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Application of Central Composite Design in the Development and Optimization of Solid Dispersions System for Enhanced Solubility of Carvedilol

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Abstract:-

Carvedilol is an antihypertensive drug is a poorly water-soluble drug and low oral bioavailability. Solid dispersion is techniques of solubility enhancement of poorly soluble drugs. The aim of the present work is to enhance the poor solubility of carvedilol using solid dispersion techniques.Nine formulations prepared by solvent evaporation and fusion method using polymers Hydroxy-methylcellulose (HPMC), Locust bean Gum (LBG), PEG 6000 and sodium starch glycolate (SSG). The samples were evaluated by solubility, stability, dissolution rate and characterized by Scanning electron microscopy (SEM), Powdered X-ray Diffractometry(PXRD), Differential Scanning Calorimetry(DSC) and Fourier Transform Infra-red (FTIR). 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 and follows Peppas model. The FTIR was observed that Shifting of peaks confirmed the interaction of polymers with the pure drugs .SEM results shows 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. The enhancement of solubility was dependent on a combination of factors including the weight ratio, preparation techniques and carrier properties.

Introduction

Solubility of poorly water soluble drugs is allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. The rate and extent of dissolution of the active ingredient from any dosage form often determines the rate of extent of

absorption of the drug. When an active agent given orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation[1,2]. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas focus on improving oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs[3,4]

The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms. The Oral route is most desirable route of administering the dosage form. The major problem faced during the oral administration of active agent is the bioavailability. Solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. Solubility

parameter is used to achieve desired concentration of drug in systemic circulation for pharmacological response.[3-5]

A poorly water soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract.

Drugs with low aqueous solubility have low dissolution rates and hence suffer from oral bioavailability problems. Solubility is an intrinsic property of any dosage form, i.e. drug.[4-6] property of drug product, wherein properties or nature of active compound can be improved by external modification i.e. by size reduction, due to which effective surface area of active component will be increased and enables more contact with intestinal fluids for better absorption of drug. [4-6] improved by internal modification i.e. by complexation of poorly soluble compounds with water soluble carrier. [4,5,7] The common aim for all of the drug delivery system is to increase the drug solubility. Some traditional and novel approaches to improve the solubility are Particle Size Reduction, Solid Dispersion, Nano suspension, Supercritical Fluid Technology, Cryogenic Technology, Inclusion Complex Formation Techniques, Floating

Granules etc. [4-6]The term 'Solid Dispersion' refers to a group of solid products consisting of at least two different components, generally 'a Hydrophobic Drug and a Hydrophilic Carrier'. The carrier can be either crystalline or amorphous form.[4, 5, 8]

Solid dispersion technique is a very useful method for pharmaceutical point of view because of its capability to solve the solubility problems by using solid dispersion method.[5, 9].Solid dispersion technique has been used for a variety of poorly aqueous soluble drugs such as Nimesulide, Ketoprofen, Tenoxicam, Nifedipine, Nimodipine, etc. Various hydrophilic carriers such as PEG 6000, PVP, HPMC, gums, sugars, and Mannitol have been used for improvement of dissolution characteristics and solubility of poorly water soluble drugs. Solid dispersions can be prepared by various methods such as melting, solvent evaporation, solvent melting, spray drying, supercritical fluid techniques, etc.[4, 3, 9].

MATERIALS AND METHODS

Materials

Carvedilol was obtained as a gift sample Aurbindo Pharma Pvt Ltd. Hyderabad, India. HPMC, Locust Bean Gum, Peg 6000, Sodium Starch Glycolate and methanol were purchased from Himedialaboratories. All other chemicals were of analytical grade.

Drugs-excipient compatibility study

Optimization using Central Composite Design

Design Expert Software, version 11.0 (Stat-Ease, Inc. Minneapolis, MN, USA) was employed to fit polynomial equations with attached interaction terms for the correlation of studied responses with chosen variables. Drug content and % drug release were selected as response variables for systematic optimization. Optimized formulation was found by locating feasible space as well as exhaustive grid search was done for tracing the possible solution. Optimum solution was also provided by the software using the overlay plots. The optimized formulations were utilized for all the *in vitro* studies.[19- 21].The central composite design was selected for optimization

because central composite design require 5 levels of each factor -α, -1, 0, 1, and +α. A statistical model incorporating interactive and polynomial terms were used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b2X2 + b12X1X2 + b11X12 + b22X22$$

One way ANOVA (analysis of variance) was used for statistical analysis of targeted response at 5% significant level and the significance of model, factors were determined using Design- Expert 11.0. In above equation, b_0 is the intercept representing the arithmetic averages of all 13 runs and b1, b2, b12, b11 and b22 are the coefficients computed from the observed experimental values of responses Y1 , Y2, and X1 and X2 stand for main response of independent variables. The terms X1, X2, X11 and X2 represent interaction and quadratic terms of independent variables respectively.[19- 21]

Table 1: Formulation design of carvedilol with amount of HPMC, SSG, LBG& PEG 6000

Sr.No	Carvedilol(mg)	HPMC(mg)	SSG(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

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectra were obtained using Shimadzu FTIR- 8400S spectrometer, Japan. Samples of carvedilol, gelucire 50/13, physical mixtures and solid dispersions were ground and mixed thoroughly with potassium bromide at a 1:5 sample/KBr ratio. The KBr discs were prepared by compressing the powders at a pressure of 5 T for 5 min in a hydraulic press. The scanning range was 40 to 4000 cm-1 and the resolution was 4 cm.[21, 22]

Differential Scanning Calorimetry

It is a thermoanalytical technique which is used to measure the temperature and heat flow associated with a transition in material as a function of time and temperature. [20, 21, 23, 24] Surface morphology of the agglomerates was accessed by SEM. The crystals were splutter coated with gold before scanning. The samples were then randomly scanned and microphotographs were taken on different magnification and higher magnification was used for surface morphology. The accelerator voltage wasset at 30.0 KV during scanning.[20, 21,19]

Powder X-Ray Diffractometry:-

Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material. Recently developed X-ray equipment is semi-quantitative.(Dhirendra K *et al* 2009).XRD patterns were recorded using Philips PW 1729 X- ray generator, USA fitted with a copper target, a voltage of 40 kV, and a current of 30 ma. The scanning rate was 1°/min over a 2 θ range of 1-50°. PXRD patterns were traced for carvedilol, physical mixture and solid dispersions. The samples were slightly ground and packed into the aluminum sample container.[18-22]

