APPLICATION OF CENTRAL COMPOSITE DESIGN IN THE DEVELOPMENT AND OPTIMIZATION OF SOLID DISPERSIONS SYSTEM FOR ENHANCED SOLUBILITY OF CARVEDILOL

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Abstract:

Objective:- Carvedilol drug, is poorly water-soluble and show low has oral bioavailability. Solubility enhanced of low water soluble drug enhanced by solid dispersion method.

Method:-Design expert-11 software used to enhance the solubility of poorly water soluble drug carvedilol by solid dispersion techniques. Using central composite designs(CCD) to study the effect of independent variables on solid dispersion of carvedilol and Nine formulations prepared by solvent evaporation and fusion method using different natural and synthetic polymers Hydroxy-propyl methylcellulose (HPMC), Locust bean Gum(LBG) , PEG 6000 (polyethylene glycolate) 6000 and sodium starch glycolate . Prepared formulation evaluation check by solubility, stability, Percentage yields, dissolution rate studies and characterized by Scanning electron microscopy (SEM), Powdered X-ray Diffractometry (PXRD), Differential Scanning Calorimetry (DSC) and Fourier Transform Infra-red (FTIR).

Result:-Based on physicochemical evaluation and *in-vitro* characterization, the solid dispersion drug content, percentage yield and drug release was found to be 94.06%, 66.532%, 93.20%

respectively and follows Peppas model. In FTIR studies Shifting of peaks confirmed the interaction of polymers with the pure drugs .SEM results show that the prepared agglomerates were spherical in shape, which enabled them to flow very easily. The PXRD, SEM and DSC indicated a change in the crystalline state of Carvedilol..

Conclusion:-Based on evaluation, in-vitro characterization drug content, Drug percentage yield, drug release was maximized because of the increase in the amount of hydrophobic polymer maximize drug release and increased polymers concentration to produce reproducible results. This study indicated that the solubility of carvedilol was increased by solvent evaporation and fusion method.

Keywords-Carvedilol, drug release, Solubility, locust bean gum,polymers

Introduction:

Low water solubility combined with sluggish medication absorption results in insufficient and unpredictable bioavailability as well as toxicity to the gastrointestinal mucosa. The pace and extent of medication absorption are typically determined by the rate and extent of active component dissolution from any dose form. When an active substance is administered orally, it must first dissolve in the stomach and/or intestines before it can pass through the GI tract's membranes and enter the bloodstream[1,2]. Carvedilol is widely used in clinics, however it has a poor oral bioavailability (between 25% and 35%) and is subject to first-pass metabolism (26). As a result, a medicine with low water solubility would usually display restricted absorption due to dissolving rate, and a drug with poor membrane permeability will usually exhibit limited absorption due to penetration rate. Hence, boosting the solubility and rate of dissolution of poorly water-soluble medications and improving the permeability of weakly permeable pharmaceuticals are two areas of attention for improving oral bioavailability of active agents[3,4].

Aqueous solubility, drug permeability, dissolving rate, first-pass metabolism, pre-systemic metabolism, and sensitivity to efflux mechanisms are some of the variables that affect oral bioavailability. The preferred method of taking the dose form is orally. Bioavailability is the main issue encountered while administering medication orally. For researchers and pharmaceutical professionals, improving the solubility of diverse weakly soluble substances is a difficult challenge. The solubility parameter is utilised to get the required drug concentration in systemic circulation for pharmacological response. [3-5]

A poorly water soluble medicine is one that takes longer to dissolve in gastrointestinal fluid than it does to be absorbed in the gastrointestinal system, according to a more modern definition.

Low water solubility drugs have slow dissolving rates, which causes oral bioavailability issues. Each dosage form, or medicine, has the inherent quality of solubility. [4-6] properties of drug products, in which the nature or properties of active compounds can be enhanced by external modification, i.e., by size reduction, the effective surface area of the active component will be increased, allowing for greater contact with intestinal fluids and improved drug absorption. [4-6] Internal modification, or the combination of weakly soluble chemicals with

water-soluble carriers, may further increase solubility. [4,5,7]. As a result, laboratory research are the only application for the manufacture of Solid dispersion using solvent techniques. Although at a wider scale it was unable to avoid greater preparation costs, environmental concerns, and solvent residuals in the final product [28]. All medication delivery methods strive to make their medicine more soluble. Particle size reduction, solid dispersion, nano suspension, supercritical fluid technology, cryogenic technology, inclusion complex creation techniques, floatation granules, etc. are some conventional and cutting-edge methods for enhancing solubility. [4-6]

Generally speaking, "a hydrophobic medication and a hydrophilic carrier" make up a solid dispersion, which is a collection of solid products made up of at least two separate components. The carrier might have either an amorphous or crystalline shape. [4, 5,8]

From a pharmaceutical perspective, the solid dispersion approach is particularly beneficial due to its ability to employ the solid dispersion method to resolve solubility issues. [5, 9]. Many medications with limited water solubility, including nimesulide, ketoprofen, tenoxicam, nifedipine, and nimodipine, have been processed using the solid dispersion method. Several hydrophilic carriers, including PEG 6000, PVP, HPMC, gums, sugars, and mannitol, have been employed to increase the solubility and dissolving properties of medications that dissolve poorly in water. There are several ways to make solid dispersions, including melting, solvent evaporation, melting, spray drying, supercritical fluid techniques, etc.[4, 3, 9]. The current study's objective is to increase the drug's solubility via the use of solid dispersion technology.

MATERIALS AND METHODS

Materials:-

Carvedilol was received as a free sample from Hyderabad, India's Aurbindo Pharma Pvt Ltd. Methanol, HPMC, Locust BeanGum, PEG 6000, Sodium Starch Glycolate, and Molecular Weight(MW = 204.23 g/mol)[29] were acquired from Himedia Laboratories. Other compounds were all of the analytical kind.

Drug Excipient compatibility research for drugs:

Using Central Composite Design for Optimization

The correlation between the analysed answers and the selected variables was calculated using the Design Expert Program, version 11.0 (Stat-Ease, Inc. Minneapolis, MN, USA). Drug release % and drug content were chosen as the response variables for methodical optimization. Findinga viable space and doing an extensive grid search to find the potential answer led to the discovery of an optimised formulation. The overlay plots were used by the programme to provide an optimal solution. All of the in vitro investigations used the optimised formulations. [19- 21]. Since the core composite design needs five levels of each factor—-1, 0, 1, and +—it was chosen for optimization. The replies were assessed using an interactive and polynomial statistical model.

$$Y = b0 + b1\ X\ b2\ X\ b12\ X\ b22\ X$$

The desired response was statistically analysed using one-way ANOVA (analysis of variance) at a 5% level of significance, and the relevance of model elements was assessed using Design-Expert 11.0. In the equation above, b0 stands for the intercept, which represents the arithmetic averages of all 13 runs, and b1, b2, b12, b11, and b22 are the coefficients, which were calculated from the observed experimental values of the responses Y1 and Y2 and X1 and X2, which represent the main responses of independent variables. Interactions and quadratic terms of independent variables are represented, respectively, by the terms X1, X2, X11, and X2. [19–21].

Table:1 Shows Using design expert software Formulation design of carvedilol drug and polymers

Sr. No	**Carvedilol (mg)**	**HP MC (mg)**	**SS G (mg)**	**LBG (mg)**	**PEG 6000 (mg)**
1	100	200	200	100	50
2	100	200	200	100	100
3	100	200	200	100	150
4	100	200	200	200	50
5	100	200	200	200	100
6	100	200	200	200	150
7	100	200	200	300	50
8	100	200	200	300	100
9	100	200	200	300	150

*** HPMC-**Hydroxy propyl methyl cellulose
* **PEG**-Polyethylene glycolate
*** LBG-**Locust bean Gum
*** SSG-**Sodium starch glycolate

Fourier Transform Infrared Spectroscopy

Using a Shimadzu FTIR-8400S spectrometer, fourier transform infrared spectra were produced. Potassium bromide was extensively pulverised and combined with samples of carvedilol, gelucire 50/13, physical mixes, and solid dispersions at a sample-to-KBr ratio of 1:5. The powders were compressed in a hydraulic press for 5 minutes at a pressure of 5 T to create the KBr discs. The resolution was 4 cm, and the scanning range was 40 to 4000 cm-1. [21, 22] at a sample to KBr ratio of 1:5. The powders were compressed in a hydraulic press at a pressure of 5 T for 5 min to create the KBr discs. The resolution was 4 cm, and the scanning range was 40 to 4000 cm-1. [21, 22]

Calorimetric Differential Scanning

It is a thermo analytical method for determining the temperature and heat flow connected with a material transition as a function of temperature and time. [20, 21, 23, 24] SEM allowed access to the agglomerates' surface morphology. Prior to scanning, the crystals received a gold sputter coating. After a random scan of the samples, microphotographs were made using various magnifications; a greater magnification was employed to capture surface morphology. During scanning, the accelerator voltage was set at 30.0 KV. [20,21,19]

X-Ray Diffractometry of Powder:

To identify material with a long range order qualitatively, employ powder X-ray diffraction. More crystalline material is indicated by sharper diffraction peaks. Modern X-ray technology is semi-quantitative (Dhirendra K et al. 2009). The United States' Philips PW 1729 X-ray generator, equipped with a copper target, a voltage of 40 kV, and a current of 30 ma, was used to record the X-ray diffraction patterns. The scanning speed was 1°/min, and the range was 1 to 50°. Carvedilol, physical mixes, and solid dispersions all had their PXRD patterns drawn. The materials were put into the aluminium sample container after being gently pulverised. [18–22]

Electron microscopy for scanning (SEM)

The technique of manufacture and chemical composition may be used to determine the distinctive qualities of drug crystals, such as particle size and morphological surface. Moreover, a set of parameters collected automatically by attaching the SEM to an image processor may be used to describe the form and granulometric characteristics of the powder particle shapes. [18,19]

Release Kinetics of Drugs

Mathematical models including the Zero-order, First-order, and Higuchi models were utilised to characterise the kinetics of the drug release from the matrix. The goodness-of-fit test was used as the foundation for choosing the most suited model. [24-26]

Drug Release Investigations in Vitro

The USP XXIII paddle (Apparatus 2) was used in the in-vitro dissolution investigations on the pure drug (12.5mg), physical mixes, and soliddispersion formulations of carvedilol. The dissolving medium used was 900 mL of 0.1 N HCL at 100 rpm and 370.5 C. At regular intervals, an aliquot sample (10 mL) was taken out and

replaced with an equal volume of dissolving media. Using a double beam UV-visible spectrophotometer, the samples were examined at 241.2 nm on the spectrophotometer. [19–21]

Release Mechanism for Drugs:

To represent the kinetics of the drug release process from dosage forms, many mathematical models may be used. The solution that best matches the outcomes of the experiment is the most suitable. The formulas were chosen by choosing the zero order, first order, Higuchi, and Korsmeyer-Peppas plots that best matched the release data. [24- 26]

Release Model with Zero Order

Q.o. = Q.o.

t is the time, Ko is the zero-order rate constant represented in units of concentration/time, Q is the quantity of drug present at time t, and Qo is the starting amount of drug. If the release complies with zero-order release kinetics, the percentage of drug released vs time will be shown linearly.

