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Research Article

Preparation and Evaluation of Carvedilol Microsphere by Spray Drying Technique: Effect of Process Parameters on Formulation

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ABSTRACT

The aim of this study was to preparation and evaluation of carvedilol microsphere using spray drying technique and to optimize the spray drying parameters to get the optimum formulation. The carvedilol microsphere were prepared by spray drying technique using ethyl cellulose and PEG 6000 as sustained release polymers. Nine batches were prepared by using ethyl cellulose and PEG 6000 in different polymer ratios and prepared microspheres were evaluated for the particle size, percentage drug entrapment and percentage drug release.Experimental designs were built to investigate the effects of five parameters on production yields and particle size of spray-dried microspheres of carvedilol. These factors concerned aspiration speed, flow rate, drug polymer ratio, temperature difference between inlet temperature and outlet temperature. Three formulations containing ethyl cellulose, PEG 6000 and carvedilol were tested. The aim of the study was to optimize the operating conditions to maximize production yields while minimizing the particle size. The characterization of microsphere revealed the poor flowability of the spray-dried products due to significant cohesiveness and very small size (less than 20μm).

INTRODUCTION

Spray-drying is extensively used in the pharmaceutical industry to produce raw drug or excipients or as microencapsulation process. This technique transforms liquid feed into dry powder in a one step, continuous particle processing operation and can be applied to a wide variety of materials[9]. Despite the main advantages of spray-drying, processing variables must be well controlled to avoid difficulties such as low yields, sticking, or high moisture content, which are often encountered with laboratory scale spray-dryers. The optimization of spray-drying process involves the evaluation of parameters concerning both spray-dryer and feed formulation[8].

Carvedilol is a competitive adrenoreceptor antagonist that inhibits activity at the β_1, β_2, and $\alpha_1$adrenergic receptors and exhibits a number of ancillary properties, such as antioxidant effects, inhibition of smooth muscle proliferation, and calcium antagonistic blocking activity. The original formulation of Carvedilol is approved by the US Food and Drug Administration (FDA) to be administered twice daily, but it is also administered four times a day to twice a day and is widely used alone or in combination with other agents for the treatment of essential hypertension, as well as for improving survival in patients with mild-to-severe heart failure and reducing cardiovascular mortality in patients with systolic dysfunction after MI. Sustained release formulation of Carvedilol been developed that may provide levels of exposure to Carvedilol similar to those achieved after administration of the current twice-daily formulation over extended period[5].

The aim of this study is to evaluate the effects of process and formulation parameters on process yields and particle size of spray-dried products in order to optimize the process (production yields ≥50% and particle size ≤20μm). Statistically designed experiments were used as they allow the evaluation of both the different factors and their interaction.

Carvedilol is a lipophilic molecule, so it is advisable to use combination of Hydrophilic and hydrophobic polymer to prepare its sustained release formulation. Ethyl cellulose is a non-biodegradable and biocompatible polymer and it is one of the extensively studied encapsulating materials for sustained release formulation. Polyethylene glycol has been used extensively as a hydrophilic carrier for increasing dissolution of poorly water soluble drug as it creates hydrophilic environment. Hence for preparation of sustained release microsphere, combination of Ethyl cellulose and PEG 6000 was selected as matrix forming polymers[2]. The matrix of ethyl cellulose is capable of sustaining release of drug so it sustains release of drug beyond limit; hence in order to control the release of drug, hydrophilic polymer PEG 6000 was added[1].

3^2 full factorial design was initially built to estimate formulation parameters on in vitro drug release and particle size and to determine the optimal values to be applied[7].

Process validation was carried out using the optimal conditions to assess the repeatability and reproducibility of spray-drying technique. Finally the spray-dried products were characterized.