Scanning Electron Microscopy (SEM)

The characteristic properties of drug crystals like particle size and morphological surface can be known by the preparation method and chemical composition. Additionally, the shape and granulometric properties of the powder particles can be explained through the range of parameters automatically obtained by connecting SEM with an image processor.[18, 19]

Drug Release Kinetics

To describe the kinetics of the drug release from matrix, mathematical model such as Zero-order, First order and Higuchi, models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness- or fit test. [24-26]

***In- vitro* Drug Release Studies**

The *In-vitro* dissolution studies on pure drug (12.5mg) and physical mixtures and solid dispersion formulations of carvedilol were carried out in triplicate, employing USP XXIII paddle (Apparatus 2) using 900 mL 0.1 N HCL, as the dissolution medium at 100 rpm and 37±0.5˚C. An aliquots sample (10 mL) was periodically withdrawn at suitable time intervals and volume replaced with equivalent amount of dissolution medium. The samples were analyzed on spectrophometer at 241.2 nm using UV-visible spectrophotometer. [19-21]

Mechanism of Drug release:

The different mathematical models may be applied for describing the kinetics of the drug release process from dosage forms the most suited being the one which best fits to the experimental results. From formulations were determined by finding the best fit of the release data to zero order, first order and Higuchi and Korsmeyer- Peppas plot.[24-26]

Zero - Order Release Model

$$\mathbf{Q = Qo – Ko.t}$$

Where, Qo is the initial amount of drug, Q is amount of drug remaining at time t; Ko is zero-order rate constant expressed in units of concentration/ time and t is the time. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First – Order Release Kinetic Model

$$\mathbf{Log\ Q = Log\ Q_o – K1.t/\ 2.303}$$

Where, Qo is the initial amount of drug, Q is amount of drug released at time t and k1 is first order constant. Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi Square Root Model

$$Q = K.t1/2$$

Where, Q is amount of drug released at time t and K is the constant reflecting the design variables of the system. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

Korsmeyer – Peppas Model

Mt / M infinity = Ktn

Mt / M infinity is fraction of drug released at time t, K is the rate constant and n is the relase exponent .the n value is used to characterize different release mechanisms. . A plot between logof Mt/Mα against log time will be linear if the release obeys Peppas and Korsemeyer equation and the slope of this plot represents "n" value.

Results and Discussion

Melting Point of Drug

The melting point of carvedilol was determined by capillary method, melting point of carvedilol was found to be 114˚C -116.24˚C.

Fourier Transform Infrared Spectrophotometer(FTIR) Studies

Potassium bromide disc technique was employed to obtain the FTIR spectra of the drug and formulations using an FTIR spectrophotometer. The drug was identified by infrared spectroscopy and characteristics peak obtained compared with standard spectra of pure drug, physical mixture and formulation in figures. The IR spectra of pure drug showed the characteristics peaks at

3340.11cm^{-1}(N-H, stretching), 2978.17cm–1(C-H stretching),1399.84aromatic planbending,1647.61(MethyleneCyclohexane),1713.12(C=O),1598.26(C=C),2992.39(CH),1712.20(C=0),1660.66(methylenecyclohexane),1058.18(sulfoxides),1411.76(aromatic plane bending) and in physical mixture showed the peak at 2992.39(C-H),1712.20(C=O),1660.66(methylene cyclohexane),1058.18(sulfoxides),1411.76(aromatic plan bending), 1541.44(C=C) aromatic. But in case of formulation different peaks are shown at2973.20(C-H), 1054.07(sulfoxides), 1267.15(aromatic plane bending). Shifting of peaks confirmed the interaction of polymers with the pure drug.

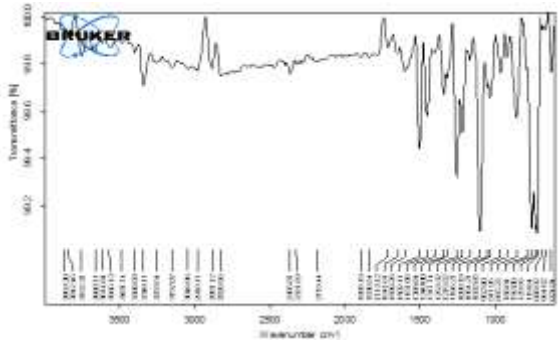


Figure 1 FTIR Spectra of Carvedilol

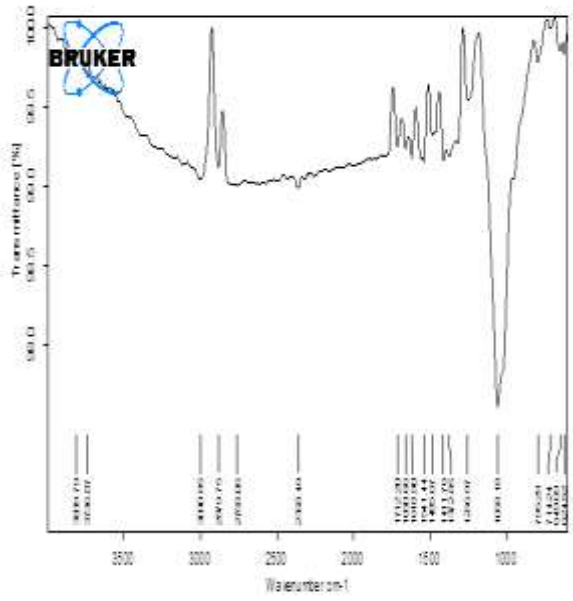


Figure 2.FTIR of Optimized Batch (F7)

Flow properties of solid dispersion method:-

Angle of repose

Angle of Repose determined by 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.

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.

Table2.Powder Characteristics of Different Batches of Formulations (SE1-SE9)

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

Table 3: 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

Percentage Yield

Percentage yield is the percent ratio of actual yield to theoretical yield. It is calculated to be the experimental yield divided by the theoretical yield multiplied by 100%.If the actual and theoretical yield are same. The percentage yield 100%.Usually percentage is lower than 100% because the actual yield is often less than the theoretical value.

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 above table shows that the solvent evaporation method percentage (%) Yield of formulation was maximum as compare to fusion method.