The best technique to enhance the therapeutic impact and reduce pharmacological adverse effects is via zero-order drug release. (13,14) The drug concentration-time profile is flat because the drug is released from the carrier at a constant rate.

First-Order Release Kinetics Model

Log Q equals Log Qo / 2.303.

Where Q is the drug's release quantity at time t, Q is the drug's beginning amount, and k1 is the first order constant. If the release follows first order release kinetics, a plot of the logarithm of the proportion of drug left over vs time will be linear.

Square-root Higuchi model

Q = K.t1/2

Where K is a constant representing the system's design factors and Q is the quantity of medication delivered at time t. If the release follows the Higuchi equation, a plot of the percentage of drug released versus the square root of time will be linear. According to this equation, drug release is a diffusion process that depends on square root time and is based on Fick's rule.

Peppas Model: Mt/M infinite with Korsmeyer Ktn

K stands for the rate constant, n for the release exponent, and Mt/M infinite for the percentage of the medication released at time t.Different release methods are characterised using the n value.If the release follows the Peppas and Korsemeyer equation, a plot of logof Mt/Ma versus log time will be linear, and the slope of this plot will give the "n" number.

To investigate the impact of independent factors on the carvedilol solid dispersion, central composite designs

(CCD) were used in the formulation of the carvedilol solid dispersion. Formulations for solid dispersion vary according to the procedures.

Design expert software-11 is used to optimise the effects of carvedilol. Two independent components, X1 (locust bean gum) and X2 (Peg 6000), are used in optimization. The range of the optimised batch's yield percentage is 66.5328. The percentage yield is increased when locust bean gum and peg 6000 are combined. Drug release diminishes as locust bean concentration rises. Drug release rises with a higher peg 6000 concentration. 90.2833 is the optimal medication release value. The interaction of the polymers enhances the drug content. The range that is optimal is 94.0643. The solvent evaporation method's maximal drug release in the in vitro drug release trial was 93.46, compared to the fusion method's 93.20. The R2value in the solvent evaporation approach is 0.9686, while in the fusion method is 0.9878. Both models adhere to the Peppas model, and the drug release in both cases is 93.20. Finally, scanning electron microscopy data and the optimised batch X-ray diffraction value 2 indicate that the generated agglomerates were spherical in form, allowing for extremely easy flow.

Result and Discussion:-

Fourier Transform Infrared Spectrophotometer (FTIR) Studies

The FTIR spectra of the medication and formulations were obtained using an FTIR spectrophotometer and the potassium bromide disc method. By using infrared spectroscopy, the drug was detected, and the distinctive peak was compared in figures to benchmark spectra of pure drug, physical mixture, and formulation. The IR spectra of the pure drug displayed characteristic peaks at 3340.11 cm-1 (N-H stretching), 2978.17 cm-1 (C-H stretching), 1399.84 (aromatic plan bending), 1647.61 cm-1 (methylenecyclohexane), 1713.12 cm-1 (C=O), 1598.26 cm-1 (C=C), 2992.39 cm-1 (CH), 1058.18 cm-1 (sulfoxides), and 1411. Nevertheless, distinct peaks at 2973.20 (C-H), 1054.07 (sulfoxides), and 1267.15 (formulation) are seen (aromatic plane bending). The shifting of peaks proved that polymers and the pure drug interacted.

FTIR spectra of carvedilol:-

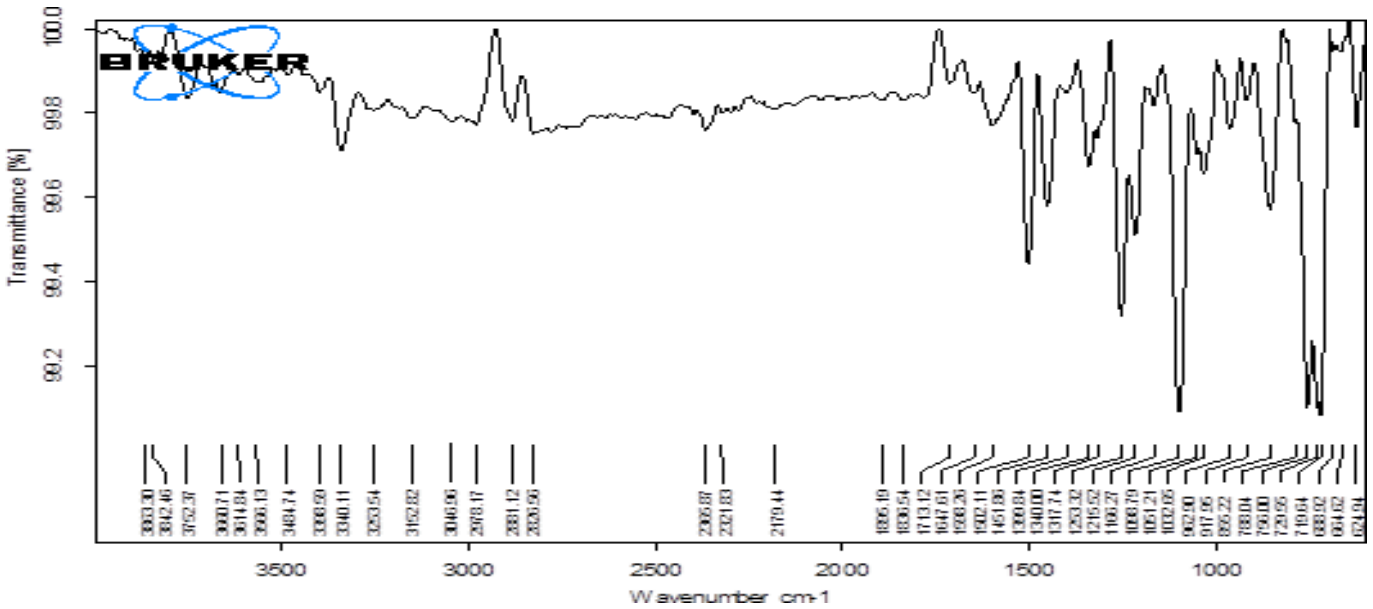
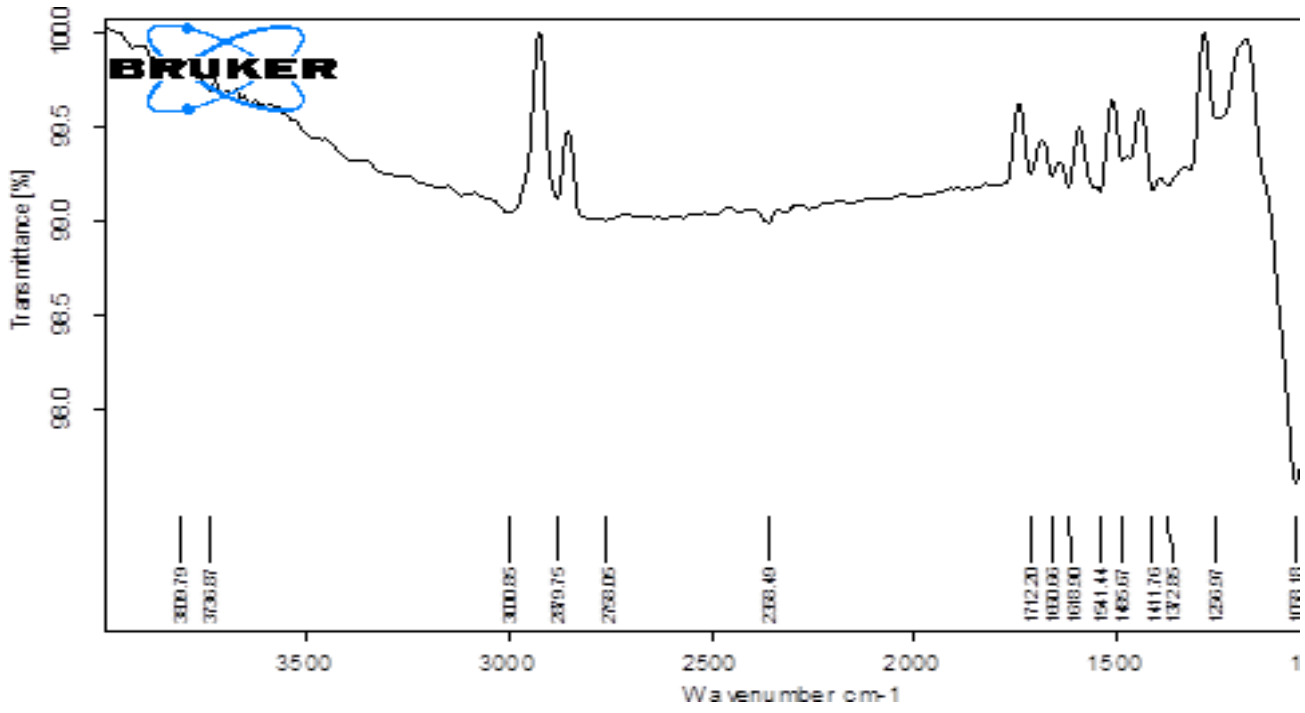


Figure 1-FTIR spectra of optimized batch(F7) in fusion method of carvedilol



Physiochemical properties:-

Flow properties of solid dispersion method:-

Angle of repose

Angle of Repose determined by using funnel method. The values were found to be within the range from 23.61±0.015 to 27.91±1.002. This indicated that powder blend having good flow property.

