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SOLUBILITY ENHANCEMENT OF CARVEDILOL BY USING FLUIDIZED BED PROCESSOR

Patil Pravin[1*], Asst. Prof. Sonawane Mitesh [2]

Department of Pharmaceutics

Loknete Dr. J.D. Pawar college of Pharmacy, Manur, Kalwan.

Abstract:

The beta-blocker carvedilol is non-selective. that inhibits alpha-1 receptors. For cardiac issues, carvedilol is an often-prescribed drug. Carvedilol is one BCS Class II medication that has a high permeability and poor water solubility. Enhancing the medication carvedilol's solubility and rate of dissolution is the main objective of this study in order to achieve the necessary pharmacological response and the intended drug concentration in the systemic circulation. Fluidized bed granulation is a new method that employs a several carriers, including PVP K30 and Tween 80 as a super disintegrant, to accomplish this For 30 minutes, the formulation F3 demonstrated improved solubility and a rate of dissolution of the medication carvedilol, releasing about 95.18%. Therefore, out of the nine formulations, it was chosen as the best one.

Keywords: *Carvedilol, Fluidized bed granulation technique, Solubility, Dissolution.*

INTRODUCTION:

When the drug is taken orally, it undergoes a series of steps that include dissolution and passage through the gastrointestinal barrier before entering the bloodstream. The solubility and dissolution of the medicine are two of the main elements that influence its bioavailability. One of the main issues with the majority of medications is their solubility in aqueous gastrointestinal fluid. Drugs with low water solubility make up at least 40% of newly discovered chemical entities examined, which causes variations in bioavailability. Dispersion that is solid is most preferred and successful approach among the several solubility enhancement techniques for improving the oral bioavailability, dissolving rate, and solubility of weakly water-soluble medications. The Dispersion of solids approach improves the rate of dissolution and solubility of weakly water-soluble medicines by decreasing their particle size and increasing their surface area. The primary goal of this study is to use a novel technique, fluidised bed granulation, to increase the solubility and rate of dissolution of the drug Carvedilol in order to attain the required pharmacological response and the intended level of medication in the bloodstream. Because of instability brought on by a high ratio of excipients to therapeutic ingredients, FBG was chosen for this investigation over the traditional granulation approach. The increased surface exposure of medications, excipients, moisture, and manufacturing equipment might lead to chemical instability. reduced potency due to a reduction in manufacturing. Differences in content homogeneity in low-dose medications can cause more problems than in high-dose medications.

Fluidized Bed Processor:

The tablet coating method was developed in 1953 by Dale Wurster, who used a heated air bed stream maintained in warm air to apply the coating solution on tablets. This method is sometimes referred to as the Wurster process. Dr. Dale Wurster continued the granulation of powders in 1960. Particulate material is coated, granulated, drug-layered, and dried during fluid bed processing.

Fluidized Bed Granulation:[1-7, 19, 30]

Agglomeration is another name for granulation. The pharmaceutical sector frequently uses the Granulator with fluidized bed (FBG), a very cost-effective and effective one-pot method, to achieve particle size expansion. Recently, the fluidized bed granulation technology was developed as a way to prepare solid dispersions utilizing the fluid bed granulation process. Because the fluidized bed granulation technique for solid dispersion eliminates several flaws and issues that arise in traditional multistep granulation and solid dispersion production methods, it has been gaining popularity as a manufacturing method. A fluid bed granulator allows us to carry out a number of unit activities, including granulation, drying, and preblending. The capsule shell is subsequently filled with

the granules produced during this procedure and tableting. This is crucial for scaling up. Fluidized bed granulation uses fewer production stages, which saves manufacturing time. The fluid bed granulation and drying process also minimizes raw material handling, which lowers operator exposure to irritants and poisons. The crucial process of fluidized bed granulation is where different granule properties are influenced by both process and product factors.

Principle:

A bed of solid particles is called a fluidized bed. or powdered material. The process known as fluidization occurs when hot air passes past an air distribution plate positioned at the bottom under high pressure, lifting particles from the plate and suspending them in the air stream. In Particles suspended in an air stream during the process of fluid bed granulation are sprayed onto a physical combination using a binding solution, dispersion, or suspension, such as a powder bed. Liquid bridges are created when these particles collide after being moistened by the binder solution.

The particles subsequently dry out, resulting in the production of granules.

Advantages:

- To increase compressibility for ongoing use and tableting.
- Suitable for both small and big operations and labor cost savings.
- Economical and time-efficient. Boost worker safety and housekeeping.

Disadvantages:

- Cleaning required a lot of work and time.
- Trying to increase in size from smaller to larger industrial units is frequently challenging due to the intricacy of fluidized bed behavior.