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

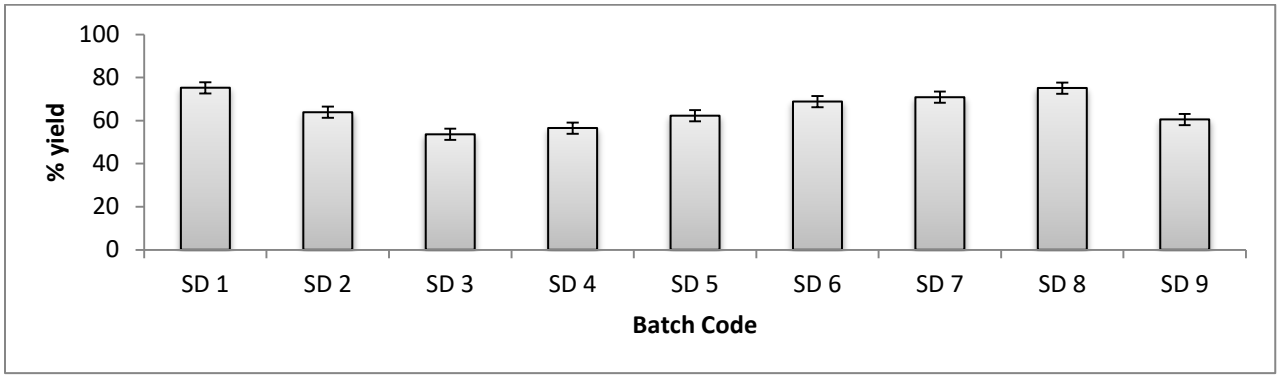


Figure 3.PercentageYield of the Formulation SD1-SD9 for Solvent Evaporation Method.

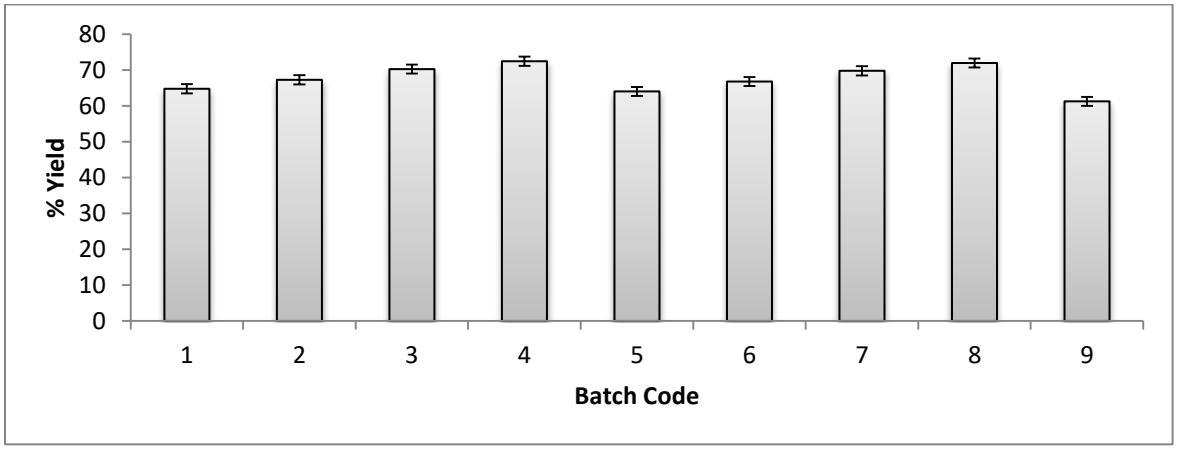


Figure 4.Percentage Yield of the Formulation 1-9 for Fusion Method.

Dissolution Study

All the prepared carvedilol solid dispersion were subjected to dissolution using paddle apparatus with 6.8 phosphate buffer solution and the results obtained for drug release were plotted as %

cumulative drug release versus time in hours. The release data (0-90 minute) were fitted to different kinetics models, Zero models, First order, Higuchi Model and KorshmeyerPeppas model in order to study the mechanism of drug release in solid dispersion.

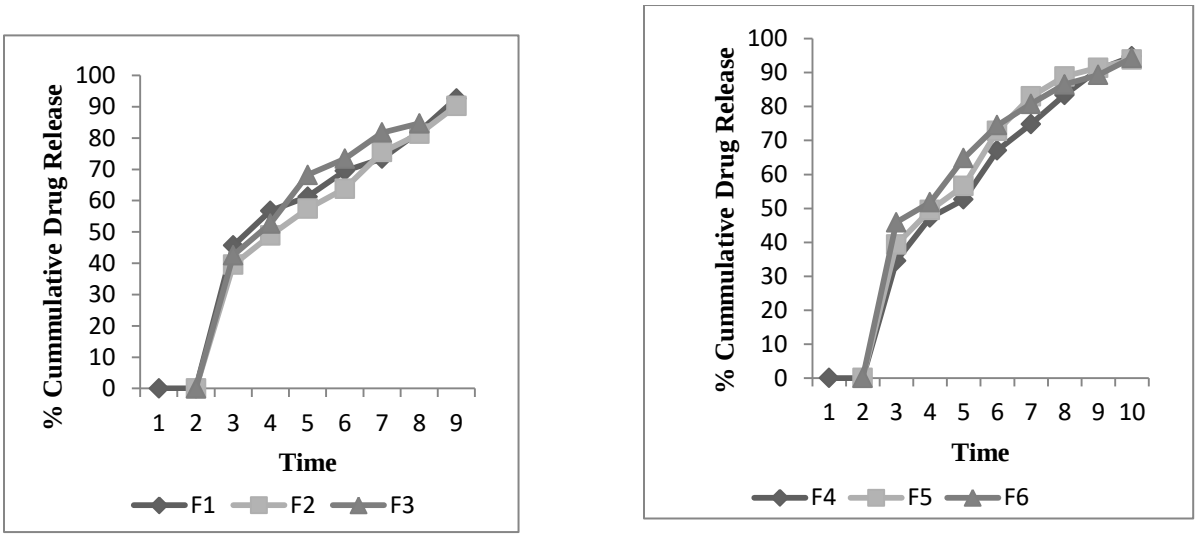
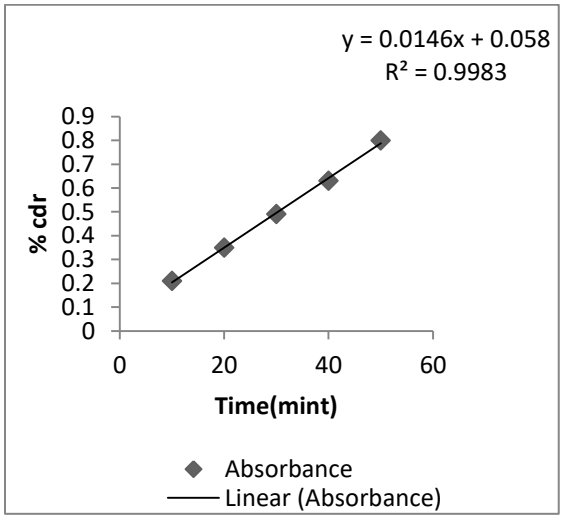


