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Original Article

Design and Development of Reconstitutable Sustained Release Suspension of Linezolid by Spray Drying Technique

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Reconstitutable sustained release suspension,
Linezolid.

Abstract

The purpose of this research work was to design and evaluation of a stable reconstitutable Sustained release suspension for pediatric and geriatric patients using spray drying techniques. Linezolid is the drug of choice in treatment of infections caused by multi-resistant bacteria. The microcapsules were prepared by spray drying method. Drug loaded microcapsule were prepared using Eudragit RS and RL100 and ethyl cellulose in three different polymer ratio. The influence of the drug to polymer ratio and feed flow rate was studied on the properties of microcapsule using a 3^2factorial design. The drug to polymer ratio (X1) and feed flow rate (X2) were selected as independent variable and percentage yield, particle size, encapsulation efficiency, Q_6, Q_8, $t_{90\%}$ were selected as dependent variables. Accelerator stability study of reconstitutable SR suspension was performed as per ICH guideline. From the study of the preliminary and factorial batches, all the physical characteristics of microcapsules are in acceptable range. Results was clearly indicated that drug to polymer ratio and feed flow rate had significant influence on percentage yield, particle size, encapsulation efficiency, Q_6, Q_8, t_{90}, Diffusion coefficient (n) and Release rate constant (k). Form the study, the optimized formulation (S3) showed 99.12% drug release at the end of 12 hrs with drug to polymer ratio (1:1.3) and feed flow rate (5 ml/min) respectively for obtaining the higher percentage of yield, maximum encapsulation efficiency, Particle size of microcapsules which is found to be 87.82%, 99.07% and 16.06µm consequently. SEM showed that microcapsules were spherical with smooth surface. The dissolution profile of optimize batch exhibits similarity factor (f_2=82.35) and dissimilarity factor (f_1=2.90) with theoretical release profile of linezolid. Microcapsule prepared with 1:1.3 drug to polymer ratio were selected for SR suspension formulations since they have higher loading efficiency and suitable micromeritic properties to disperse in aqueous medium. Results reported the release profiles of suspension prepared from microcapsules had no significant difference (P>0.05) was observed in CPR for sustained release suspension on 1day and after 15days which indicates the suspension stability. Results clearly revealed that drug release studies of SR suspension formulation did not show any statistically significant differences (P>0.05) from the properties of microcapsule alone.

1. Introduction

The basic goal of any treatment is to cure the sign and symptom of disorders and provide comfort to the patients. Tablets and capsules are unsuitable for administering with high dose of active pharmaceutical ingredient and since individual large dose is difficult to swallow or require the administration of several tablets or capsule at a time, making it less patient compliant. Also chewable tablets are also not ideal with pediatric and geriatric patients due to need of chewing, poor taste masking and lack of control release possibility. Oral drug delivery is most preferred route of drug delivery [1, 2]. Oral liquid suspensions are majorly designed for the patients with difficulty in swallowing. Sustained release dosage forms aimed at controlling the rate of release as well as maintaining desire drug levels in the blood for long duration of time. An oral suspension could be the best suitable dosage form for geriatric and pediatric patients. They include improvement of the rate and extent of drug absorption, higher patient compliance, reduction of side effects and taste masking of bitter drug [3, 4]. There are several of approaches to design and development of sustained release suspension of variety of drugs. Formulation of sustained release suspension will be benefited to avoid fluctuations in blood drug plasma concentration and gives its action for an entire period of time [5, 6].

Linezolid is poorly water soluble drug (3 mg/ml) of BCS class II. Linezolid is an neutral drug and it has a short half-life, due to which it requires frequent administration to maintain the therapeutic effect for a long period of time and also it is not sustained to own due to short half-life, so sustained release formulation are formulated. Linezolid has low plasma protein binding (approximately 31%, but highly variable) and apparent volume of distribution at steady state of around 40-50 liters. Peak serum concentrations are reached up to one hour after administration of drug. Linezolid is readily distributed to all tissues in the body apart from bone matrix and white adipose tissue.