MATERIALS AND METHODS

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Table 1: Formulation of Eudragit based Floating Microspheres

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carvedilol(mg)	250	250	250	250	250	250	250	250	250
Ethyl cellulose(gm)	2	2	1.5	2	1.5	1	1.5	1	1
PEG 6000(gm)	0.25	0.75	0.5	0.5	0.75	0.5	0.25	0.25	0.75
Aerosil(%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Methanol(ml)	50	50	50	50	50	50	50	50	50

Table 2: 3^2 full factorial design

Formulation	Code Value*	
	X_1	X_2
A_1	-1	-1
A_2	0	-1
A_3	1	-1
A_4	-1	0
A_5	0	0
A_6	1	0
A_7	-1	1
A_8	0	1
A_9	1	1

Table 3: Levels of Independent Variables

Code Value	Actual value*	
	X_1 (gm)	X_2 (gm)
-1	1	0.25
0	1.5	0.5
1	2	0.75

**X_1 – conc of ethyl cellulose X_2 - conc of PEG 6000*

Materials: Carvedilol was obtained from Matrix Laboratories, Nashik as a gift sample. Ethyl cellulose (EC 18-22 centipoise) was obtained from Pharmaceutical coating ltd., Mumbai.

PEG 6000(hydroxyl no 16-23) was obtained from Loba chemie, Mumbai. Aerosil was obtained from Aroma chemical, Mumbai. Potassium dihydrogen orthophosphate and Sodium hydroxide pellets were obtained from merck specialities , Mumbai. All solvents used were of analytical grades and were used as obtained.

Preparation of microspheres: Sustained release microspheres of Carvedilol were prepared by using spray drying technique. Different ratio of Ethyl cellulose and PEG 6000 were dissolved in mixture of solvent system (100 ml) of methanol. Solution was sonicated for 30 min to completely dissolve polymers. After polymers completely dissolved, Carvedilol was added and again same solution was sonicated for 15 min. Finally solution was sprayed through 0.7 mm nozzle of a spray dryer (labultima mini spray dryer, Mumbai). The difference between inlet temperature and outlet temperature was kept to be 20°C. Aspirator speed was set between 30 and 35. Feed pump flow rate was kept to be 5ml/min. Concentrations of the ethyl cellulose and PEG 6000 were optimized based on the % drug release, particle size. (Table1).

3^2 Full Factorial Design for Carvedilol Sustained Release Microspheres Formulations: A 3^2 full factorial design was selected for this experiment. It consists of 9 full factorial design points. This design involves two independent formulation variables viz. concentration of Ethyl Cellulose(X_1) and the concentration of PEG6000(X_2). The dependent variables investigated were the % drug release after 12 hrs (Y_1), and particle size (Y_2).(Table 2 and 3). Values for independent variables were decided i.e. concentration of Ethyl cellulose 1gm to 2gm and concentration of PEG 6000 0.25gm to 0.75gm (Table 1, 2 and 3)

DATA ANALYSIS

Various computations for the current optimization study using Response Surface Methodology (RSM) were carried out, employing the Design Expert Software (Version 7.1.4, Stat-Ease Inc., Minneapolis, MN). Statistical second-order model including interaction and polynomial terms were generated for all the response variables using multiple linear regression analysis (MLRA). The general form of the model is represented as in equation.

$$Y = \beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_1X_2+\beta_4X_1^2+\beta_5X_2^2$$

Where β_0, the intercept is the arithmetic average of all quantities outcomes of 9 runs, β_1 to β_8 are the coefficient computed from the observed experimental values of Y, and X_1 and X_2 are the coded levels of the independent variable(s). The terms X_1X_2 and X_i^2 (i = 1, 2) are the interaction and polynomial terms, respectively. The

statistical validity of the polynomials was established on the basis of Yate's ANOVA provision in the Design Expert Software. Subsequently, feasibility as well as grid search was performed to locate the composition of optimum formulations

Validation Of Optimization Model: Four optimum formulations were selected by feasibility grid search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations[8]. The criterion for selection of optimum was primarily based on the highest possible values of release of drug after 12 hrs, and smaller size of particle size for the sustained release microspheres formulations. The resultant experimental data of response properties were subsequently quantitative compared with predicted values.

Process ValidationTo estimate the effect of process variables on the final product; the process validation of spray drying was carried considering aspiration speed, flow rate, drug: polymer concentration, and temperature difference as the process variables. Based on the optimization study and initial trail the appropriate ranges of process variable were set.

Three replicates were produced on three different days to evaluate the fidelity of the technique table 6.