Figure 5. Percentage Cumulative Drug Release Vs Time for Formulations F1-F3&F4-F6

In-vitro dissolution profiles of pure drug and polymers and their respective mixtures in distilled water for 90 minutes are shown in figure. At the end of 90 minutes 62.47%,71.28%, 72.38%, 80.62%, 80.31%, 86.06%, 88.66% &93.46% release was observed. Carvedilol released from pure drug sample.All of the samples of mixture showed improved dissolution of carvedilol. The solid evaporation method shows enhanced dissolution rate of the drug. The Solvent evaporation method increase the solubility and maximizing the surface area of the drug that came in contact with the dissolution medium as the carriers dissolved. This might due to effects of polymers in formulation. The drug release of 27.62% -93.46% was showed by solvent evaporation method.

Kinetics Models of Drug Release

Various kinetics models were applied on different batches of solid dispersion. Based on regression coefficients, F6 was selected to calculate kinetic parameters for drug release.



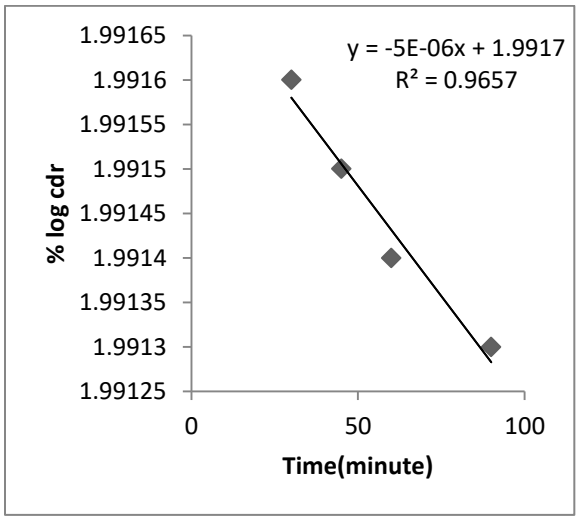
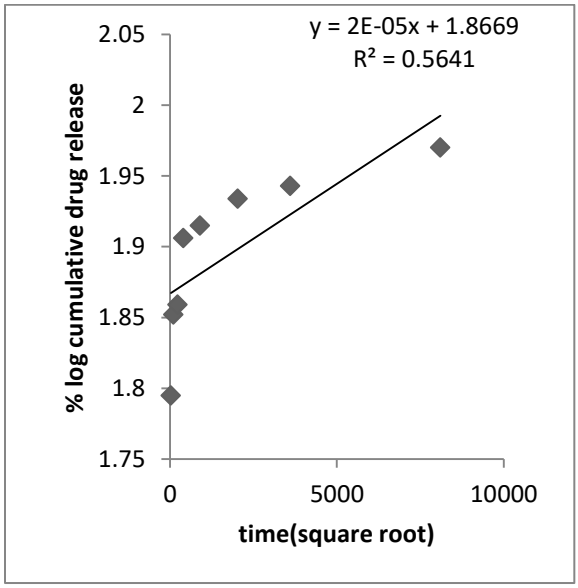


Figure6.The Zero order plot & First Order Plothaving regression coefficients (R^2) of 0.9983 & 0.9757



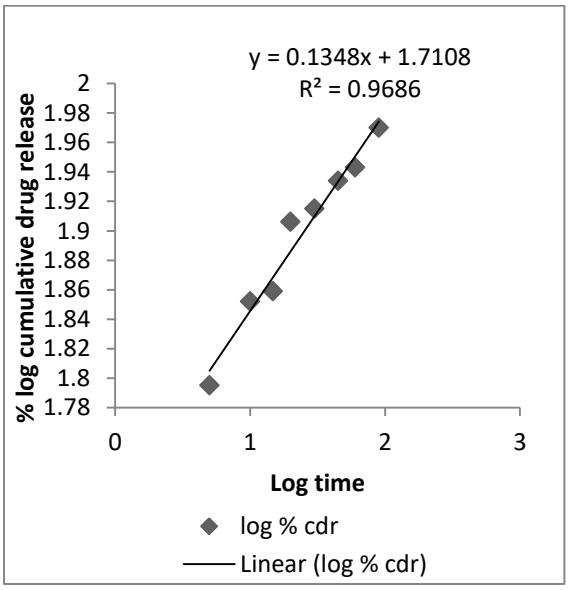
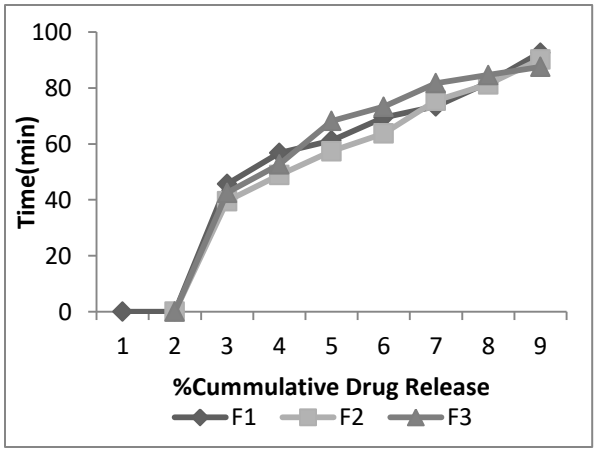


Figure 7.Higuchi Plot&Korshmeyer-PeppasModel Showing Regression Coefficients (R^2) of 0.9657& 0.9686

Table 7.R^2value of Various Kinetic Models Using Solvent Evaporation Method.