In this work, we will use novel techniques such fluidized bed granulation to accelerate and make more soluble of dissolution of several Carvedilol formulations. Additionally, we use the Granulation in a fluidized bed technology (FBP, or top spraying) to create the granules. and to investigate how the method affects carvedilol's dissolving efficiency. and other formulation-related characteristics by utilizing appropriate optimization methods for formulation creation and control measures. Lastly, we will contrast the commercially available version of Carvedilol with the optimized formulation.

MATERIALS: [13,14,15,26,21]

IPCA Pharmaceuticals supplied the carvedilol drug, along with Citric acid, Tween 80, PVP K30, colouring agent, lactose, magnesium stearate, and Silicon Dioxide.

Reformulation Study:[21,27,28]

a) **Organoleptic Characteristics:** Color, smell, and look
b) **Solubility:** Solubility in a range of solvents was noted.
c) **Melting point:** Ascertained by the application of Thiele's tube method.
d) **Ultraviolet visible (UV) spectroscopy** [21,27,28]

The measurement of the maximum absorption of wavelength (ʎ max)

Methanol stock solutions containing 100µg/ml of carvedilol were made. With a UV spectrophotometer, the UV spectrum was captured between 200 and 400 nm. λ max, the wavelength of maximum absorption, was found.

Making a standard stock solution of carvedilol (100µg/ml) in Methanol

An exact weighed 10 mg of carvedilol is dissolved in a little amount. Use a 100 ml volumetric flask to make a standard stock solution of methanol. A stock solution of 100µg/ml was then obtained by adding methanol to get the volume up to 100ml.

Carvedilol's standard calibration curve in HCL at pH 1.45

A 100 µg/ml concentration stock solution was made & dissolving 10 mg of precisely weighed carvedilol in 100 ml of methanol. Pipette out the stock solution of 10 ml into a 10 ml volumetric flask in aliquots 2, 4, 6, and 8. HCL pH 1.45 was used to bring the volume up to par. Carvedilol concentrations at this Dilution are 20, 40, 60, 80, and 100 µg/ml, respectively. Then, using a UV spectrophotometer, all solutions were scanned at a wavelength of up to 242 nm in comparison to the HCL pH 1.45 blank solution.

Method of Preparation:

Table No: 1 Formulation Code for each batch

Sr. No	Ingredients	F1	F2	F3	F4
1	Carvedilol	12.5 mg	12.5 mg	12.5 mg	12.5 mg
2	PVP K30	10 mg	10 mg	15 mg	15 mg
3	Tween 80	0.009 ml	0.014 ml	0.014 ml	0.009 ml
4	Mg. Stearate	2mg	2mg	2mg	2mg

5	Citric acid	1mg	1mg	1mg	1mg
6	Silicon dioxide	4mg	4mg	4mg	4mg
7	Lactose	Up to 200 mg	Up to 200 mg	Up to 200 mg	Up to 200 mg

Solid dispersion grains were made in a fluidized bed granulator using a top spray approach. Methanol was used to dissolve the polymer (PVP K30) and nonionic surfactant (Tween 80). Then, to achieve a homogeneous condition, slowly add the carvedilol powder to the solution and mix for five minutes. In the fluidized bed granulator, the resulting solution contained citric acid, lactose, and Silicon Dioxide. The spray rate was 1.50–2 rpm, the atomizing air pressure was 1.0–1.5 bar, the product temperature was 40–50ºC, the inlet temperature was 50–60ºC, and the fluidizing pressure was 1.0–1.5 bar. At the same time, the granules were dried and the fluidizing air passed. Granules were made in accordance with the quantity specified in the formulation table. A further drying procedure was conducted for 15 to 20 minutes after the granules formed in the fluidized bed granulator. In order to increase the lubricating power of the solid dispersion granules, magnesium stearate was added. The resulting powder was sieved before being formed into tablets.

Drug content: [21]

A glass mortar and pestle were used to grind five weighing tablets into powder. 12.5 mg of carefully metered powder in a 50 ml volumetric flask of carvedilol was dissolved in methanol, and the mixture was then filtered using Whatman filter paper. A solution with a known concentration of around 0.125 mg per milliliter was created by collecting the filtrate and appropriately diluting it with methanol to volume. The drug content was measured using a UV spectrophotometer at 240 nm, and it should be compared to that of a reference standard solution that was made in a similar manner.

Disintegration Time:

According to Indian pharmacopoeia, the pills' disintegration time was calculated. Tablet disintegration equipment was used for the test. At 37 ± 0.2 0C, 900 milliliters of distilled water were utilized as a disintegrating medium. It was observed how long it took for every pill to completely disintegrate.