For these experiments the processing parameters used were the optimal conditions determined from the response surface designs. Yields and residual moisture obtained in the nine experiments were analyzed and an analysis of variance was performed. Repeatability and reproducibility were estimated.

Evaluation 0f Microsphere: 3.1 % Drug entrapment: Microspheres equivalent to 50 mg of drug was dissolved in 10 ml methanol and shaken vigorously for 30 min to dissolve polymer and to extract the drug. After filtration through whatman filter, the drug concentration in the methanol phase was determined spectrophotometrically at 241 nm. The drug content was determined by using following formula.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Particle size: Particle size analysis was carried out by using optical microscopy and motic microscopy. About 200 microspheres randomly selected and their size was determined by using optical microscope fitted with standard micrometer scale.

Process yield: Dried microspheres were accurately weighed, and considering the total amount of drug and polymers used for preparing the feed solution, the process yield was calculated, as a percentage, using the following formula.

$$\% \text{ Process yield} = \frac{\text{Total weight of microsphere}}{\text{Total weight of drug polymer}} \times 100$$

Morphology: The external and internal morphology of the microspheres were studied by scanning electron microscopy (SEM). For SEM the samples were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Afterwards, the stub containing the coated samples was placed in the scanning electron microscope (JSM-6360A, JEOL, Tokyo, Japan) chamber.

In vitro release study: The dissolution studies were carried out using USP apparatus type II. The operating conditions were: dissolution media: 900 ml phosphate buffer pH 6.8. The temperature was controlled at 37.5^0C and the rotational speed was maintained at 100 rpm. Each run was carried out in triplicates; each formulation was enclosed in muslin cloth and placed one in each dissolution vessel. Drug content was determined spectrophotometrically by using a Jasco-530 UV/ Vis-spectrophotometer. The concentration was determined by using calibration curves of Carvedilol in phosphate buffer pH 6.8. The drug concentration was determined by calibration curve equation Y = 0.1154X-0.0527 (r^2).

RESULT AND DISCUSSION

Evaluation of Dependent Variables and Mathematical Modeling for Sustained Release Microspheres

The values of dependent variables of sustained release microspheres formulations are described in Table 4. These values are necessary to get polynomial equations from Design Expert software for the respective dependent variable.

Regression analysis : The coefficients of the polynomial equations were generated using multiple linear regression analysis (MLRA) for % drug release and particle size. The coefficients (b1 to b5) were calculated with b_0 as the intercept. The coefficients b_1 to b_5 represent various quadratic and interaction terms as shown in equation

% DRUG RELEASE =+68.34+17.77*X2-3.97*X2*X2-8.57*X12+1.09*X1*X1+1.05*X2*X1-0.32*X2*X2*X1+3.76*X2*X1*X1-2.44*X2*X2*X1*X1

The Model F-value of 41.82 implies the model is significant. There is only a 0.0003

% possibility of high model F value occurs due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant. The "Pred R-Squared" of 0.9881 is in reasonable agreement with the "Adj R-Squared" of 0.9731." A ratio greater than 4 is desirable. Here a ratio of 17.391 indicates an adequate signal.

R^2 =0.9881

In this case factor conc. of ethyl cellulose (X1) and concentration of PEG 6000 (X2) is a significant model term and which significantly affects the drug release.

The quadratic models generated from the regression analysis for % drug release were used to construct the 3-dimensional graphs. The effects of independent variables

Table 4 : Values of dependent variables of sustained release Microspheres

Formulation	Code		Particle size (µm)	% Drug release after 12 hr
	X1	X2		
F1	-1	-1	14	45.25
F2	-1	0	22	64.07
F3	-1	1	19.9	63.01
F4	0	-1	19.2	54.31
F5	0	0	17	74.61
F6	0	1	13.2	90.96
F7	1	-1	18	55.48
F8	1	0	15.4	78.59
F9	1	1	17.8	88.78

indicate model terms are significant.