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

Table shows that the method follows the Peppas model and R^2 value is 0.9686 is maximum in this model.



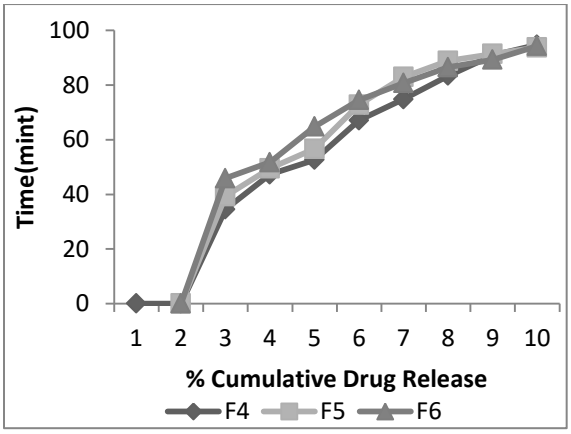


Figure8. PercentageCumulative Drug Release of Fusion Method Formulation F1-F3&F4-F6

In vitro dissolution profiles of pure drug and polymers and their respective mixtures in distilled water for 90 minutes are shown in figure. At the end of 90 minutes 45.87%, 51.78%, 64.81%, 74.52%, 74.52%, 80.76%, 86.54%,89.32% &94.34% Carvedilol released from pure drug sample FM1 –FM6. All of the samples of mixture showed improved dissolution of carvedilol. The Fusion method increase the solubility and maximizing the surface area of the drug that came in contact with the dissolution medium as the carriers dissolved. This might due to effects of polymers in formulation. The drug release 45.87%-94.34 in the Fusion method.[19, 20, 21]

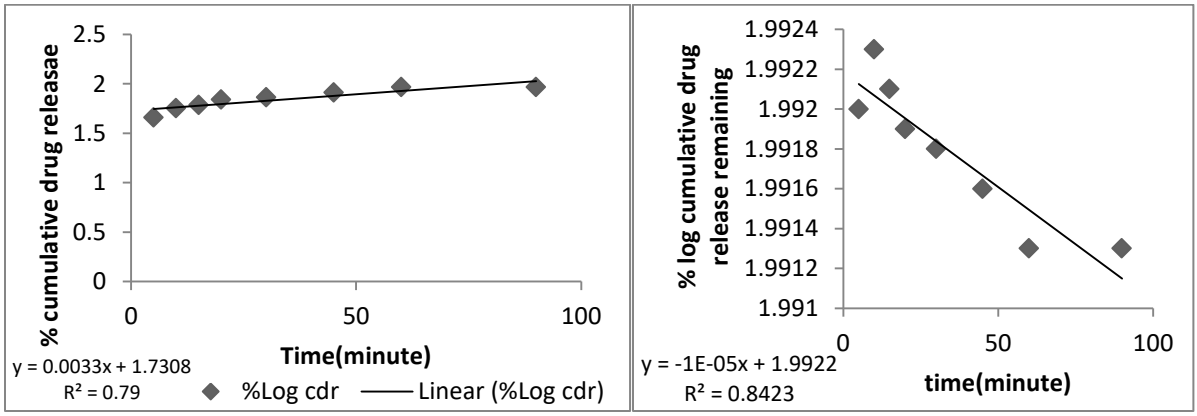
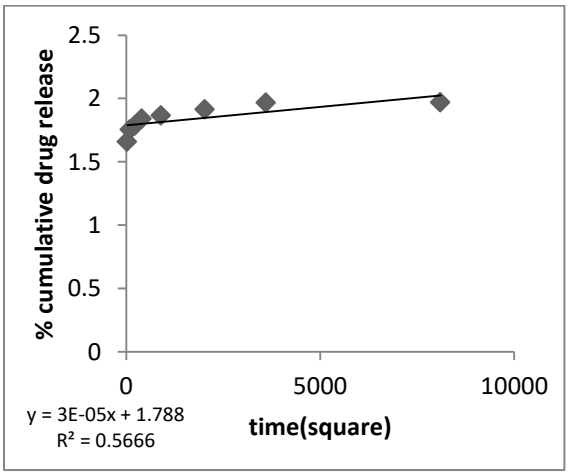


Figure 9.ZeroOrder&First Order Drug Releaseof the Fusion Method



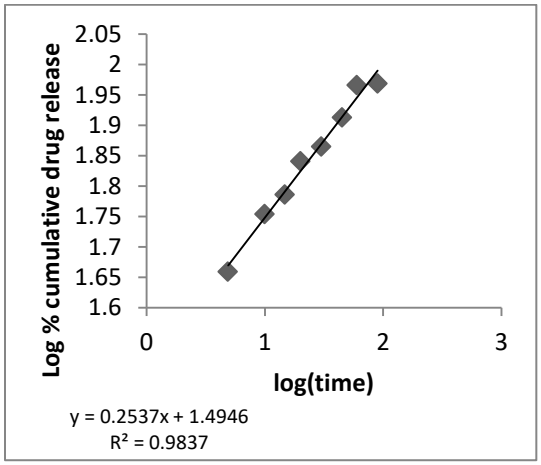


Figure 10.HiguchiModel&Peppas Model of Fusion Method

Table 6.R^2Value of Various Kinetic Models Using Fusion Method

Sr no	Model	R^2 Value
1	Zero- order	0.8061
2	First order	0.8061
3	Higuchi	0.5878
4	Peppas	0.9878

Table 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 was found to be maximum in solvent evaporation method as compared with fusion method .Solvent evaporation method 96.34 ±0.03 and fusion method 95.20 ±0.02.

Table 7.Comparative Drug Content of carvedilol Solid Dispersions Using Solvent Evaporation & Fusion Method

Batch code	Drug Content of Solid Dispersion Solvent Evaporation method	Batch Code	Drug Content of Solid Dispersion 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 11software

Optimization was done by using Central composite design (CCD).Two variables X1(PEG 6000), X 2(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.

The model F value for percentage yield was 7 and P-value was 0.0146 and R^2 value is 0.5102 and adjusted value of R^2 is 0.4013.It indicates that model is significant. Polynomial equation is 90.965 +1.64583A-0.844665B. Graph indicate in solvent evaporation method the percentage yield range 61.24-72.42.When we take the combination of proportion of locust bean gum and peg 6000 the drug percentage yield increases.Contour Plot Showed the effects of PEG 6000 and

Locust Bean Gum and Concentration of HPMC and SSG Drug Content on % yield& it was obtained in range of 61.24-72.42.