2. Materials and methods

2.1 Materials

Linezolid was obtained as a gift sample from Cadila healthcare Ltd., Ahmadabad, India. Eudragit RS100 and Eudragit RL100 were obtained as gift sample from Evonic Degussa, India. Ethyl cellulose, Xanthan gum, Acacia and Gaur gum were obtained as gift sample from Finar chemicals, Mumbai, India. All others reagents and chemicals used were of analytical reagent grade.

2.2 Methods

2.2.1 Preparation of Microcapsules and Reconstitutable Sustained Release Suspension Microcapsules

Microcapsules were prepared by spray drying technique using varying ratios of drug and polymers in 1:1, 1:2 and 1:3 ratios like (Eudragit RS100, Eudragit RL100 and Ethyl cellulose) and the effects of various polymers on release of drug from microcapsules were studied by constant feed flow rate 5ml/min. Preliminary study formulas of all different microcapsule formulation of linezolid are listed in Table **1**.

Reconstitutable SR suspensions were prepared using optimize batch of microcapsules mixed with various suspending agent (xanthan gum, acacia, gaur gum), Sweetener (sucrose), preservative (Na benzoate), buffering agent (citric acid) and flavoring agent (cherry). Optimize batch formulas of all different reconstitutable sustained release suspension formulations of linezolid are listed in Table 2.

Table 1: Microcapsules Formulations of Linezolid (F1-F9)

Batch code	Polymer	Polymer ratio	Feed flow rate	Solvent
F1	Eudragit RS100	1:1	5 ml/min	Dichloromethane
F2	Eudragit RS100	1:2	5 ml/min	Dichloromethane
F3	Eudragit RS100	1:3	5 ml/min	Dichloromethane
F4	Eudragit RL100	1:1	5 ml/min	Dichloromethane
F5	Eudragit RL100	1:2	5 ml/min	Dichloromethane
F6	Eudragit RL100	1:3	5 ml/min	Dichloromethane
F7	Ethyl Cellulose	1:1	5 ml/min	Dichloromethane
F8	Ethyl Cellulose	1:2	5 ml/min	Dichloromethane
F9	Ethyl Cellulose	1:3	5 ml/min	Dichloromethane

Table 2: Composition of reconstitutable sustained release suspension formulations

Ingredient	N1	N2	N3	N4	N5	N6	N7	N8	N9
Microcapsule	1380	1380	1380	1380	1380	1380	1380	1380	1380
Xanthan gum	30	40	50	-	-	-	-	-	-
Gaur gum	-	-	-	30	40	50	-	-	-
Acacia	-	-	-	-	-	-	30	40	50
Sucrose	400	400	400	400	400	400	400	400	400
Sodium benzoate (preservatives)	3	3	3	3	3	3	3	3	3
Citric acid (buffering agent)	3	3	3	3	3	3	3	3	3
Cherry flavour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

* The entire ingredient is taken in the mg and in % w/w of microcapsule
* 1380 mg microcapsule contain equivalent to 600 mg of linezolid

2.2.2 Optimization of Variable Using Factorial Design

A 3^2 randomized full factorial design was used in the present study. In this design, 2 factors were evaluated; each 3 levels and experimental trials were performed for all 9 possible combinations (Table 5). The polymer concentration (X1) and feed flow rate (X2) were chosen as independent variable in 3^2 full factorial design (Table 4), while percentage yield, particle size and encapsulation efficiency were taken as dependent variables (Table 3).

A 3^2 randomized full factorial design was used in development of dosage form. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

Table 3: List of Independent Variables and Dependent Variables

Independent Variables:	
Polymer Ratio (X1)	Feed flow rate (X2)
Dependent Variables:	
% yield	Time required for 90% drug release (t_{90})
Microencapsulation efficiency (%)	% drug release after 6 hrs (Q_6)
Mean Particle size	Diffusion coefficient (n)
Time required for 50% drug release (t_{50})	Release rate constant (k)

Table 4: Coded value and independent variable

Coded value	Selection of level of independent variable	
Coded value	X1 (polymer ratio)	X2 (feed flow rate)
-1	1:1.1	5
0	1:1.2	10
+	1:1.3	15

* X1=Polymer ratio *X2=Feed flow rate

$$Y=b_0+b_1X_1+b_2X_2+b_{11}X_1X_1+b_{22}X_2X_2+b_{12}X_1X_2$$

Where,

Y = dependent variable

b_0 = arithmetic mean response of the 9 runs

b_i =estimated coefficients for the factor X_i

The main effect (X_1andX_2) represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are change simultaneously. The polynomial terms (X_1X_1, X_2X_2) are included to investigate nonlinearity [7].