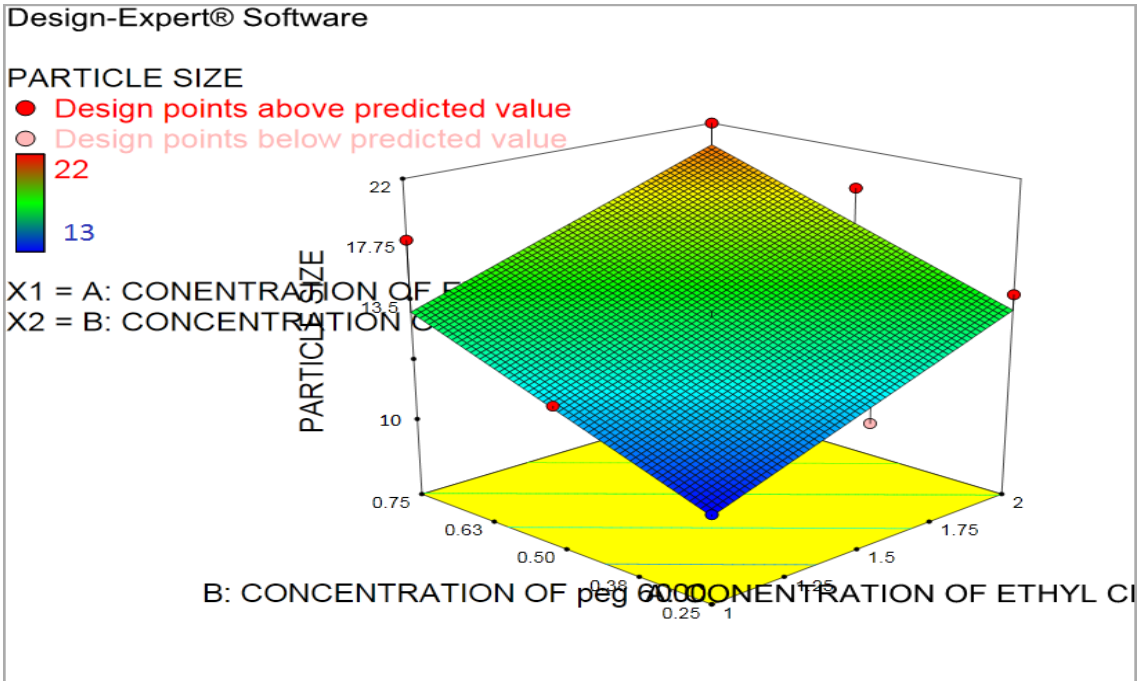


Figure 1: Three dimensional response surface plots for particle size

on the response parameters were visualized from the contour plots (figure1).

The 3-D plots shows that as the concentration of Ethyl Cellulose increase the % drug release from the microsphere get decreased significantly and as the concentration of PEG 6000 increases the % drug release get increased from the microsphere. The equation suggests that factor X_1 has positive effect on % drug release. As level of X_1 increases % drug release also increases. X_2 had negative effect on the % drug release that leads to decrement in the % drug release as levels of X_2 increases.

The mathematical model generated for Entrapment efficiency was found to be significant. The Model F-value of 378.69 implies the model is significant. There is only a 0.003% possibility of high model F value occur due to noise. Values of "Prob > F" less than 0.0500 Values greater than 0.1000 indicate the model terms are not significant model. The "Pred R-Squared" of 0.9816 is in reasonable agreement with the "Adj R-Squared" of 0.9958." A ratio greater than 4 is desirable. Here a ratio of 6.784 indicates an adequate signal.

R^2=0.9984

Particle size =+12.83-2.03*X2.53*X2*X2-3.7*X1-0.067*X1*X1-1.7*X2*X1+2.4*X2*X2*X1-1.53*X2*X1*X1+0.67*X2*X2*X1*X1

In this case factor conc of Ethyl Cellulose (X_2) as well as concentraion of PEG 6000 does not significaly affects the % Entrapment efficiency Which is also indicated by higher F value i.e. 5.75

The quadratic models generated from the regression analysis for particle size were used to construct the 3-dimensional graphs. The effects of independent variables on the response parameters were visualized from the contour plots (figure 2).