Angle of repose : tan-1(2h/d)

Bulk density and tapped density values

The range of formulation was found to be 0.240±0.020 to 0.850±0.010 and 0.320±0.010 to 0.610±0.01 respectively.

Hauser's ratio values and Carr's index

The range of formulation were found to be 1.06±0.02 to 1.33 ±0.045 and 12.09±0.51-27.1±0.01.It shows that powder blend having good flow property.

Formulation code	Angle of repose (± SD)	Bulk Density (gm/ml)(± SD)	Tapped Density (gm/ml)(± SD)	Carr's Index(%)(± SD)	Hausner's Ratio(± SD)
SE 1	25.89 ± 0.06	0.53 ±0.01	0.57 ±0.01	13.49 ± 0.03	1.15 ±0.14
SE 2	26.02 ± 0.04	0.76 ±0.02	0.60 ± 0.01	14.96 ± 0.05	1.13 ±0.02
SE 3	26.14 ± 0.03	0.85 ± 0.01	0.59 ± 0.01	16.24 ± 0.05	1.06 ± 0.02
SE 4	25.54 ± 0.04	0.73 ±0.01	0.57 ±0.02	13.49 ± 0.14	1.09 ± 0.05
SE 5	26.07 ± 0.02	0.39 ±0.05	0.61 ±0.01	18.60 ± 0.13	1.09 ± 0.05
SE 6	26.23 ± 0.06	0.43 ±0.01	0.57 ±0.01	13.45 ± 0.05	1.11 ± 0.03
SE 7	27.24 ±0.05	0.68 ± 0.01	0.58 ±0.02	14.15 ± 0.08	1.14 ± 0.05
SE 8	26.45 ± 0.10	0.38 ±0.015	0.59 ±0.02	16.61 ± 0.09	1.13 ± 0.03
SE 9	26.54 ± 0.10	0.52 ±0.01	0.60 ±0.01	17.31± 0.03	1.07 ± 0.01

- SE-Solvent evaporation
- SD-Solid dispersion

(± SD)-Solid dispersion values are expressed in mean(± SD, n=3)

Table 2:-Powder Characteristics of different batches of formulation in solvent evaporation technique method

Table3: Powder Characteristics of Different Batches of Formulations (FM1-FM9)

Formulation code	Angle of Repose(± SD)	Bulk Density (gm/ml)(± SD)	Tapped Density (gm/ml)(± SD)	Carr's Index(%)(± SD)	Hausner's Ratio(± SD)
FM 1	27.07 ±0.01	0.327 ±0.03	0.389 ±0.04	15.21 ±0.07	1.09 ±0.04
FM 2	25.71 ±0.06	0.26 ±0.01	0.336 ±0.01	15.27 ±0.01	1.15 ±0.01
FM 3	26.16 ±0.04	0.312 ±0.02	0.356 ±0.01	16.31 ±0.05	1.18 ±0.04
FM 4	25.53 ±0.30	0.394 ±0.002	0.449 ±0.002	12.09 ±0.51	1.175 ±0.007
FM 5	24.52 ±0.3	0.389 ±0.002	0.455 ±0.002	14.74 ±0.53	1.170 ±0.012
FM 6	25.1 ±1.001	0.24 ±0.01	0.320 ±0.01	24.98 ±2.79	1.33 ±0.045
FM 7	27.1 ±1.002	0.25 ±0.01	0.32 ±0.01	27.1 ±1.002	1.27 ±0.015
FM 8	27.36 ±0.015	0.445 ±0.001	0.529 ±0.002	16.00 ±0.02	1.17 ±0.015
FM 9	27.91 ±0.025	0.456 ±0.002	0.539 ±0.001	15.40 ±0.02	1.18 ±0.015

*FM-Fusion method

*SD-Solid dispersion

Percentage Yield:-

Percentage yields represent the percentage difference between theoretical and actual yield. It is computed as the predicted yield multiplied by 100% divided by the experimental yield. whether the yield is the same in theory and practise. 100% of the percentage was yielded. Since the actual yield is often lower than the theoretical value, percentages are typically lower than 100%.

Table 4:-Percentage Yield of Solid Dispersions

Sr. No	Method	Range
1	Solvent evaporation method	53.60-75.23
2	Fusion method	60.40-72.21

The following table demonstrates that, as compared to the fusion process, the formulation yield from the solvent evaporation method was at its highest percentage (%).

Formula For percentage yield:-

$$\% \text{ Percentage Yield} = \frac{\text{Actual yield X100}}{\text{Theoretical yield}}$$

Table 5 :- Comparative % Yield of Solvent Evaporation and Fusion Method

Formulation Code	%Yield (Solvent Evaporation Method)	Formulation Code	% Yield (Fusion Method)
SD 1	72.42	FM1	72.15
SD 2	67.24	FM2	69.28
SD 3	70.22	FM3	67.33
SD 4	64.74	FM4	60.40
SD 5	64.01	FM5	66.12
SD 6	69.33	FM6	64.35
SD 7	66.76	FM7	65.76
SD 8	71.93	FM8	67.11
SD 9	65.54	FM9	72.21

Figure 2:-Percentage Yield of the Formulation SD1-SD9 for Solvent evaporation methodand FM1-FM9 for fusion method.

***SD1-SD9=Solvent evaporation sample numbering 1 to 9**

***FM1-FM9=Fusion method sample numbering 1 to 9**

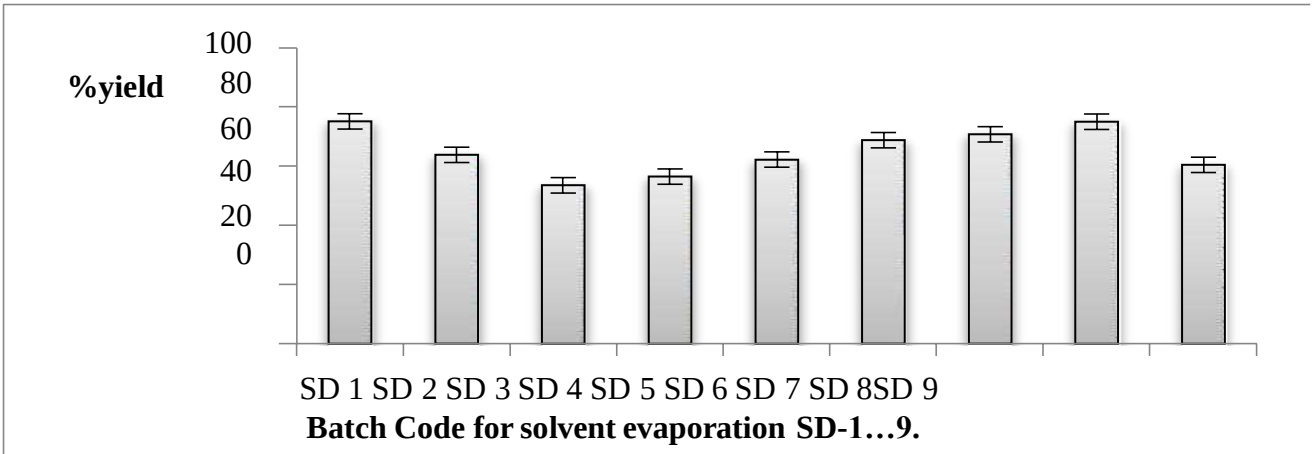
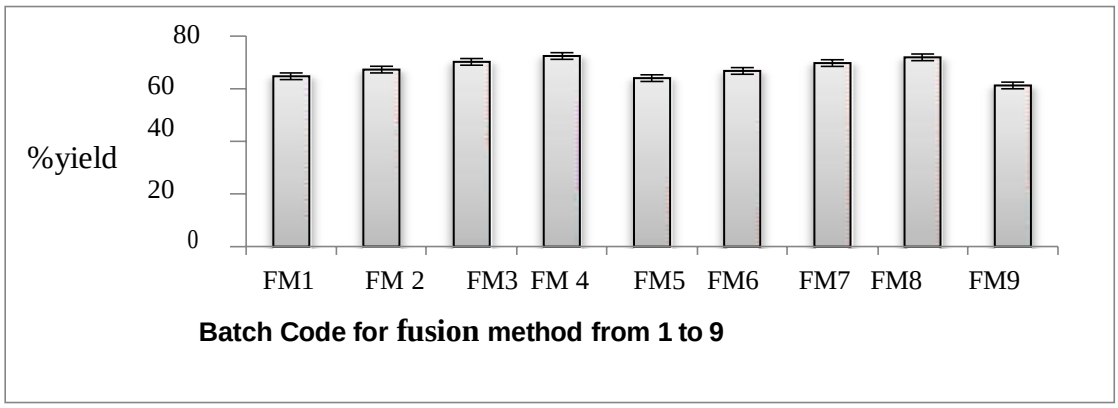