***In vitro* Drug release:** [21]

To ascertain the in vitro drug release, the dissolution profile was calculated. The paddle was spun at 50 rpm using a USP II paddle device. A dissolving medium consisting of 900 milliliters of hydrochloric acid with the pH of 1.45 was employed. the dissolving medium's temperature was 37^{i}0.5°C. Up to 30 minutes, 5 ml samples were taken out at prearranged intervals and replaced with brand-new dissolving media. After being appropriately diluted, the samples' drug content was examined. UV spectroscopy was used to detect absorbance at 242 nm.

Comparative Study with Marketed Preparation

The formulation characteristics examined in this test include weight, color, weight, shape fluctuation, drug content, disintegration time, diameter, hardness, friability, and percentage CDR. Each of these elements will be contrasted with the commercially available formulation.

Saturation solubility:

Using the FBG Technique, a saturated solution of pure medication and its granules is prepared in a fixed amount of acidic buffer (pH 1.45). and a distilled water At room temperature, these combinations were agitated for twenty-four hours in a mechanical shaker.

To confirm that the mixture contained more particles, which would indicate saturation had been attained, a rigorous visual check was conducted. To ascertain the samples' saturation solubility, Each sample was filtered using 0.45 µm Whatman filter paper in aliquots, and the filtrate was then suitably diluted. Using the appropriate medium as a reference, the drug's solubility was assessed spectrophotometrically at 242 nm using a UV visible spectrometer.

Measurements of saturation solubility were carried out three times.

Stability studies: [29]

Stability testing aims to evaluate the impact of the Environmental factors like humidity, temperature, and light on the quality of drug ingredients or products over time. Essentially, it assesses a pharmaceutical product's ability to retain its microbiological, chemical, physical, & biopharmaceutical characteristics within certain bounds throughout its intended shelf life and under suggested conditions for storage.

RESULT AND DISCUSSION:

Pre-Formulation Study:

Drug Identification and characterization:

Organoleptic Properties

Carvedilol is a white powder that is odourless and crystalline. Therefore, it is established that the model medicine has good features because all of its attributes conform with I.P.

Melting point

Using the capillary technique, the melting point was found to be between 116 and 117^{0}C (observed value) and 114^{o}C and 115^{o}C (standard value). Carvedilol's melting point, for example, conforms with I.P.

Solubility

Carvedilol's solubility in several solvents was investigated, including water (insoluble), ethanol (sparingly soluble), chloroform (soluble), and methanol (freely soluble).

UV-Spectrum of Carvedilol

Carvedilol's λ max in methanol was determined by measuring its ultraviolet spectroscopic absorbance in methanol at the 242 nm λ max.

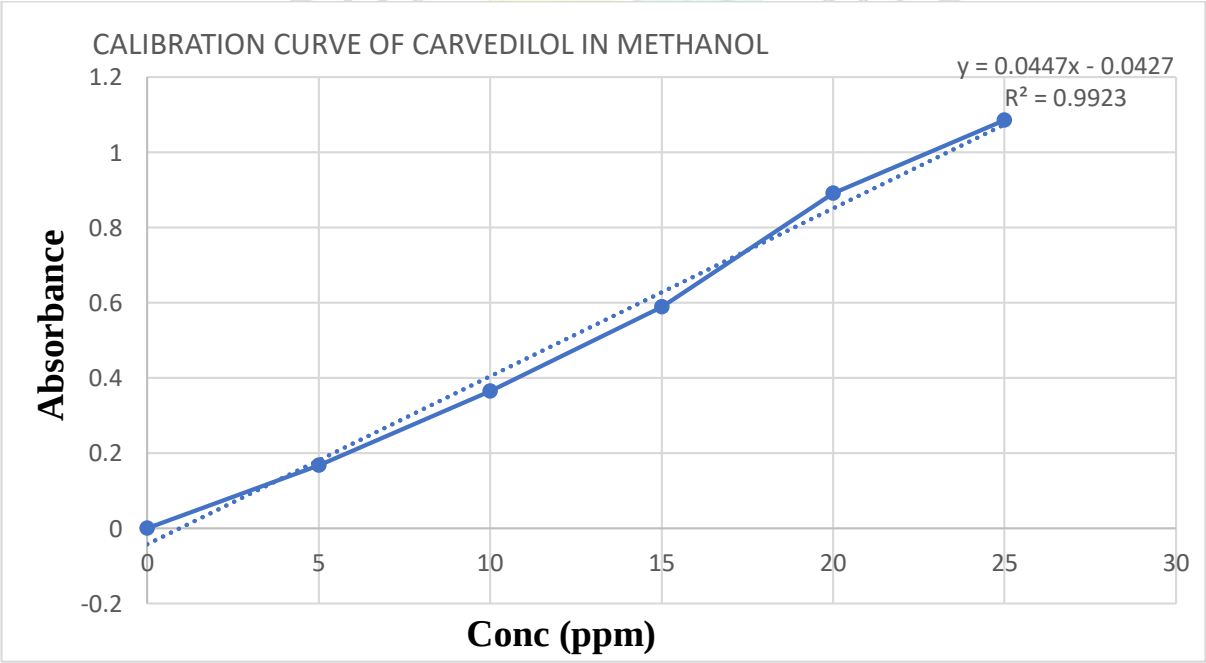


FIG NO: 1. STANDARD CALIBRATION CURVE OF CARVEDILOL IN METHANOL

The correlation coefficient was found to be 0.9923, and the regression line formula was discovered to be Y=0.0447X+0.0427. The medication complies with Beer's law in the concentration range of 2 to 20 µg/ml, as indicated by the calibration curve's straight line.