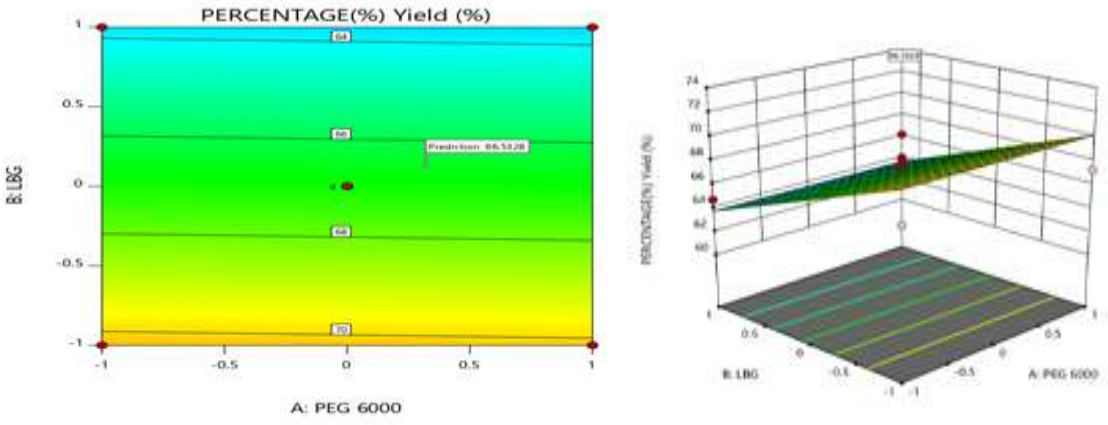


Figure11. Contour Plot of % Yield &3D Surface Plot Showing Effects of Locust Bean Gum And PEG- 6000on Percentage Yield.

The model F value for percentage yield was 4.55 and P-value was 0.02431 and R^2 value is 0.5027 and adjusted value of R^2 is 0.3922.It indicates that model is significant. Polynomial equation is 95.785+0.213306A+0.24125313+0.275AB-0.54 A^2-1.29$B^{2.}$ Percentage Drug release in solvent evaporation method the drug release range 78.34-93.54. In this graph indicate when the value of Locust bean is increase the drug release is decreases. When we increase the PEG6000 concentration the drug release is increase.

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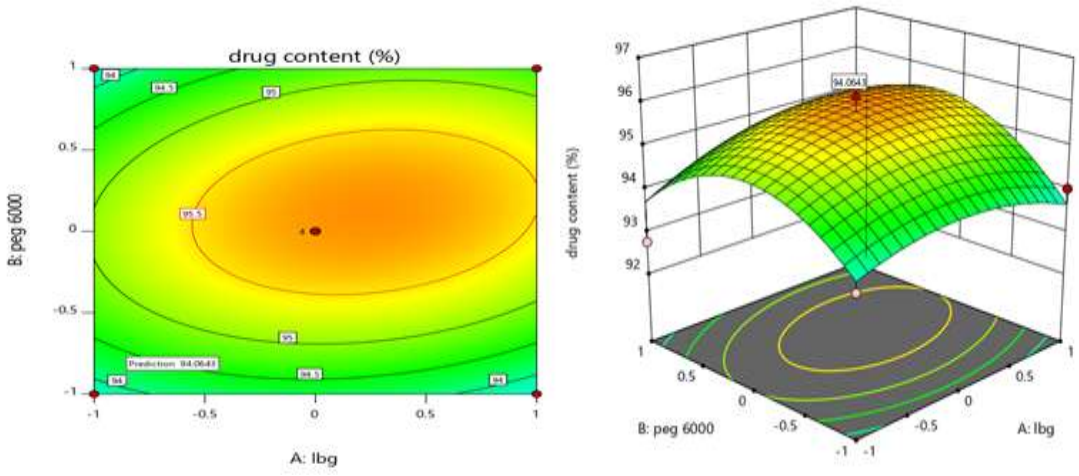

Figure 13. Contour plot showing effects of PEG 6000 and locust bean gum and concentration of HPMC and SSG drug content on Drug Content &3D Surface plot showing effect of locust bean gum and PEG 6000 on drug content.

X-Ray Diffraction

Powder X-ray diffraction analysis can be used to judge any changes in crystallinity of the drug which precipitated in an amorphous form, when formulated into a solid dispersion, which could be one of the mechanisms responsible for improved dissolution. X-ray diffraction of pure drug and polymers [°2θ] range is 5.8318-44.8085.Numerous diffraction peaks of carvedilol were observed a 12.9676, 14.826, 18.4392, 19.1257, 23.2702, 23.4898, 27.5381 indicating the presence of crystalline carvedilol

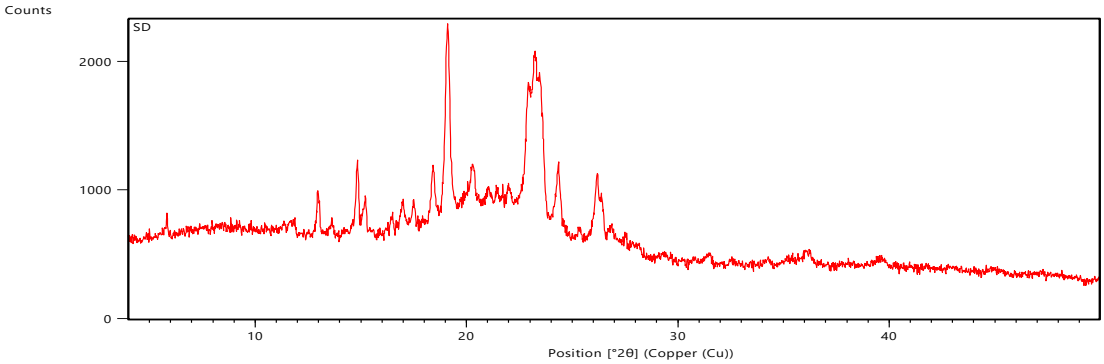

Figure 14. XRD Graph of Solid Dispersion of Optimized Batch

Scanning Electron Microscopy

The SEM (JEOL-JSM-6100)used SEM grids which were prepared by placing a small amount of solid dispersion formulation on a gold coated grid and drying under lamp SEM photomicrographs of carvedilol solid dispersion shown in figure. SEM photomicrographs of carvedilol solid dispersion indicated the solid dispersion was spherical in shape, which enabled them to flow very easily. These findings demonstrated that the drug was thoroughly mixed in the carriers with the loss of little crystallinity. Carvedilol crystals appeared to be incorporated into the particles of polymers.