Fig:- PercentageYield of the Formulation FM1-FM9 for fusion method



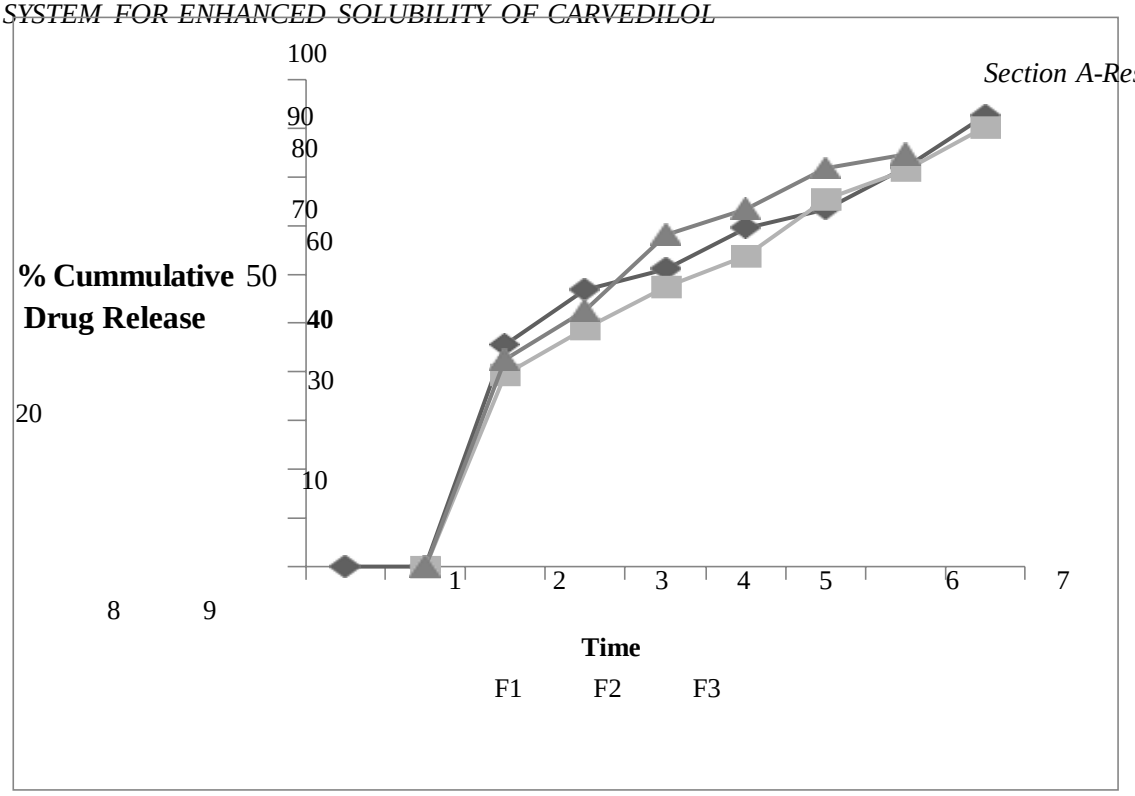
Dissolution study:

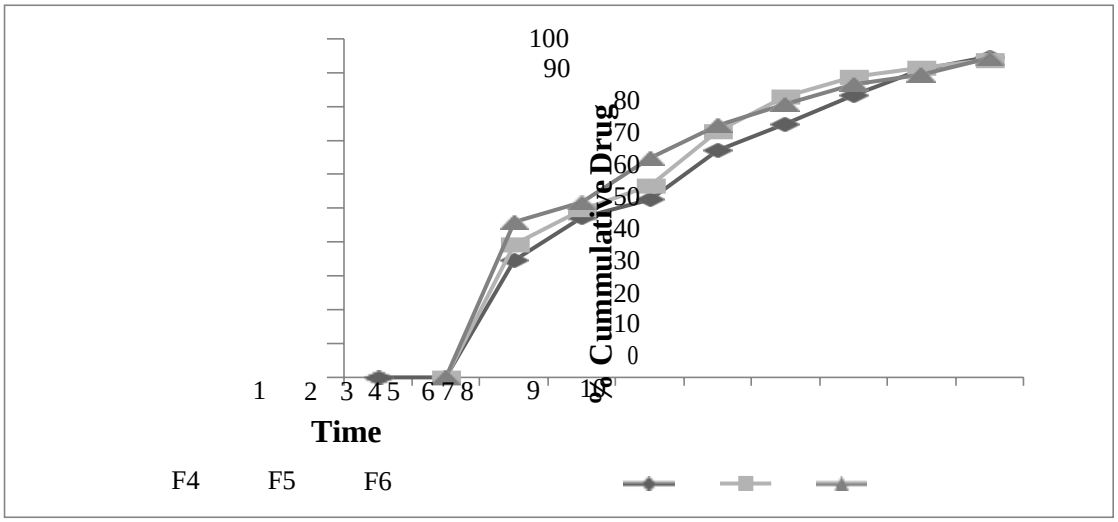
The findings for drug release were plotted as % cumulative drug release against time in hours for all the generated carvedilol solid dispersions utilising a paddle device and 6.8 phosphate buffer solution. The release data (0-90 minutes) were fitted to several kinetics models in order to explore the mechanism of drug release in solid dispersion: zero

The picture displays the in-vitro dissolution profiles of pure medicines, polymers, and their corresponding mixes in distilled water for 90 minutes. By the conclusion of the 90 minutes, there was a discharge of 62.47%, 71.28%, 72.38%, 80.62%, 80.31%, 86.06%, 88.66%, and 93.46%. Pure medication sample releases carvingilol. The solubility of the carvedilol was enhanced in every sample of the combination.

Cumulative percentage release (%)=Volume of sample withdrawn(ml)/bath volume(v)xP(t-1)+Pt

Where Pt=Percentage release at time t





On x-axis is time and on y-axis is percentage(%) cumulative drug release for fusion method formulation F1 to F6.

Kinetics Models of Drug Release

Various kinetics models were applied onmodels, first order, Higuchi Model, and KorshmeyerPeppasmodels.

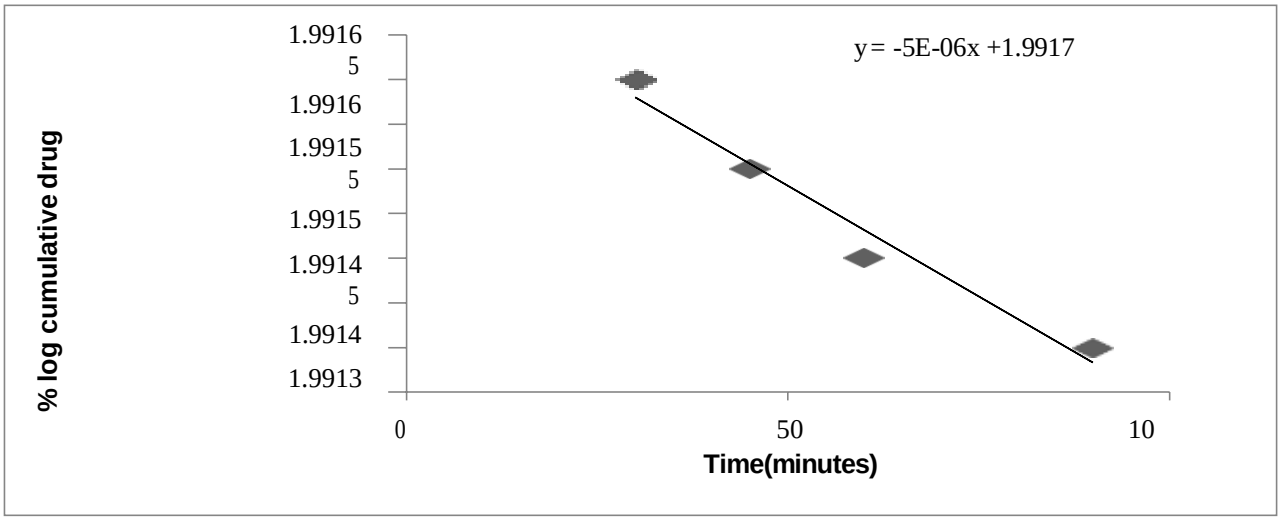


Figure 3:-Zero order plot & First Order Plot having regression coefficients (R^2) of 0.9983 & 0.9757.On x-axis taken time and on y-axis is percentage cumulative drug release

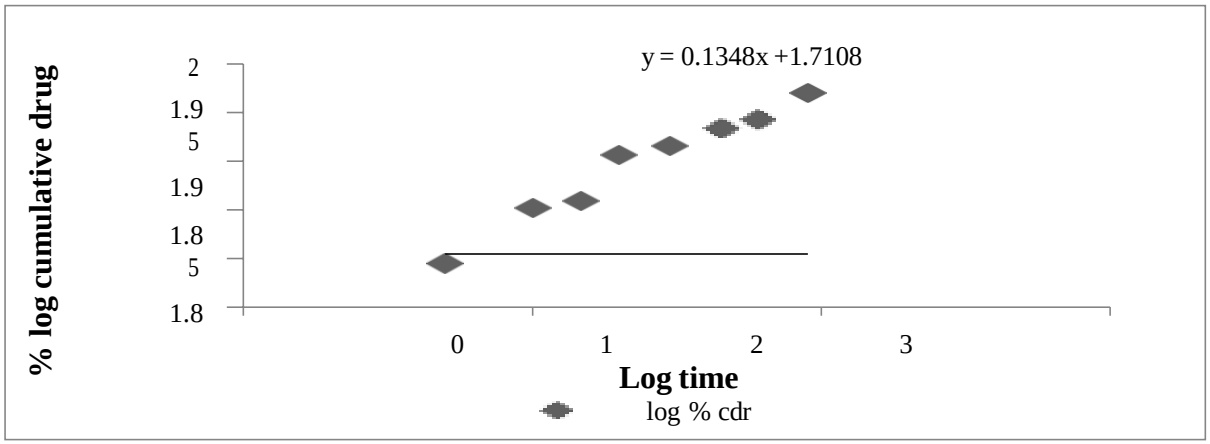
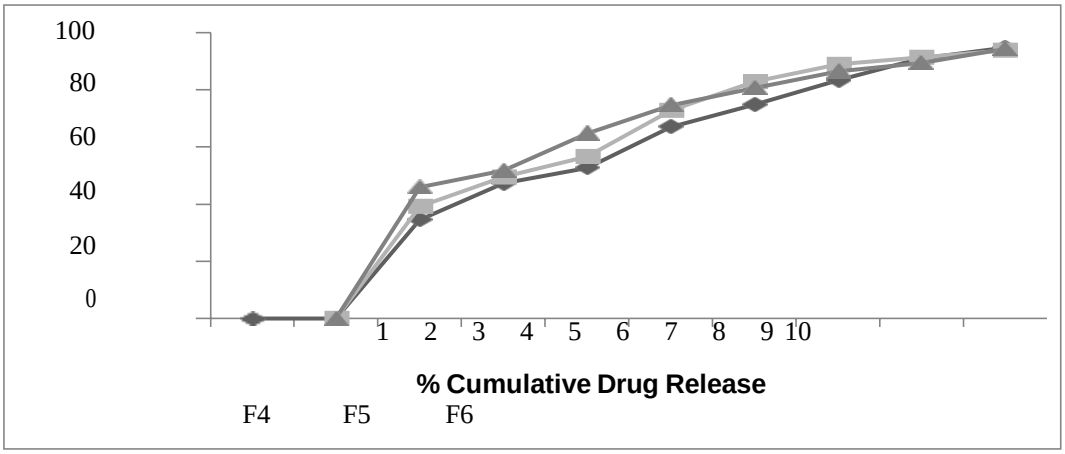