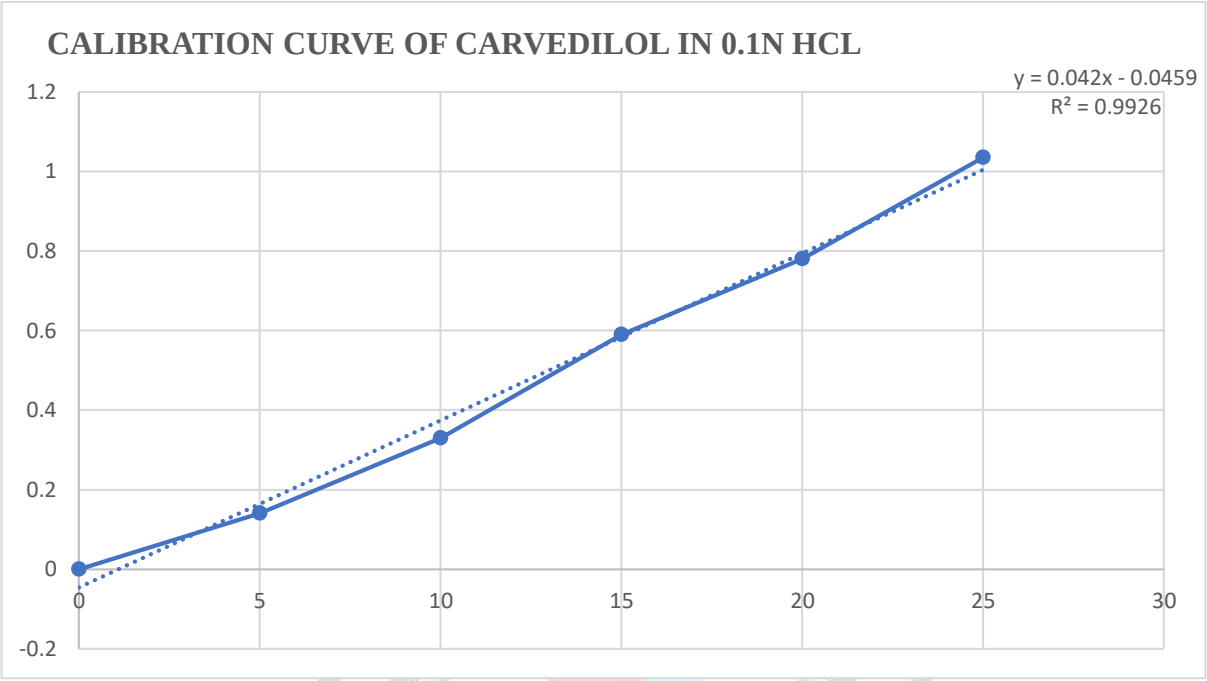
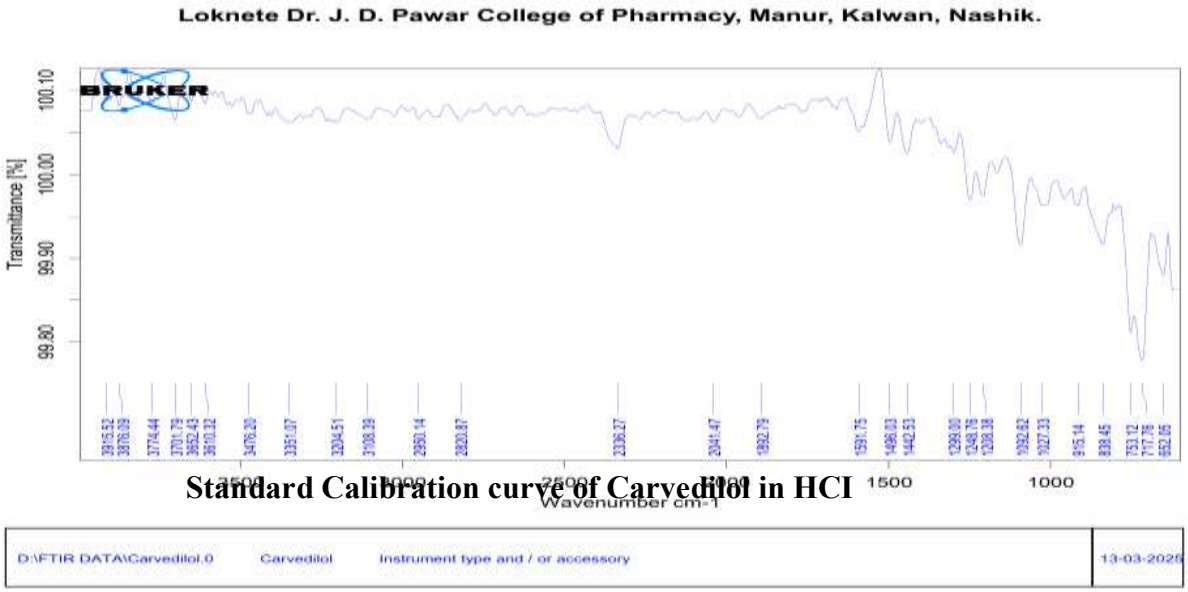