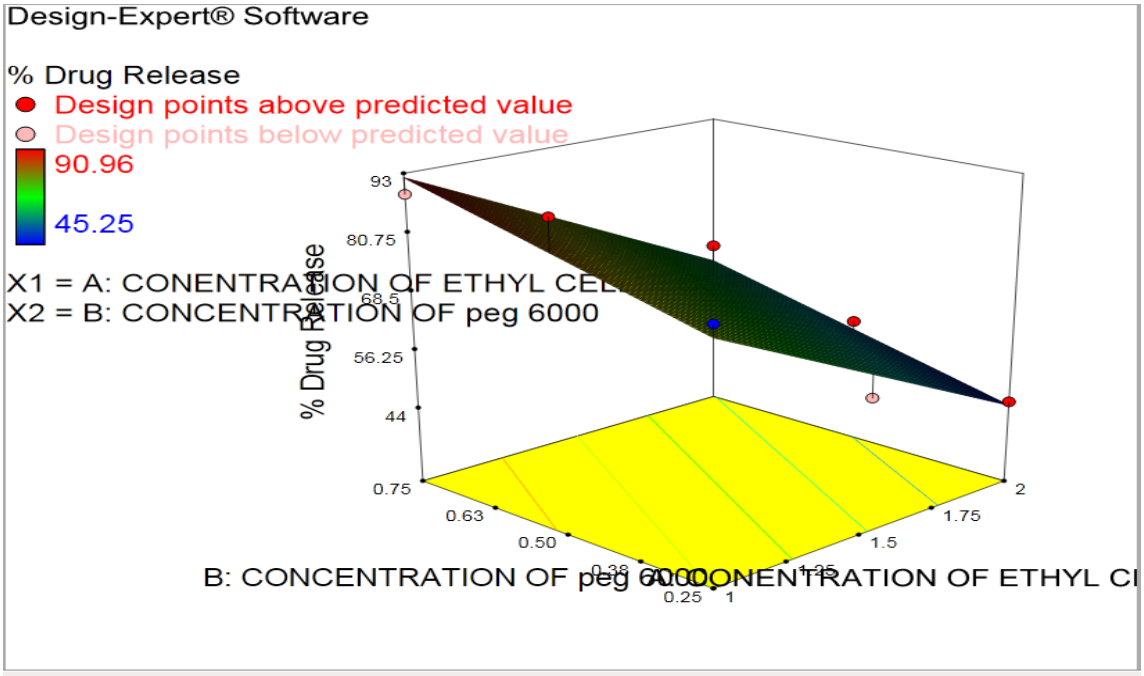


Figure 2: Three dimensional response surface plots for % Drug Release

Table 5: Comparison of experimental results with predicted responses of Sustained release microsphere formulations

Batch code	Composition X1 (gm)	X2(gm)	Response	Predicated value	Experimental value	Residuals	% Error
O1	1	0.75	Particle size	13.863	13.801	-0.04	0.54
			% Drug release	92.39	92.67	0.28	0.001
O2	1.01	0.75	Particle size	13.77053	13.75	-0.02	0.93
			% Drug release	92.22156	92.76	0.54	0.07
O3	1.01	0.74	Particle size	13.68866	13.64	-0.04	0.55
			% Drug release	91.88746	91.91	0.03	0.22
O4	1	0.74	Particle size	13.60582	5.33	-0.02	0.37
			% Drug release	97.00125	97.12	-0.118	0.12

The 3-D plots shows that as the concentration of Ethyl Cellulose as well as concentration of PEG 6000 does not significantly increase or decrease the particle size.

The mathematical model generated for particle size was found to be significant. The Model F-value of 5.75 implies the model is significant. There is only a 0.0402% possibility of high model F value occurs due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant. The "Pred R-Squared" of 0.9870 is in reasonable agreement with the "Adj R-Squared" of 0.9870. A ratio greater than 4 is desirable. Here a ratio of 6.784 indicates an adequate signal.