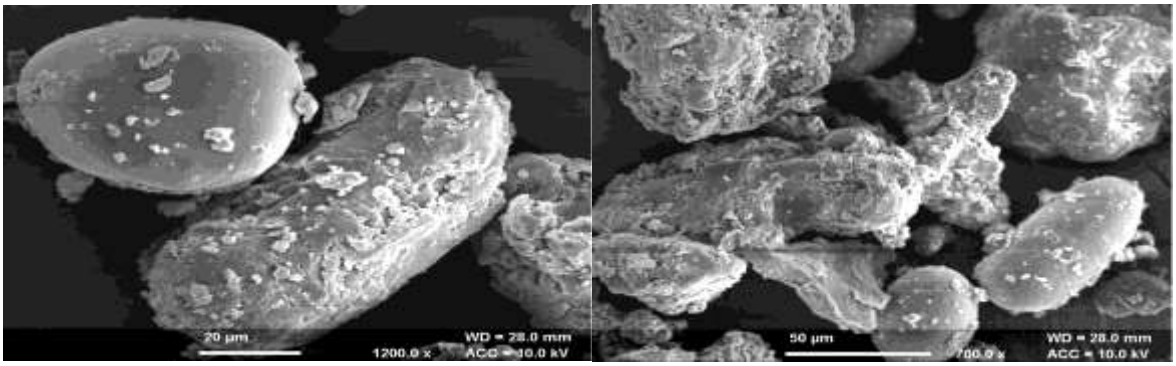

Figure 15. SEM photograph of optimized solid dispersion

Discussion:-

Solid dispersion is the most usable technique for improved solubility of poorly water soluble drugs and also increases the bioavailability of drug by avoiding the first pass metabolism and increases the therapeutic efficiency of drug by reaching into systemic circulation. Solid dispersion basically a drug-polymer with two component system. Carvedilol is a antihypertensive drug which is practically insoluble in water and used for treating mild to severe congestive heart failure(CHF),left ventricular dysfunction(LVD) following heart attack in people who are otherwise stable and for treating high blood pressure. The present study solubility enhancement of antihypertensive drug (carvedilol) using solid dispersion method using different carriers HPMC, Locust bean gum, PEG 6000&Sodium starch glycolate.

Locust bean gum is a galactomannan vegetable gum extracted from seeds of carob tree and used as a binding agent, flavorings agent etc. HPMC is used as a viscosity increasing agent in formulation.PEG 6000 is used as a plasticizer which increases the solubility of formulation using solid dispersion in appropriate polyethylene glycol. Sodium starch glycolate is used as a disintegrants in formulation. In this study we prepared the solid dispersion of carvedilol using solvent evaporation method and fusion methods. In both the methods various carriers are used in formulations. The results produced were characterized by X-RD, SEM, *in vitro* dissolution studies.

Potassium bromide disc technique was employed to obtain the FTIR spectra of the drug and formulations using an FTIR spectrophotometer. The drug was identified by infrared spectroscopy and characteristics peak obtained compared with standard spectra of pure drug, physical mixture and formulation in figures. The IR spectra of pure drug showed the characteristics peaks at 3340.11 cm^{-1} (N-H, stretching), 2978.17 cm–1 (C-H), 1399.84 aromatic plane bending, 1647.61(MethyleneCyclohexane),1713.12(C=O),1598.26(C=C),2992.39(CH),1712.20(C=0),1660.66(methylenecyclohexane),1058.18(sulfoxides),1411.76(aromatic plane bending) and in physical mixture showed the peak at 2992.39(C-H),1712.20(C=O),1660.66(methylene cyclohexane),1058.18(sulfoxides),1411.76(aromatic plan bending), 1541.44(C=C) aromatic. But in case of formulation different peaks are shown at 2973.20(C-H),1054.07(sulfoxides),1267.15(aromatic plane bending). Shifting of peaks confirmed the interaction of polymers with the pure drugs .

The formulations were prepared by direct solvent evaporation, physical mixing and fusion method .The angle of repose values for formulations range from 23.61±0.015 to 27.91±1.002. and respectively .Bulk and tapped densities were used for the measurement of compressibility index .The bulk and tapped values for formulations range from 0.240±0.020 to 0.850±0.010 and 0.320±0.010 to 0.610±0.01 respectively. The Carr's index and Hauser's ratio values for formulations range from 12.09±0.51-18.60±0.13 and 1.06±0.02 to 1.33 ±0.045 respectively. Thus all formulations exhibited good flow characteristics.

Carvedilol solid dispersion were formulated according to central composite designs(CCD) to study the effect of independent variables on solid dispersion of carvedilol. The methods differs in the process of solid dispersion formulations. Optimization of carvedilol is done by using design expert software-11.In optimization two independent factors X_1 (locust bean gum),X_2(Peg 6000).In percentage yield range of optimized batch is 66.5328.The combination of proportion of locust bean gum and peg 6000 the percentage yield increases. In the drug release the concentration of locust bean increases drug release decreases, when we increase the peg 6000 concentration drug release is increases. The optimized drug release value is 90.2833. In drug content combination of polymers increase the drug content increases the optimized range is 94.0643. *In vitro* drug release study solvent evaporation method 93.46 is maximum drug releases and in fusion method 93.20.Both the model follows the peppas models and R^2 value in solvent evaporation method is 0.9686 and in fusion method is 0.9878 and follows the peppas model and drug release is 93.20.At last the optimized batch X-ray diffraction value is 2θ is 5.8318- 44.8085 and scanning electron microscopy the results shows that the prepared agglomerates were spherical in shape, which enabled them to flow very easily.

Conclusion

The study was done to perform the solubility enhancement of carvedilol using solid dispersion method.