Fig No: 2. CALIBRATION CURVE OF CARVEDILOL IN 0.1N HCL

The equation of the regression line was obtained Y=0.042X-0.0459 and the correlation coefficient was obtained 0.9926.

Drug- excipient compatibility study:

FTIR (Fourier Transform Infrared Spectroscopy): The FTIR spectra of pure drug and pure drug + excipient was taken and shown in figure 3



Standard Calibration curve of Carvedilol in HCl

Figure No. 3: FTIR Spectrum of Pure Carvedilol

When comparing pure drug + excipient to pure drug, these spectra showed no discernible shift or alteration in the absorption peaks. It shows that there is no discernible interaction between the medication and the excipients.

Evaluation of Final Batches:

Table No: 2 Pre-compression evaluations of formulations

Sr. No	Formulation Code	Bulk Density (gm/mol)	Tapped Density (gm/mol)	Hausner's Ratio	Carr's Index (%)	Angle of Repose (º)
1	F1	0.48	0.602	1.25	20	26.29
2	F2	0.62	0.78	1.25	20.5	28.41
3	F3	0.345	0.399	1.15	13.53	24.21
4	F4	0.61	0.72	1.18	15.49	26.32

DISCUSSION:

The results demonstrated the powder combination's superior compressibility and powder flow. For every formulation, the bulk density, Carr's index, tapped density, Hausner's ratio, and angle of repose were all within the acceptable or good range.

Table No: 3. Post-compression evaluation of formulations

Sr. No	Formulation Code	Weight Variation (mg)	Diameter (mm)	Thickness (mm)	Friability (%)	Hardness (kg/cm^2)	D.T (min/sec)	Drug Content (%)
1	F1	198	8	3.61	0.81	4.35	2	89.76
2	F2	198	8	3.63	0.90	4.30	1.5	93.56
3	F3	199	8	3.68	0.95	4.37	1	98.7
4	F4	192	8	3.62	0.91	4.20	1.7	94.42

Discussion:

Disintegration, hardness, friability, thickness, diameter, and weight fluctuation time were all measured for each formulation and were all within the acceptable or good range.

DISSOLUTION STUDY OF FINAL BATCHES:

Table No: 4 In-vitro dissolution study of Different formulation

Time (min)	F1	F2	F3	F4
0	0	0	0	0
5	19.73 ± 1.0727	20.67 ± 1.2227	30.16 ± 0.1228	28.41 ± 0.3821
10	25.67 ± 0.1285	35.10 ± 0.0302	48.71 ± 0.1216	42.10 ± 1.4953
15	38.18 ± 1.1832	45.91 ± 0.8357	55.10 ± 0.2523	49.89 ± 1.0001
20	47.61 ± 0.5538	49.28 ± 0.1216	73.24 ± 1.1328	70.22 ± 1.2189
25	56.98 ± 0.5352	65.38 ± 0.4079	85.82 ± 0.1401	81.12 ± 1.9831
30	66.53 ± 1.2251	72.88 ± 0.5546	95.18 ± 0.2456	81.66 ± 1.2356