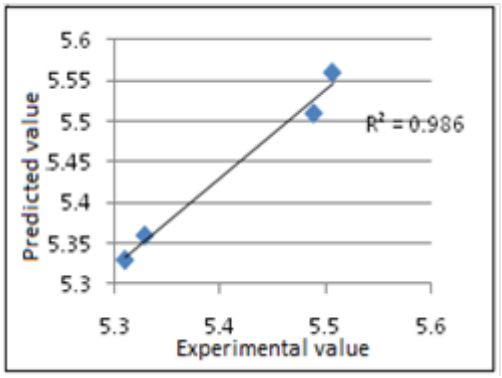
R^2 =0.9870

The criteria for selection of suitable feasible region were primarily based upon maximum % drug release and minimum particle size.

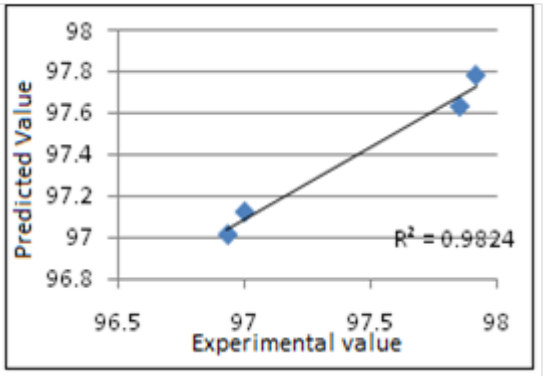
Based on the region: rel $_{12h}$ > 90%; particle size range: ≤20µm.

Validation of Optimum Floating Microspheres Formulations: For all 4 checkpoint formulations, the results were found to be within limits. Table 5: lists the composition of the checkpoints, the predicted and experimental values of all the response variables, and the percentage error in prognosis.

Figure 3 shows linear correlation plots between the observed and predicted values of efficiency, % drug and rel_{12hrs}, and particle size. The linear correlation plots drawn between the predicted and observed responses demonstrated higher values of R^2, indicating excellent fitting of model. Upon comparison of the observed responses with that of the anticipated responses, the prediction error varied between -0.07 and 0.92%. Thus, the low magnitudes of error as well as the significant values of R^2 in the current study indicate a high



(a)



(b)

Figure 3: Linear plots between observed and predicted values of (a) rel $_{12h}$(b) particle size

It also shows as polymer concentration increased particle size increased. This is expected as same volume of liquid droplet contained greater amount of dissolved polymer hence when this droplet dried in the heating environment of spray dryer leads to formation of larger particles.

Table 6: Effect of process parameters on formulation properties

Batch no	Temp. Difference	Polymer conc. (EC:PEG 6000)	Aspiration speed	Flow rate (ml/min)	% yield	Particle size	% drug entrapment
1	10	2:1	35	5	39.42	13.2	96.72
2	20	2:1	35	5	47.42	13.5	98.06
3	30	2:1	35	5	42.85	13.7	97.37
4	20	2:1	30	5	44.32	13.8	96.78
5	20	2:1	35	5	42.19	13.1	98.88
6	20	2:1	40	5	39.9	13.5	95.89
7	20	2:1	35	5	47.42	13.1	98.99
8	20	3:1	35	5	46.85	22.6	99.23
9	20	4:1	35	5	48.82	21.1	98.99
10	20	2:1	35	5	48.32	13.3	97.67
11	20	2:1	35	10	51.42	14.6	98.34
12	20	2:1	35	15	50.85	19.4	97.99

Table 7 Evaluation Parameters for % drug entrapment of sustained release Microspheres

Formulation code	% Drug entrapment
F1	97.00
F2	96.75
F3	94.8
F4	96.08
F5	94.0
F6	93.12
F7	95.98
F8	93.92
F9	93.92

prognostic ability of sustained release microspheres formulations of Carvedilol using RSM optimization.

Effect of spray drying process variables on process yield and particle size

Particle size: As shown in above tables particle size has been majorly affected by flow rate and polymer concentration. Table shows flow rate increase particle size also increases. This is due to the fact that formation of larger droplet at higher flow rate than slow flow rate. When this larger droplet dried in the heating environment of spray drier it leads to formation of larger particle.

% Process yield: There are two main reasons for a low powder yield obtained on spray drier with formulations. First, the design of the cyclone separator, which cannot trap particles of diameter 2 µm, but lets them pass through into the outlet air. Secondly, inadequate process conditions that cause particles to adhere to the inside wall of the spray-dryer. Hence yield below 50% is being considered as a standard yield of lab scale spray drier.

