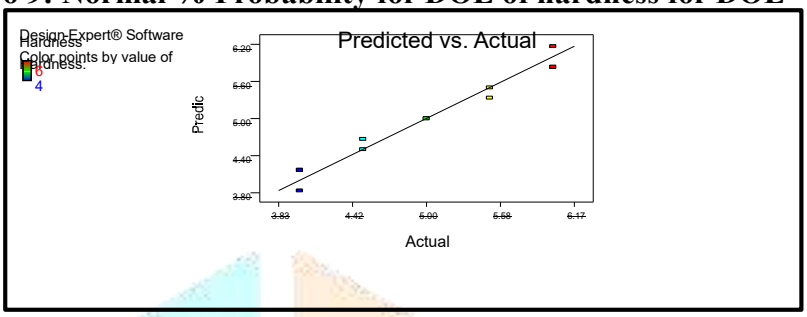

Fig No 10 : Predicted Vs Actual of hardness for DOE

5. Model Graphs of hardness: One-factor Graphs of hardness for DOE

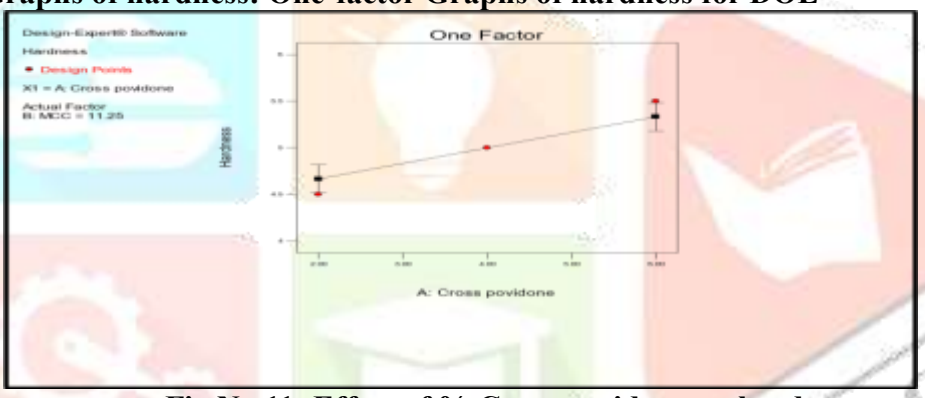

Fig No 11: Effect of % Cross povidone on hardness

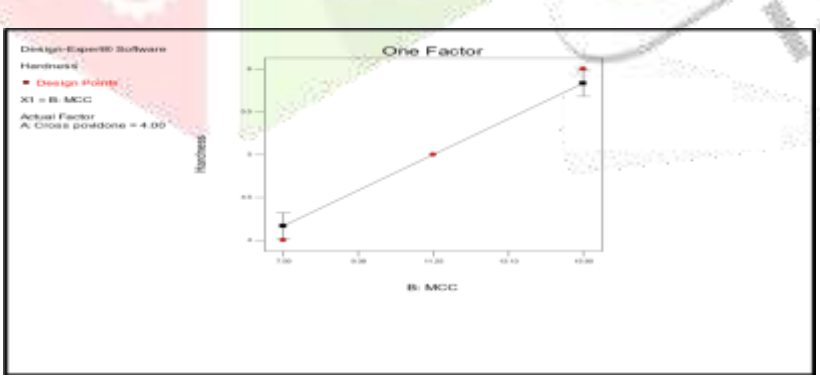

Fig No 12: Effect of % MCCon hardness

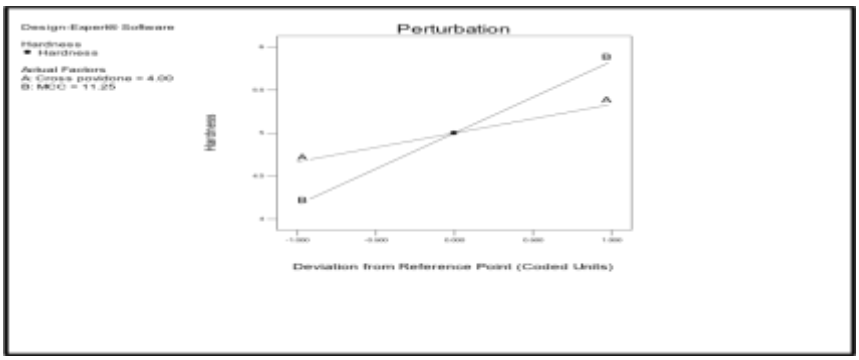

Fig No 13: Effect of All 2 independent parameters on hardness

Conclusion: Percentage of cross povidone and MCC in formulation having impact on hardness. As % cross povidone increases hardness increases. As % MCC increases in formulation hardness also increases.