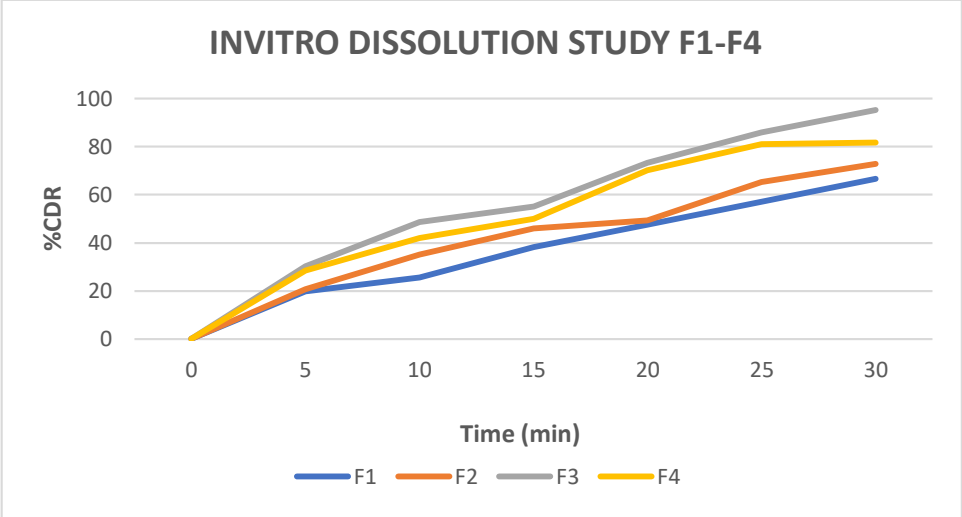


Fig No: 4. In-Vitro dissolution study of F1-F4 formulation

Formulation F3 displayed the most suitable medication release rate.

Table No: 5. In vitro dissolution studies of commercial formulations, optimized formulations, and pure medication (carvedilol) are compared.

Time (min)	PURE DRUG (P.D)	MARKETED PRODUCT (M.P)	OPTIMIZED PRODUCT (F3) (O.P)
0	0	0	0
5	8.22	50.24	35.19
10	9.79	59.46	48.74
15	12.55	69.14	65.12
20	16.07	80.17	78.27
25	20.63	88.86	85.92
30	27.3	94.94	95.21

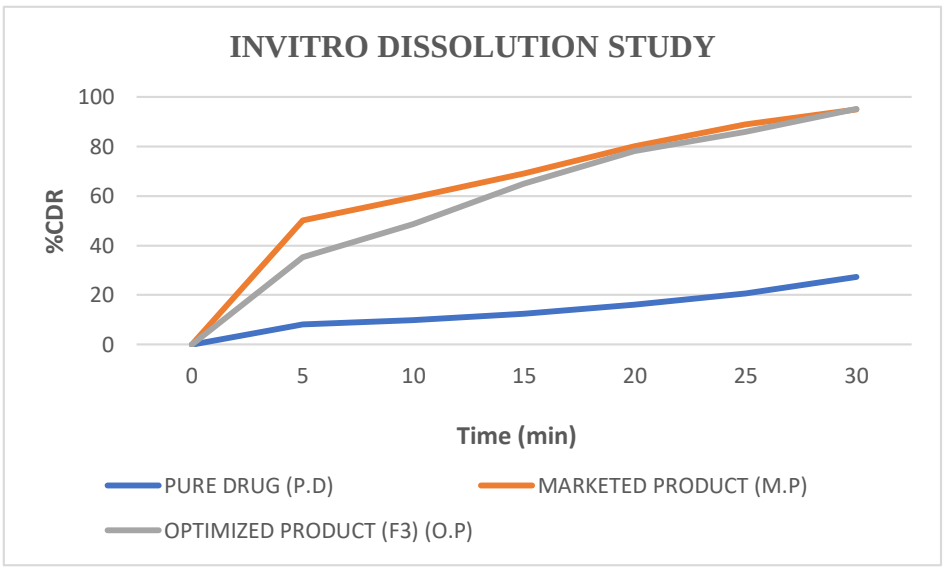


Fig No: 5. In-vitro dissolution study of Pure drug, marketed product, Optimized product formulations

Analysis of Data

When the influence of PVP K30 and Tween 80 on the percentage of drug release (Y1) was examined using a polynomial equation, it was discovered that these variables had a beneficial effect on drug release. The impact of these disintegrants on the release of carvedilol was visualized using a 3D reaction surface plot. As PVP K30 and Tween 80 concentrations were increased from 10 mg to 15 mg, the response curve for YI clearly increased drug release, indicating that greater concentrations of both excipients enhance the drug's release rate.