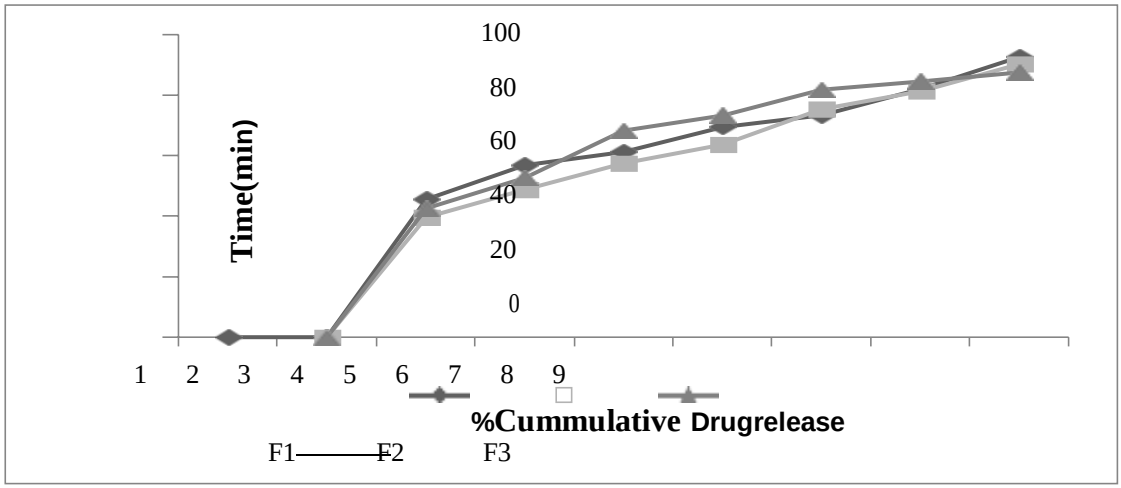
Figure 4:-Higuchi Plot & Korshmeyer- PeppasModel Showing Regression Coefficients (R^2) of0.9657& 0.9686.On x- axis is time and on y-axis is %log cumulative drug release.

Table 6 :- R^2value of Various Kinetic Models Using Solvent Evaporation Method.

In this figure we showed solvent evaporationmethod follows the Peppas model and R^2 value is 0.9686 is maximum in this model.

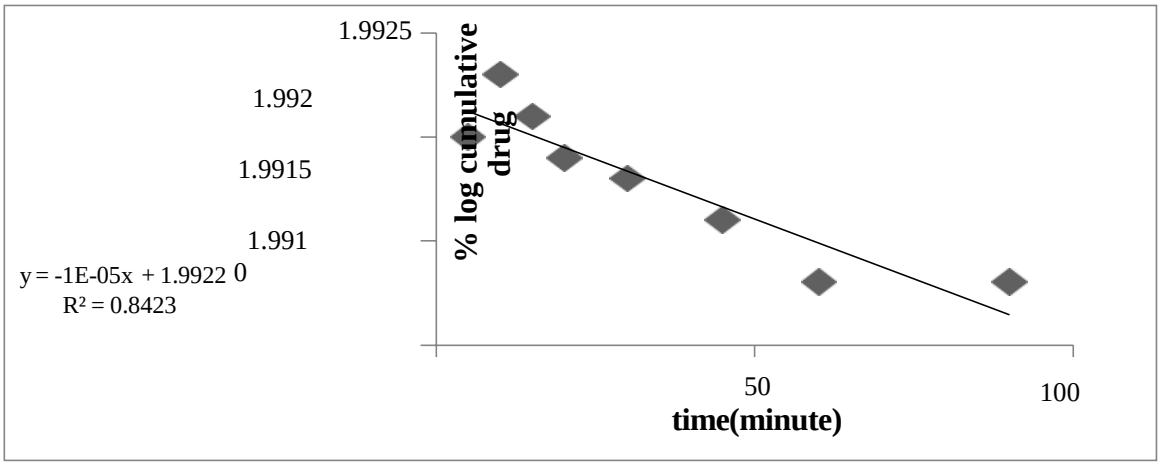
Sr No	Model	R^2 value
1	Zero order	0.7689
2	First order	0.9657
3	Higuchi	0.5641
4	Peppas	0.9686





Above figure shows. Percentage Cumulative Drug Release on x-axis and time on y-axis in FusionMethod Formulation F1-F3&F4-F6

The figure displays the in vitro dissolution profiles of pure medicines, polymers, and their corresponding mixes in distilled water for 90 minutes. 45.87%, 51.78%, 64.81%, 74.52%, 74.52%, 80.76%, 86.54%, 89.32%, and 94.34% were the results after 90 minutes. Pure drug samples FM1–FM6 release carvingol. The solubility of the carvedilol was enhanced in every sample of the combination. The Fusion approach maximises the drug's surface area that comes into touch with the dissolving medium when the carriers dissolve, increasing the drug's solubility. The formulation's use of polymers may have an impact on this. The medication release using the Fusion technique is 45.87%-94.34. [19, 20, 21]



Release in the Fusion Method.

On x-axis is time and y-axis is (%) percentage cumulative drug release and log % cumulative drug release.

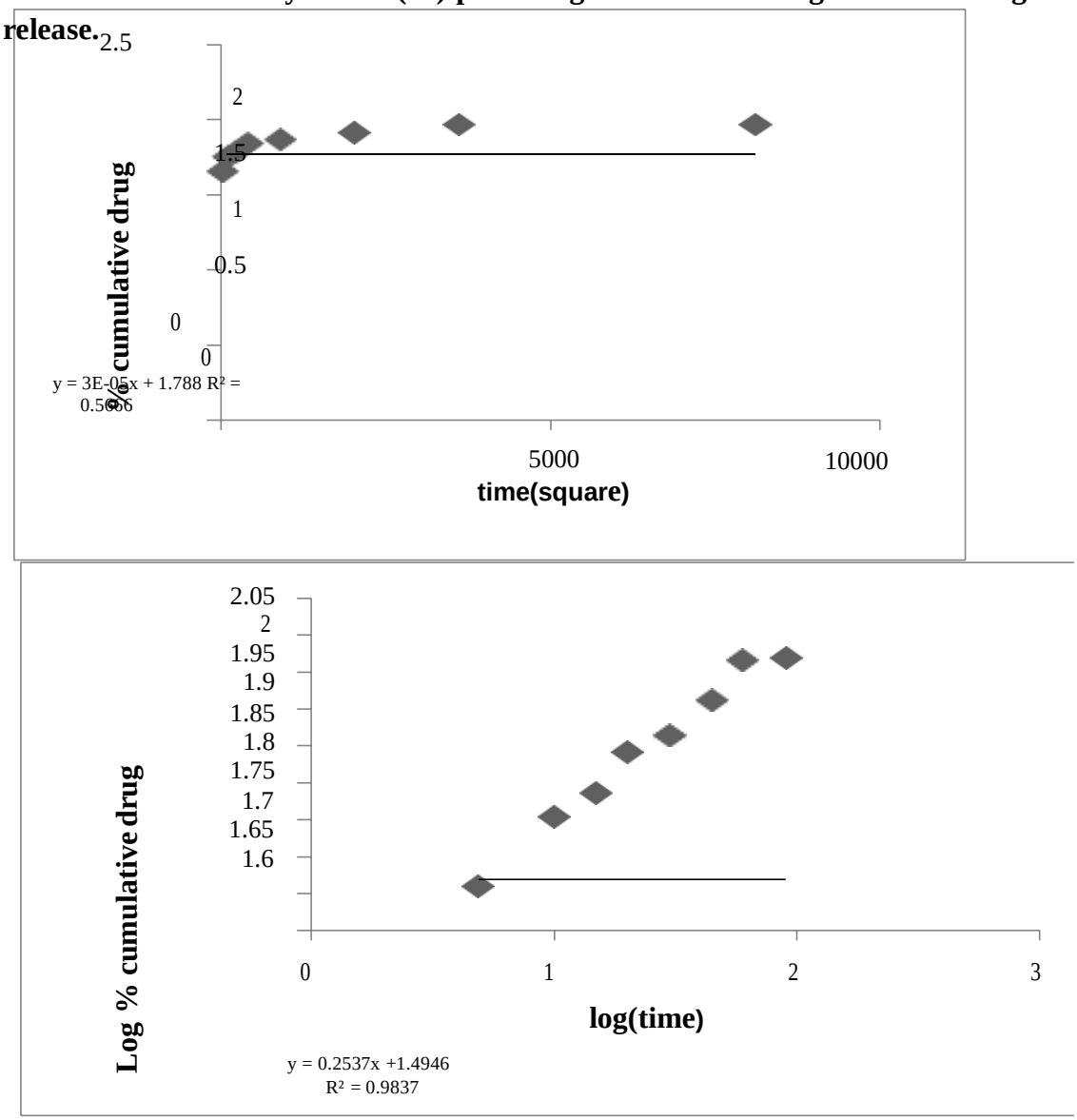


Figure 5 shows Higuchi Model &Peppas Model in Fusion Method.On x-axis is Time in (square) and on y-axisis percentage cumulative drug release.