MCC is having high impact on hardness as compare to Cross povidone as its P value is very low as compare to Cross povidone.

Table No 19: Summary of effect of independent variable on dependent variables

Sr. No.	Independent variables	Disintegration time	Hardness
1	% Cross povidone in formulation	Inversely proportional (As Cross povidone increases, disintegration time decreases)	Directly proportional (As Cross povidone increases, hardness also increases)
2	% MCC in formulation	Directly proportional (As MCC increases, disintegration time increases)	Directly proportional (As MCC increases, hardness also increases)

Conclusion: On the basis of data obtained from pre compression and post compression evaluation of batches as well as factorial design model study F7 batch was selected as optimized batch.

6. Comparative study of dissolution profile of optimized batch with marketed formulation (Fimanta 120mg Ajanta pharma):

The comparative study of dissolution profile (% CDR) of optimized batch with marketed tablet dosage form (Fimanta 120mg_Ajanta pharma) was conducted by using 0.1N hydrochloric acid as dissolution medium. Samples were withdrawn at every 5min intervals and processed over respective equation of line and % cumulative drug release was calculated as shown in table 20 and figure 21.

On the basis of results obtained from dissolution profile study it was concluded that the formulated immediate release tablet of Fimasartan gives fast disintegration as well as absorption of drug as compare to conventional marketed table dosage form.

Table No 20: Comparative study of dissolution profile (%CDR)

Time (min)	% Cumulative Drug Release (%)	
	Optimized (F7)	Marketed
5	32.65	18.65
10	65.75	34.46
15	86.28	53.49
20	94.78	71.12
25	98.85	82.75
30	99.25	92.41

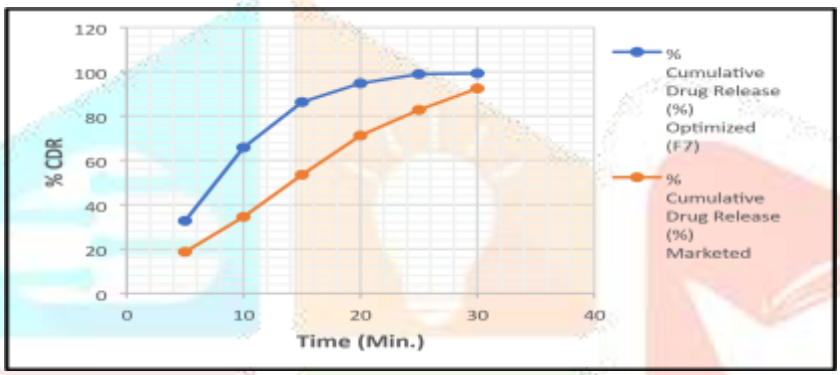

Fig No 14: Comparative study of dissolution profile (%CDR)

SUMMARY:

To create a dosage form that guarantees the best possible drug release and therapeutic efficacy, Fimasartan, an angiotensin II receptor antagonist used to treat hypertension, was formulated and evaluated as immediate-release tablets. Choosing the right excipients, figuring out the drug-to-excipient ratio, and streamlining the tablet production process were all part of the formulation process. To make sure the formed tablets complied with pharmacopeial requirements, a number of physicochemical characteristics, including weight fluctuation, hardness, friability, and drug content consistency, were assessed. Dissolution studies were also carried out to evaluate the medication release profile and guarantee that the tablets released Fimasartan quickly.

Conclusion:

The formulation and evaluation of immediate-release tablets of Fimasartan were successfully accomplished, resulting in a dosage form that meets the desired criteria for pharmaceutical quality. The tablets demonstrated acceptable physicochemical properties, including uniform drug content appropriate weight, hardness, and resistance to friability

Dissolution studies indicated that the tablets achieved the desired immediate-release characteristics, ensuring rapid drug release. This is crucial for Fimasartan, as it allows for the prompt onset of its antihypertensive effects upon administration.

Overall, the formulation and evaluation process yielded immediate-release tablets of Fimasartan that can be considered a viable option for the management of hypertension. These tablets offer convenience and efficacy

providing healthcare professionals with an effective therapeutic tool for the treatment of patients with hypertension. However, further studies, including stability testing and clinical trials, are necessary to confirm the long-term stability bioavailability, and clinical effectiveness of the formulated tablets before they can be introduced into the market and prescribed to patients.

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