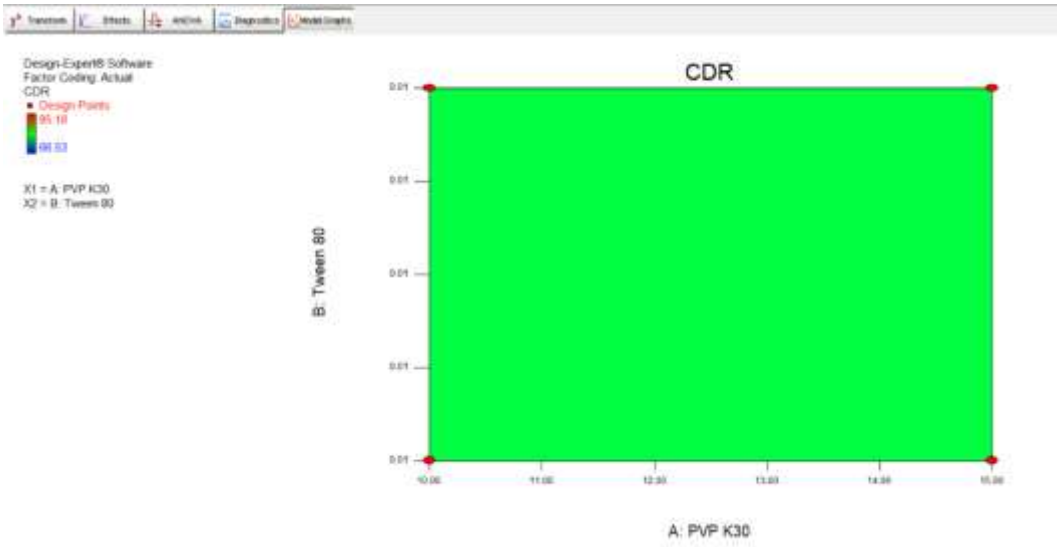


Fig No: 6. Contour plot of % drug release

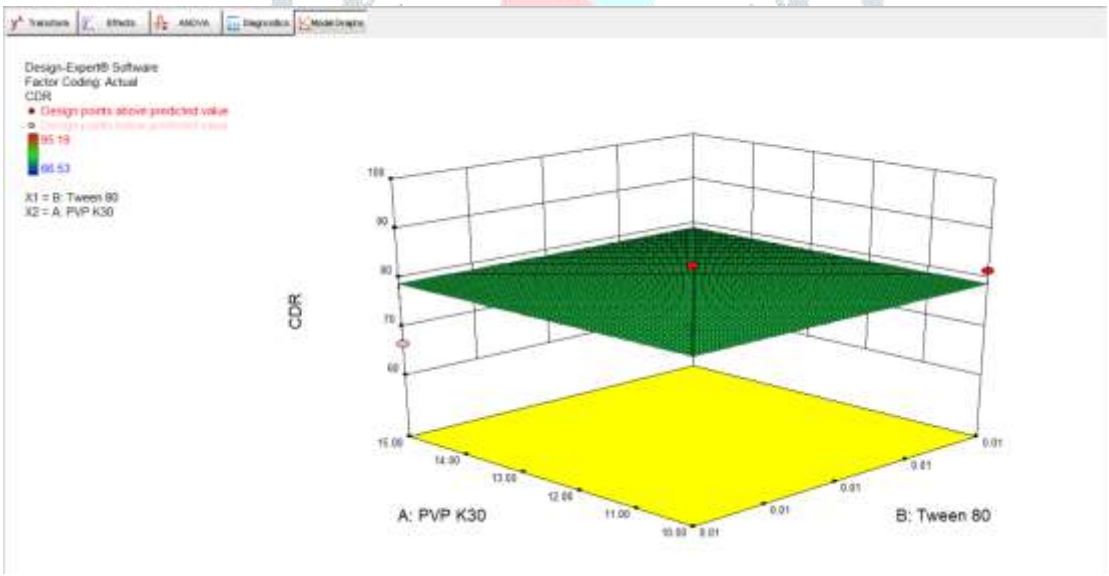


Fig. No: 7. 3D Response Surface Plot

A polynomial equation was used to evaluate the effect of independent variables on friability (Y2), and the results showed that Tween 80 and PVP K30 had a negative impact on friability. A 3D response surface plot showed that there was a noticeable decrease in friability when the quantities of these excipients rose from 10 mg to 15 mg. With a high drug release rate of 95.18% and low friability of 0.81%, the statistical model determined that the Four formulation nun was the most optimized, suggesting enhanced tablet strength and performance.