R^2value for fusion method.

Sr no	Model	R^2 Value	K_0
1	Zero order	0.8061	0.0033x
2	First order	0.8061	-1E-05x
3	Higuchi	0.5878	3E-05x
4	Peppas	0.9878	0.2537

Table 7 shows that the drug release in the fusion method follows the peppas model and R^2 value is 0.9878.

Drug Content:-

The drug content of the formulation is maximum in solvent evaporation method as compare withfusion method .Solvent evaporation method 96.34 ±0.03 and fusion method 95.20 ±0.02.

Table 8: Comparative Drug content of solid dispersion solvent evaporation and fusion method

Batch code	Solvent Evaporation method	Batch Code	Fusion Method
SE 1	95.45 ±0.28	FM 1	91.45 ±0.03
SE 2	96.12 ±0.01	FM 2	92.12 ±0.02
SE 3	94.34 ±0.02	FM 3	94.38 ±0.01
SE 4	94.87 ±0.01	FM 4	89.87 ±0.01
SE 5	95.12 ±0.02	FM 5	95.20 ±0.02
SE 6	93.54 ±0.03	FM 6	93.60 ±0.01
SE 7	94.02 ±0.02	FM 7	88.08 ±0.01
SE 8	95.23 ±0.01	FM 8	95.23 ±0.08
SE 9	96.34 ±0.03	FM 9	90.34 ±0.01

(SE-solvent evaporation, FM-Fusion method)

Optimization of solvent evaporation method using Design Expert 11 software:-

Optimization is done by using Central composite design (CCD).Two variables X1(peg 6000),X2(Locust bean gum) and independent variables are percentage yield, Drug content, drug release are independent variables. Polynomial equation shows effect of factors or response variables.

Table 9: Percentage yield Response variables results for trial batches F1-F12.

Formulation code	X 1peg6000	X 2 Locust Beangum	Response 1 percentage Yield(%)
F 1	-1	1	64.74
F 2	1	-1	67.24
F 3	0	0	70.22
F 4	-1	-1	72.42
F 5	1	1	64.01
F 6	0	0	69.33
F 7	-1.41421	0	66.76
F 8	0	-1.41421	71.93
F 9	1.41421	0	65.54
F10	0	1.41421	61.24
F 11	0	0	62.54
F 12	0	0	67.57

The percentage yield model's F value was 7, its P value was 0.0146, its R2 value was 0.5102, and its adjusted R2 value was 0.4013. That suggests that the model is important. Equation of a polynomial is 90.965+1.64583A-0.844665B. The graph shows the % yield range for the solvent evaporation process, which is 61.24–72.42. The percentage yield of the medication rises when locust bean gum and peg 6000 are combined.

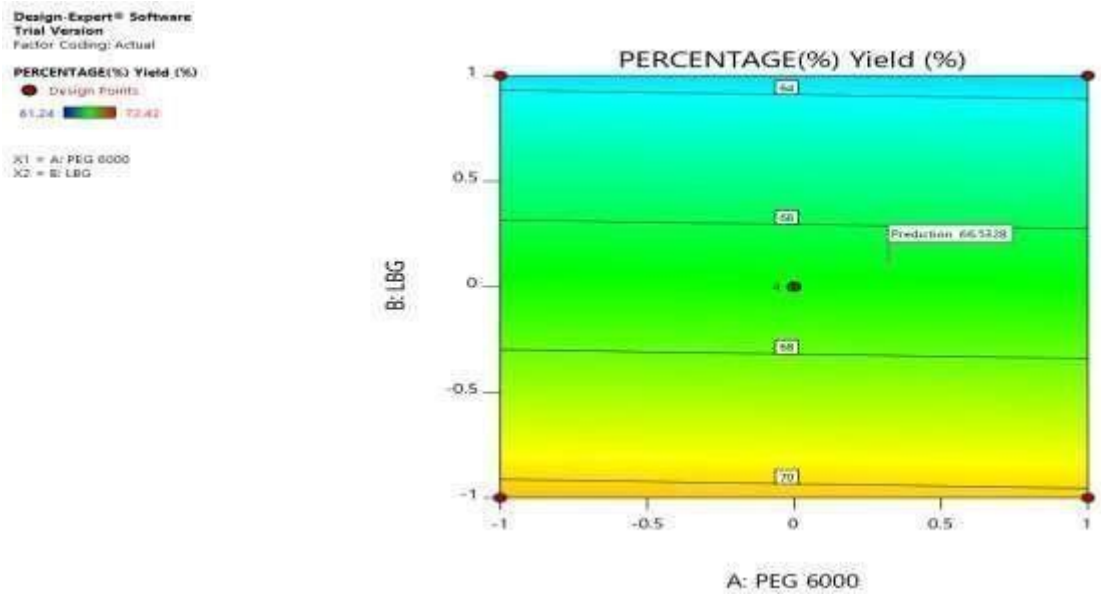


Figure 6 shows Contour plot of percentage yield showing range between 61.24-72.42.Contour plot showingeffects of peg 6000 and locust bean gum and concentration of HPMC and SSG drug content

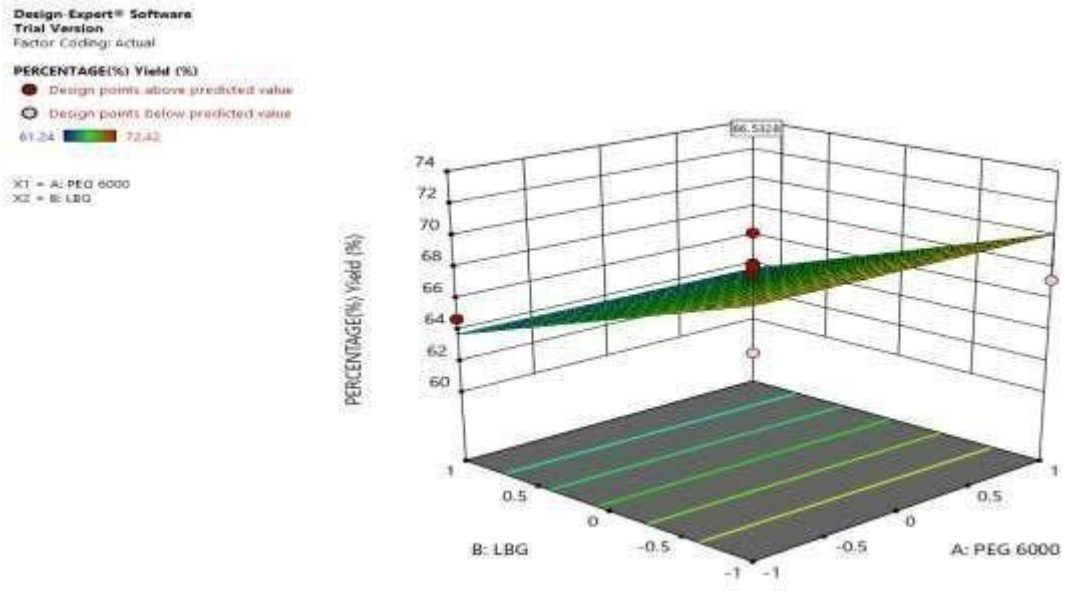


Figure 7 shows 3D surface plot showing effects of locust bean gum and peg 6000in Percentage yield.

Table 10: for Drug release Response variables results for trial batches F1-F12

Formulation Code	X-1 Locust bean gum	X-2 peg 6000	% response % drug release
F 1	0	0	90.34
F 2	0	0	87.34
F 3	-1.41421	0	92.34
F 4	0	0	87.56
F 5	1	-1	93.54
F 6	-1	1	92.95
F 7	0	0	90.76
F 8	0	-1.41421	91.87
F 9	1	1	89.71
F 10	-1	-1	88.87
F 11	0	1.41421	93.65
F 12	1.41421	0	92.65

The percentage yield model F value was 4.55, the P-value was 0.02431, the R2 value was 0.5027, and the adjusted R2 value was 0.3922. That suggests that the model is important. 95.785+0.213306A+0.24125313+0.275AB-0.54 A2-1.29B2 is the polynomial equation. The drug release range for the solvent evaporation technique is 78.34–93.54 percent. This graph shows that the medication release reduces as locust bean value increases. The release of the medication increases as the peg 6000 concentration rises.