Table 8: Evaluation Parameters for % process yield of sustained release Microspheres

Formulation code	% Process yield
F1	44.00
F2	45.81
F3	46.44
F4	46.22
F5	45.81
F6	44.14
F7	43.10
F8	44.76
F9	44.32

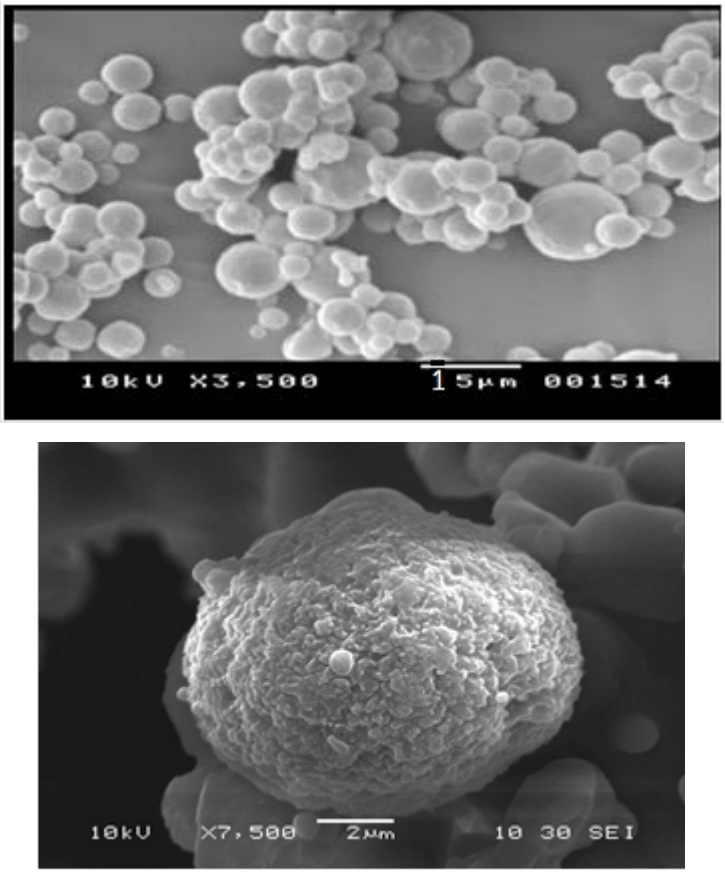


Figure 4: Scanning electron microphotographs of floating microspheres showing spherical structure and particle size

% Drug entrapment: Drug entrapment is a total amount of drug entrapped within the polymer matrix of microspheres. Entrapment efficiency depends on drug solubility in the solvent system used for processing and physicochemical properties of drug. As Carvedilol was completely soluble in methanol, homogeneous solution of drug and polymer obtained for processing and hence drug entrapment was up to it maximum level. Table shows that all the batches of validation shows drug entrapment within 95-98%.

So finally one batch was selected for further study and three consecutive batches were produced in order to determine consistency of process of spray drying process as shown in table 6

EVALUATION OF MICROSPHERES

Particle size: As shown in Table IV mean particle size of microspheres was in the range of 13.2 -20µm. During spray drying process, liquid feed is sprayed in a heating environment through nozzle where the feed comes in contact with drying air. When droplets come in contact with drying air, solvents evaporates leading to formation of solid microspheres. Feed pump speed, composition of feed, size of nozzle, rate of aspiration are the main parameters affecting particle size. As feed pump speed increases, more feed is sprayed in heating environment per unit time which leads to increase in particle size. One of the major parameters affecting particle size is a composition of feed.