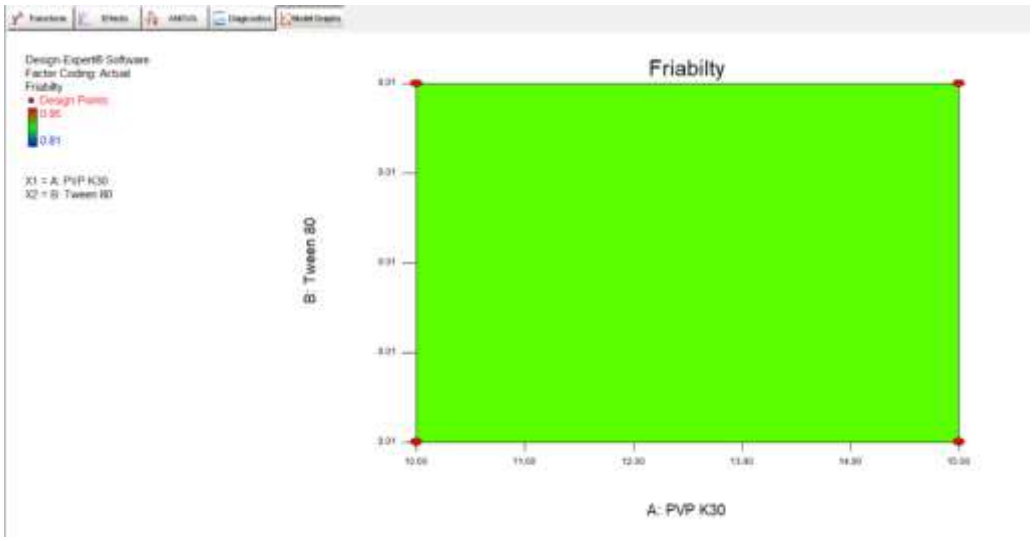


Fig No: 8. Contour Plot of Friability

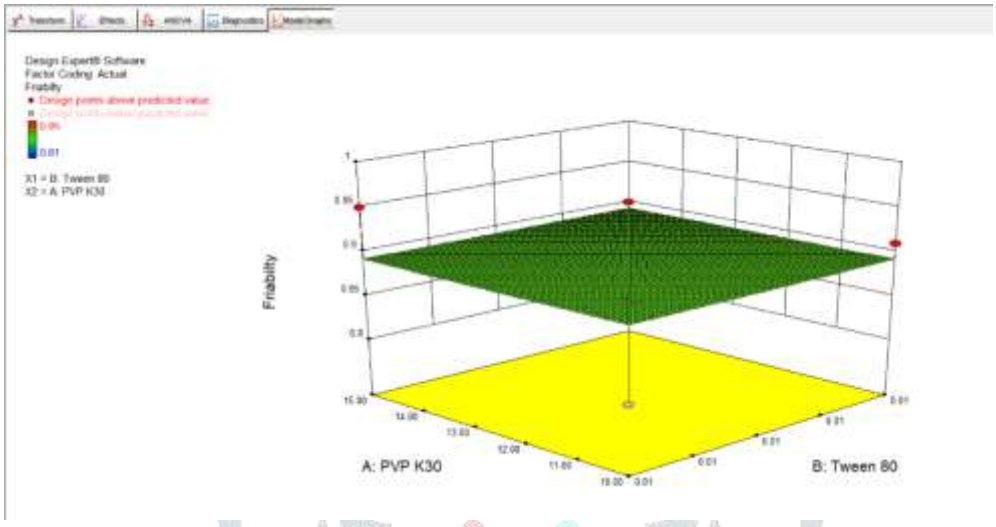


Fig No: 9. 3D Response Surface Plot

Saturation Solubility

investigation of the produced granules' and pure drug's saturation solubility in various physiological media. According to the solubility study's findings, carvedilol granules are far more soluble in all physiological media than the medication itself. It was discovered that the pure Carvedilol medication has a saturation solubility of 8.57 ug/ml in distilled water and 7.97 ug/ml in HCL pH 1.45 medium. Furthermore, Carvedilol granules were found to have a saturation solubility of 21.49 ug/ml in distilled water and 130 ug/ml in HCL pH 1.45 medium.

Comparative Study (Marketed preparation)

Stability Study

The colour did not physically alter. In contrast to the original samples of the optimized batch, There is no discernible change in the drug content, weight variation, percentage CDR, or friability of the tablets. After two months, this formulation remained constant.

Table No: 6. Comparative study of optimized formulation with marketed formulation

Test	Marketed formulation	Optimized formulation
Weight	200mg	200mg
Color	Yellow	White
Shape	Rounded	Rounded
Friability	0.70%	0.95%
Weight variation	199mg	199mg
Hardness	5.012 kg/cm^2	4.37kg/cm^2
Diameter	8mm	8mm
Drug content	99.69%	98.70%
Disintegration time	51.20 sec	1min / (60 sec)
% CDR	94.92%	95.18%

CONCLUSION

This work demonstrates that the Fluidized Bed Granulation method, which employs a range of hydrophobic and hydrophilic polymer for in-vitro studies of tablets containing carvedilol, is appropriate for improving the drug's solubility and rate of dissolution. various polymers, such as Tween 80 and PVP K30. The FBG approach appears to be the greatest option for producing solid dosage forms in large quantities, as evidenced by the granules' high flowability and other characteristics. For 30 minutes, the formulation F3 demonstrated improved carvedilol drug solubility and dissolution rate, releasing around 95.18% of the medication. Therefore, out of the nine formulations, it was chosen as the best one.

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