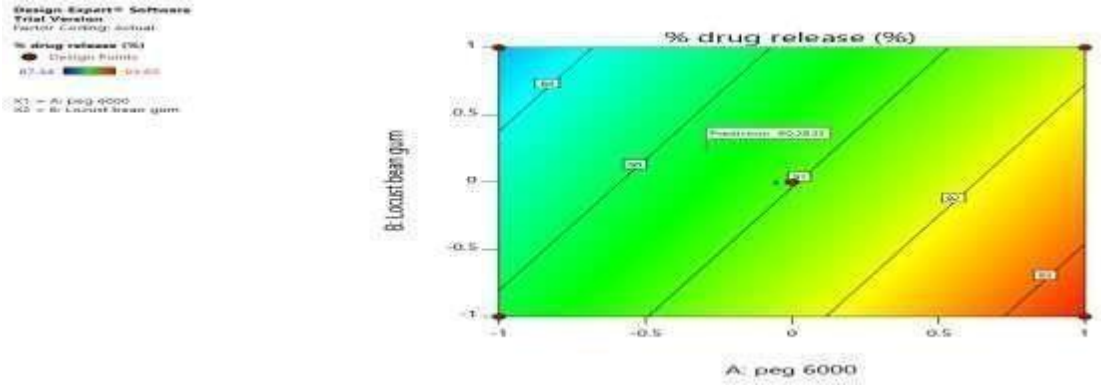


Figure8 shows Contour plot of percentage drug release showing range 87.34-93.65.Contourplot showing effects of peg 6000 and locust bean gum and concentration of HPMC and SSG drug content

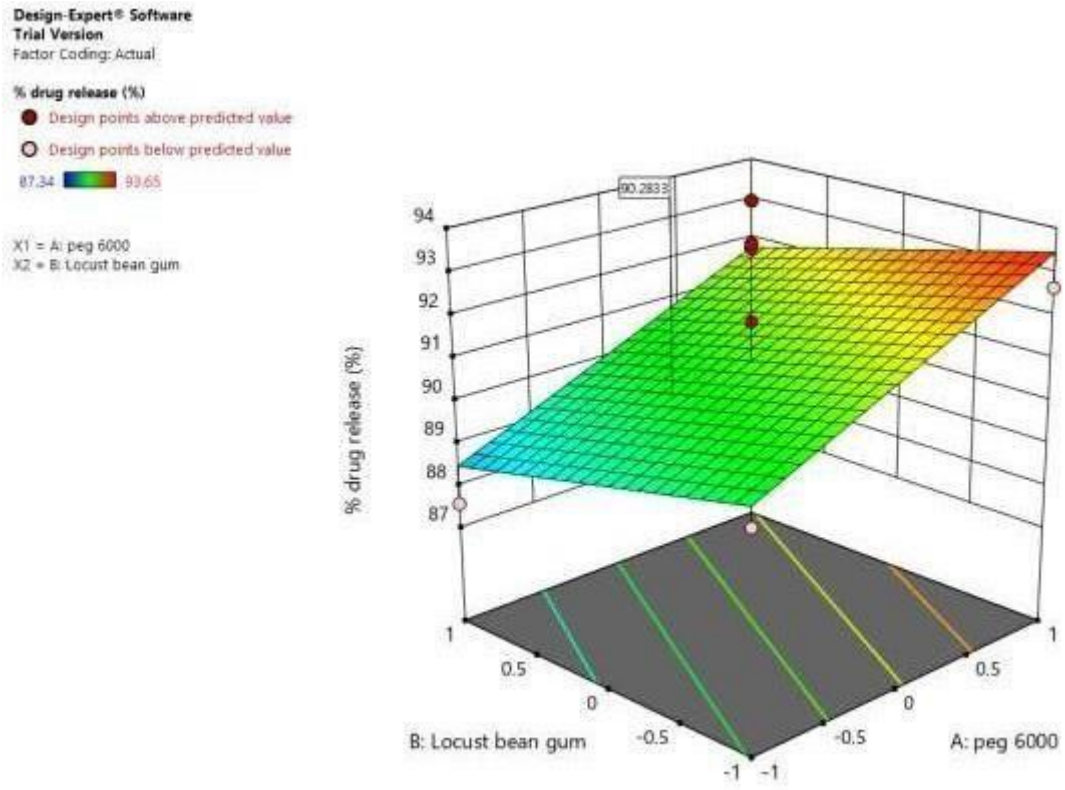


Figure 9 :-Surface plot showing the effect of locust bean gum and peg 6000 in Drug release.

Table 11:- Drug Content Response variables results for trail batches F1-F12

Formulation	Factor 1	Factor 2	Response 1
Code	A:lbg	B:peg 6000	drug content%
F 1	0	0	95.45
F 2	0	0	96.12
F 3	1	1	94.34
F 4	1.41421	0	94.87
F 5	0	1.41421	94.34
F 6	0	0	96.34
F 7	0	-1.41421	92.65
F 8	0	0	95.23
F 9	-1	1	92.76
F 10	-1.41421	0	95.12
F 11	1	-1	94.02
F 12	-1	-1	93.54

The model F value for percentage yield was 4.54 and P-value was 0.0465 and R^2value is 0.0533 and adjusted

value of $R^2$is -0.1571.It indicates that model is significant.Polynomial equation is 71.4-3.20607A+1.98139B-1.07AB+1.26375A^2-2.40125B^2. Drug content in solvent evaporation method the drug release range 92.65-96.34.The optimization graph of drug content, the combination of polymers locust bean gum and peg 6000 concentration increases the drug content increases.

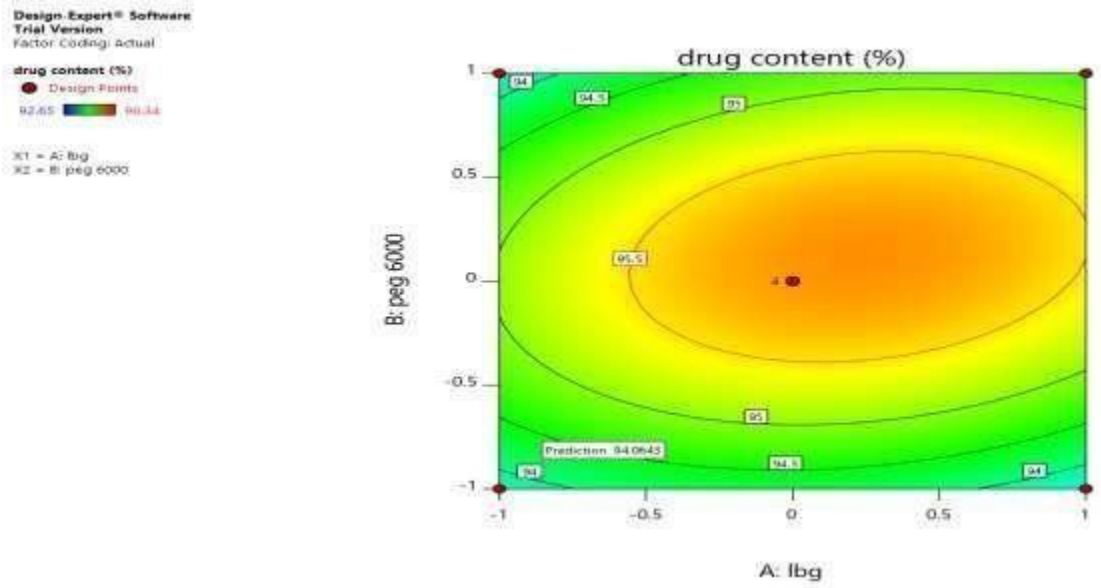
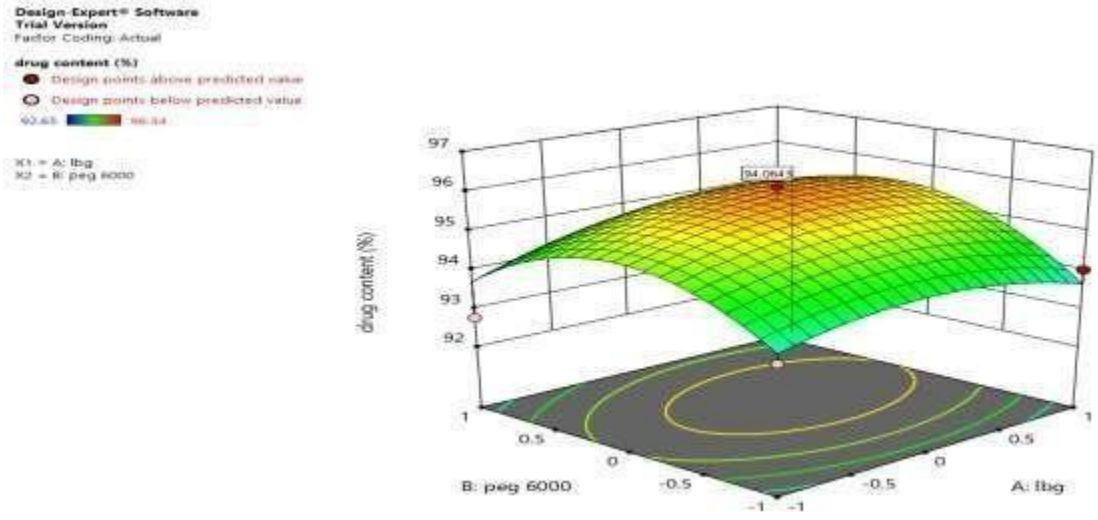


Figure 10:-Contourplot showing effects of peg 6000 and locust bean gum and concentration of HPMC and SSG drug content.



X- - Ray Diffraction

When a medication is made into a solid dispersion and precipitates in an amorphous form, powder X-ray

diffraction analysis may be performed to assess any changes in the drug's crystallinity. This might be one of the processes causing enhanced solubility. Pure pharmaceuticals and polymers have an X-ray diffraction range of 5.8318-44.8085. Carvedilol crystals could be seen in the form of several diffraction peaks at 12.9676, 14.826, 18.4392, 19.1257, 23.2702, 23.4898, and 27.5381.