As concentration of polymer in feed increases the microsphere size also gets increases. This is attributed to

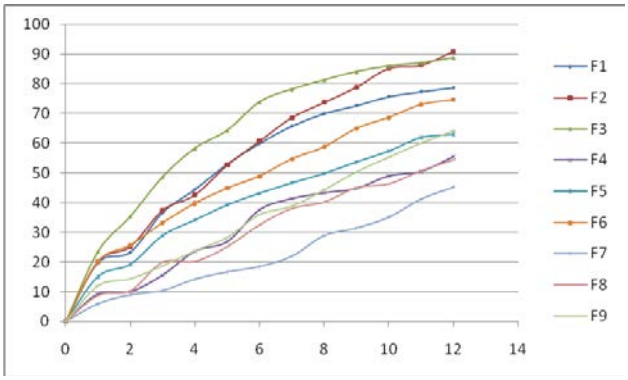


Figure5: Drug release profile of CP from formulations F1 to F9 (n=3).

the greater amount of polymer concentration in the same volume of liquid droplet as the concentration of polymer increased.

Entrapment Efficiency: Percentage Drug entrapment in the spray dried microspheres includes drug entrapped within the polymer matrices. Values were in the range of 93-97 % for spray dried microspheres (table VIII). Various co-solvents such as methanol, ethanol, and ethyl acetate have been often used for microspheres preparation since they can help to dissolve drugs in the major solvent and probably achieved higher drug encapsulation/entrapment. Entrapment efficiency depends on drug solubility in the solvent system used for processing and also on physicochemical properties of drug. As Carvedilol has maximum solubility in methanol, it was dissolved in methanol and homogeneous solution of drug and polymer obtained for processing and hence drug entrapment was up to it maximum level.

Process yield: Process yield of drug loaded microspheres of different polymer to drug ratio is shown in Table 20. Technological parameters for spray dryer produced microspheres with yield in the range of 45- 50 %.(table 8)

This result can be attributed to the loss of smaller particles of polymer in fact, the spray dryer is not equipped with a trap to recover lightest and smallest particle which are exhausted by aspirator during process.

Morphology: SEM study indicates that spray dried microspheres were small in size and their surface was slightly rough and some shows deformations, which are common characteristics of microspheres obtained by spray drying process. This morphology is mainly due to solvent evaporation process that takes place when a liquid droplet comes in contact with drying air in the heating chamber. Solvent evaporation rate of methanol is quick and this allows one to achieve microspheres with good sphericity than those obtained using solvent with high distillation temperature. Figure 4 show microspheres were spherical but there are some which shows deformation. Figure 4 shows slightly rough surface of microspheres.

In-vitro drug release study: The drug release from microspheres in phosphate buffer pH 6.8 is shown in figure 5. Release of drug from F4, F5, F7, F8 and F9 was only 45-64 % within 12 hr. Drug released from F1, F2 and F3 were 78-90% within 12 hr. Drug release from F6 was 76% within 12 hr. No formulation is showing burst release which indicates the absence of free particles on the surface of microspheres which further confirmed by SEM study. Ethyl cellulose is a pH independent material thus the release occurs by diffusion process and would not be affected by pH of medium.

Dissolution study shows that as concentration of Ethyl cellulose increased the release was decreased which may be attributed to the slower rate of diffusion medium into the microsphere due to increase in thickness of polymer matrix. This might be the reason for slower rate of release of drug from F6 as concentration of ethyl cellulose was higher. Mechanisms like Carrier controlled dissolution, the continuous drug layer formation have been proposed to account for increase in dissolution kinetics of drugs from PEG 6000. It is hydrophilic material and it modifies the surface properties by wetting material. Dissolution data shows as concentration of PEG 6000 increased the drug release also increased which may be attributed to reduction in angle of contact between dissolution media and hydrophobic material due to improvement of wetting. This Improvement of wetting of microspheres results from formation of thin film of PEG 6000 around a drug substance which modifies the hydrophobicity of their surface.

CONCLUSION

The present study reports on the development of Sustained release microspheres of Carvedilol by using ethyl cellulose and PEG 6000 as a release retarding polymer using spray drying process and to estimate the effect of process parameters on formulation properties. Microspheres were in size ranging from 13-22 micron with significant stability and shows retardation of release up to 12 hr. So present dosage form could able to control blood pressure level for extended period of time and may improve patient compliance by single dose. The process of formulation of microspheres was validated and report of validation shows consistency of process for producing microspheres meeting predetermined specification.

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