Acknowledgments

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Conflict of Interest

No conflict of interest

evaluation, in-vitro characterization, the drug release was maximized because of the increase in the amount of hydrophilic polymers to hydrophobic polymer maximize drug release and increased concentration of polymers produce reproducible results. This study indicated that the solubility of carvedilol was increased by solvent evaporation method when compared with fusion method. Incorporation of hydrophilic polymers in solid dispersion increases dissolution rate of the drug. hydrophilic polymers (HPMC, locust bean gum) and PEG 6000 and sodium starch glycolate as plasticizer and Disintegrate. evaporation and fusion method using All the prepared formulations showed good uniformity regards to drug content, percentage yield, and physiochemical parameters, drug release. Based on

References:-

1. Shrestha S, Sudheer P, Sogali BS, Soans D. A Review: Solid Dispersion, a Technique of Solubility Enhancement. Journal of Pharmaceutical Research. 2017; 16 (1):25-31.
2. Bhowmik D, Harish G, Duraivel S, Kumar BP, Raghuvanshi V, Kumar KS. Solid Dispersion-An approach to enhance the dissolution rate of poorly water soluble drugs. The Pharma Innovation. 2013; 1:24.
3. Bahmani K, Singla Y. Enhanced solubility of antihypertensive drug using hydrophilic carrier-based potent solid dispersion systems. The Pharma Innovation Journal 2018; 7(12): 432-442
4. P. Shankarguru, D. Ramya, B.N.V.Hari. Effect of water content in kneading method of solid dispersion technique for solubility enhancement. International Journal of Applied Pharmaceutics. 9, 5 (Sep. 2017), 14-21
5. Huang Y, Dai W-G. Fundamental aspects of solid dispersion technology for poorly soluble drugs. Acta Pharm Sin B 2014; 4(1): 18-25.
6. Dewan I, Hossain MA, Islam SA. Formulation and evaluation of solid dispersions of carvedilol, a poorly water soluble drug by using different polymers. Int J Res Pharm Chem. 2012; 2:585-93.
7. Sharma A, Jain CP, Tanwar YS. Preparation and characterization of solid dispersions of carvedilol with poloxamer 188. Journal of the Chilean Chemical Society. 2013; 58(1):1553-7

8. Tapas A, Kawtikwar P, Sakarkar D. An improvement in physicochemical properties of carvedilol through spherically agglomerated solid dispersions with PVP K30. Acta Pol. Pharm. 2012 Mar 1; 69(2):299-308.
9. Manohar SD, Shridhar DA, Mallikarjuna SC. Solubility and dissolution enhancement of carvedilol by solid dispersion technique using gelucire 50/13. Int J Pharm Sci Rev Res. 2014; 29:161-5.
10. Balakrishnaiah M, Gupta VR. Formulation and *In Vitro/In Vivo* Evaluation of OlmesartanMedoxomil solid dispersions incorporated E/R trilayer matrix tablets by geomatrix. International Journal of Drug Delivery. 2017; 8(4):125-33.
11. FonnerJr DE, Banker GS, Swarbrick J. Micromeritics of granular pharmaceutical solids i: Physical properties of particles prepared by five different granulation methods. Journal of pharmaceutical sciences. 1966; 55(2):181-6.
12. Wong TW, Chan LW, Heng PW. Study of the melt pelletization process focusing on the micromeritic property of pellets. Chemical and pharmaceutical bulletin. 2000; 48(11):1639-43.
13. Muatlik S, Usha AN, Reddy MS, Ranjith AK, Pandey S. Improved bioavailability of aceclofenac from spherical agglomerates: development, in vitro and preclinical studies. Pakistan journal of pharmaceutical sciences. 2007; 20(3):218-26.
14. Eloy JO, Marchetti JM. Solid dispersions containing ursolic acid in Poloxamer 407 and PEG 6000: A comparative study of fusion and solvent methods. Powder technology. 2014; 253:98-106.
15. Save T, Venkitachalam P. Studies on solid dispersions of nifedipine. Drug development and industrial pharmacy. 1992; 18(15):1663-79.
16. Craig DQ, Newton JM. Characterisation of polyethylene glycol solid dispersions using differential scanning calorimetry and solution calorimetry. International journal of pharmaceutics. 1991; 76(1-2):17-24.
17. Patil MP, Gaikwad NJ. Preparation and characterization of gliclazide-polyethylene glycol 4000 solid dispersions. Actapharmaceutica. 2009; 59(1):57-65.

18. Real D, Orzan L, Leonardi D, Salomon CJ. Improving the Dissolution of Triclabendazole from Stable Crystalline Solid Dispersions Formulated for Oral Delivery. AAPS PharmSciTech. 2020; 21(1):16.
19. Choudhury, P., Deb, P. and Dash, S. Formulation and statistical optimization of bilayer sublingual tablets of levocetirizine hydrochloride and ambroxol hydrochloride. Asian Journal of Pharmaceutical and Clinical Research.2016; 5: 228-234
20. Brion M, Jaspart S, Perrone L, Piel G, Evrard B. The supercritical micronization of solid dispersions by Particles from Gas Saturated Solutions using experimental design. The Journal of Supercritical Fluids. 2009; 51(1):50-6.
21. Izma, H., Martono et al. The optimization of RP-HPLC condition using response surface methodology box-behnken design for simultaneous determination of metformin HCL and glimepiride in spiked plasma. International Journal of Applied Pharmaceutics.2019; 12: 24-35.
22. Zinjad SS, Udmale DA, Suryawanshi AD, Jadhav SL, Gaikwad DD. Solubility Enhancment of Azithromycin by Solid Dispersion Method by using Polymer PVP K 90. Journal of Drug Delivery and Therapeutics. 2019; 9(3):121-4.
23. Sharma KS, Sahoo J, Agrawal S, Kumari A. Solid dispersions: A technology for improving bioavailability. J Anal Pharm Res. 2019; 8(4):127-33.
24. Bhatia M, Devi S. Development, Characterisation and Evaluation of PVP K-30/PEG Solid Dispersion Containing Ketoprofen. ACTA PharmaceuticaSciencia. 2020; 58(1).
25. Yang J, Grey K, Doney J. An improved kinetics approach to describe the physical stability of amorphous solid dispersions. International journal of pharmaceutics. 2010; 384(1-2):24-31.
26. Khan S, Batchelor H, Hanson P, Saleem IY, Perrie Y, Mohammed AR. Dissolution rate enhancement, in vitro evaluation and investigation of drug release kinetics of chloramphenicol and sulphamethoxazole solid dispersions. Drug development and industrial pharmacy. 2013; 39(5):704-15.