Counts

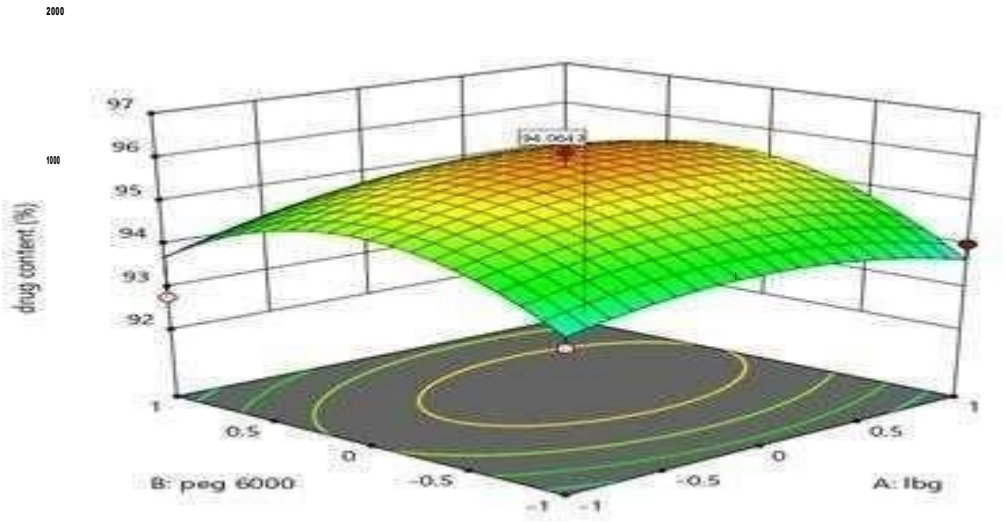
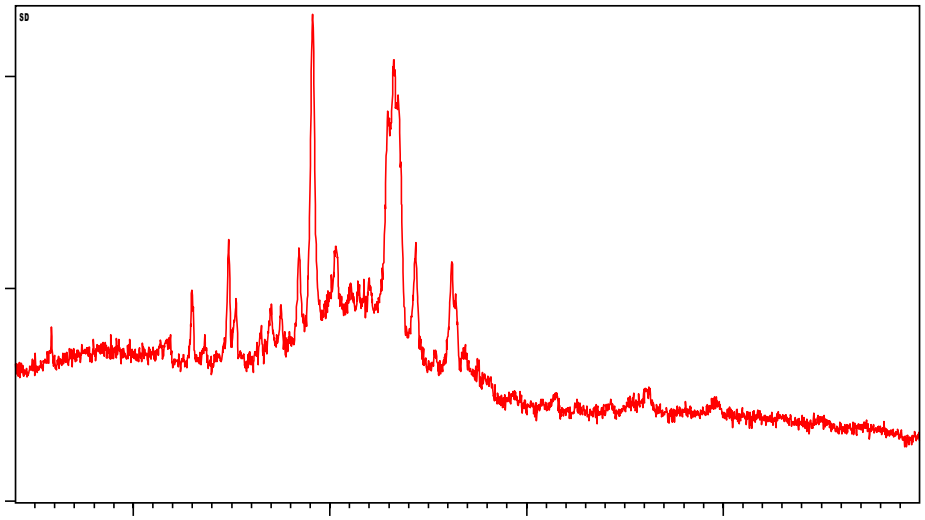


Figure11:-(XRD) X-ray diffraction Graph of Solid Dispersion of Optimized Batch



Scanning Electron Microscopy

A little quantity of the solid dispersion formulation was applied to a gold-coated grid to create the SEM grids, which were then dried off under a light. The figure displays SEM photomicrographs of carvedilol solid dispersion. Carvedilol's solid dispersion was spherical, which allowed it to flow extremely freely, according to SEM photomicrographs. These results show that the medication was fully dissolved in the carriers with little crystallinity loss. The polymer particles looked to have carvedilol crystals embedded within them.

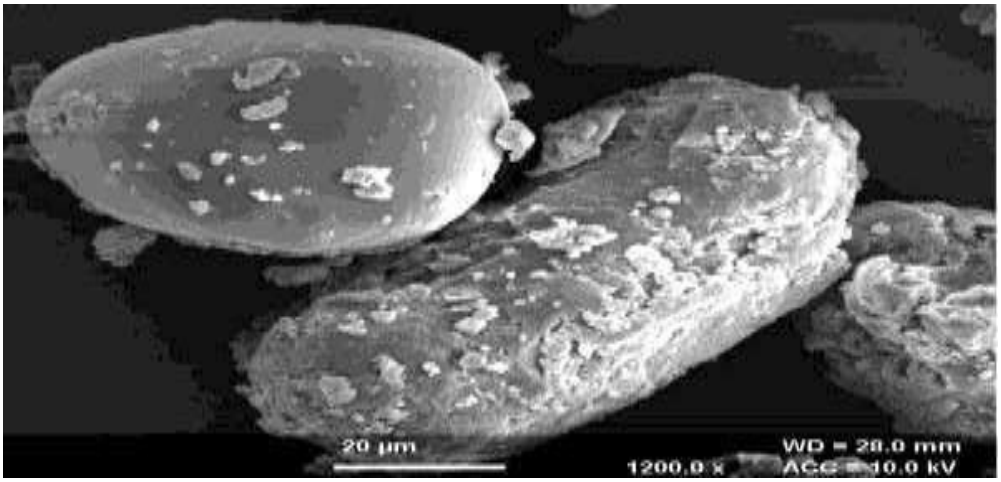
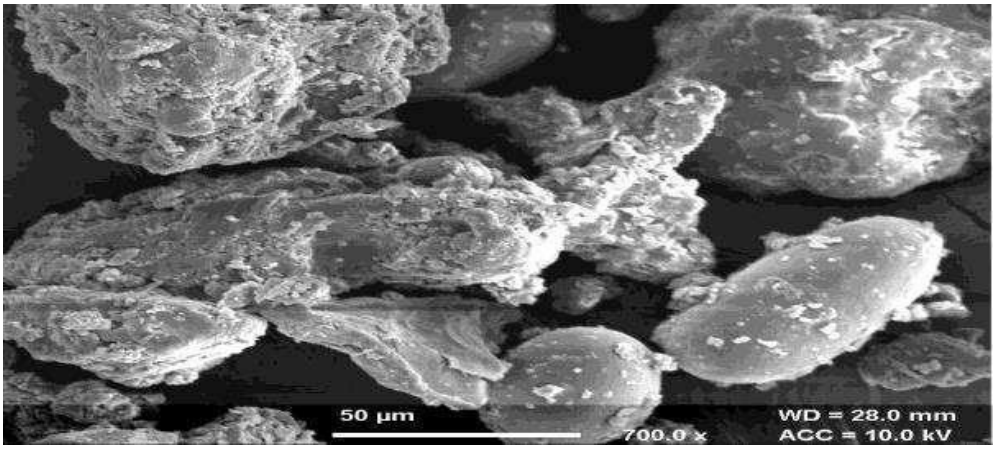


Figure 12:-Scanning electron microscopy shows photograph of solid dispersion



Discussion:-

In the present investigation, several carriers, including HPMC, locust bean gum, PEG 6000, and sodium starch glycolate, were utilised to increase the solubility of the antihypertensive medication carvedilol utilising a solid dispersion approach.

We employed sodium starch glycolate as a disintegrant, HPMC as a viscosity enhancer, PEG

as a plasticizer, and locust bean gum as a binding and flavouring ingredient.

In this work, we used both solvent evaporation and fusion procedures to create the solid dispersion of carvedilol. Different carriers are utilised in formulations for both techniques.

Using the use of X-RD, SEM, and in vitro dissolving investigations, the findings were characterised.

Using an FTIR spectrophotometer, the potassium bromide disc method was used to acquire the FTIR spectra of the medication and formulations. The pure drug's IR spectra showed distinctive peaks at 3340.11 cm-1 (N-H, stretching), 2978.17 cm-1 (C-H), 1399.84 aromatic plane bending, 1647.61 (Methylene Cyclohexane), 1713.12 cm-1 (C=O), 1598.26 cm-1 (C=C), 2992.39 cm-1 (CH), 1712.20 cm-1 (C=0), and 1660.66 cm-1 (M Nevertheless, separate peaks at 2973.20 (C-H), 1054.07 (sulfoxides), and 1267.15 (formulation) are shown (aromatic plane bending).

The shifting of peaks proved that polymers and the pure medicines interacted.

The solvent evaporation technique and the fusion process were used to create the formulations. For formulas, the values for the angle of repose vary from 23.610.015 to 27.911.002.

For formulations, the bulk and tapped values span 0.2400.020 to 0.8500.010 and 0.3200.010 to 0.6100.01, respectively.

The figures for the formulations' respective Carr's index and Hauser's ratio are 12.090.51- 18.600.13 and 1.060.02-1.330.045.

Therefore, satisfactory flow properties were seen in all formulations.

Solid agglomeration Using design expert software-11 and the core composite design, carvedilol is optimised. Two independent components, X1 (locust bean gum) and X2 (Peg 6000), are used in optimization. The range of the optimised batch's yield percentage is 66.5328.

The percentage yield is increased when locust bean gum and peg 6000 are combined. Drug release diminishes as locust bean concentration rises. Drug release rises with a higher peg 6000 concentration.

90.2833 is the optimal medication release value.

The interaction of the polymers enhances the drug content. The range that is optimal is 94.0643. The solvent evaporation method's maximal drug release in the in vitro drug release trial was 93.46, compared to the fusion method's 93.20.

The R2value in the solvent evaporation approach is 0.9686, while in the fusion method is 0.9878. Both models adhere to the Peppas model, and the drug release in both cases is 93.20. Finally, 5.8318-44.8085 is the optimised batch X-ray diffraction value 2.

The created agglomerates were found to be spherical in form by scanning electron microscopy, which made it possible for them to flow extremely freely.

Conclusion

The purpose of the research was to improve the solubility of carvedilol utilising the solid dispersion technique. By using hydrophilic polymers (HPMC, locust bean gum), PEG 6000,

sodium starch glycolate, and plasticizers as disintegrants, a solid dispersion of carvedilol was created. With reference to drug content, percentage yield, and physiochemical characteristics of drug release, all the produced formulations shown excellent homogeneity.

According to assessment and in-vitro characterization, the ratio of hydrophilic to hydrophobic polymers was increased, which maximised the drug release.

Results were repeatable as a consequence of the enhanced polymer concentration and maximised drug release.

According to this investigation, the solvent evaporation approach enhanced the solubility of carvedilol when compared to the fusion method.

Acknowledgments

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Conflict of Interest No conflict of interest.

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