Table 5: Coded value and uncoded value

Sr. No.	Coded value		Uncoded value	
	X1	X2	X1	X2
1	-1	-1	1:1.1	5
2	0	-1	1:1.2	5
3	+1	-1	1:1.3	5
4	-1	0	1:1.1	10
5	0	0	1:1.2	10
6	+1	0	1:1.3	10
7	-1	+1	1:1.1	15
8	0	+1	1:1.2	15
9	+1	+1	1:1.3	15

2.2.3 Validation of Experimental Design

2.2.3.1 Percentage relative error or bias

To assess the reliability of the model, a comparison between the experimental and predicted values of the responses is also presented in terms of % bias (relative error %). The formula for calculation of % bias or % relative error is as follows:

$$\% \text{ Bias} = \frac{\text{predicted value} - \text{actual value}}{\text{predicted value}} \times 100$$

It is calculated from the equation

$Y=b_0+b_1X_1+b_2X_2+b_{11}X_1X_1+b_{22}X_2X_2+b_{12}X_1X_2$

Where,

Y= Y is the predicted response

b_0= arithmetic mean response of the 9 runs

b_i=estimated coefficients for the factor X_i

Predicted responses are calculated from the above formula with the help of X1 and X2 variable from table no. 4.16 and actual response are taken from the experimental work.

2.2.3.2 Check point batch

Polynomial equations were generated using Statistica 8.0 for selected responses like % yield, particle size, encapsulation efficiency, Q_6.Q_8, $t_{90\%}$, Exponential constant (n) and release rate constant (k).The generated polynominal equations were further reduced on the basis of significant terms obtained by applying ANOVA. The design was validated by preparing an extra check point formulation. The predicted values for response were determined on the basis of respective polynomial equations whereas the experimental values were determined by evaluating formulation for dependent variable. The predicted and experimental values of responses were compared for statistical significance using paired *t* –test [8, 9].

2.2.3.3 Physical Characterization of Microcapsule

The prepared microcapsules were evaluated for the flow properties, such as loose bulk density, tapped density, carr's index, Hausner ratio and angle of repose [10-13].

2.2.4 Evaluation of Microcapsule

2.2.4.1 Mean Particle size determination by microscopic method

Binocular microscope was used for the particle size at 100 magnifications Particle size observed in ocular scale (µm) [14].

2.2.4.2 Particle size and shape by Scanning Electron microscopy

The surface topography of the microcapsule was investigated by SEM. Scanning electron microscopy (SEM) photographs were taken using a scanning electron microscope (JSM-5610, Japan) at room temperature. Samples were fixed on a scanning electron microscope sample holder with a double-sided adhesive tape and coated with a layer of gold of 1.5×10^{-10} m for 2 min using a sputter coater (Edwards 3-150 Å, England) in a vacuum of 30.4 kPa of argon gas. Photographs were observed for morphological characteristics and to confirm the spherical nature of microcapsule [15].

2.2.4.3 Morphological studies of microcapsule by simple binocular microscope

Morphological characteristic of microcapsule of the preliminary and factorial batches are determined by the simple binocular microscope. Spray dried microcapsule are taken on the glass slide and determine the morphological character of the microcapsule under the simple binocular microscope. Samples of spray dried microcapsule were selected randomly.

2.2.4.4 Percentage yield

The percentage of production yield (wt/wt) was calculated from the weight of dried microcapsule (W1) recovered from each of batches and the sum of the initial dry weight of starting materials (W2). The formula for calculation of percentage yield is as follows [16].

$$\% \text{ Yield} = \frac{\text{Weight of dried microcapsules (W1)}}{\text{total Weight of drug and polymer (W2)}} \times 100$$

2.2.4.5 Drug loading

Drug loading are calculated of the microcapsule by weighting the microcapsule after spray drying with polymer and drug to the total quantity of drug taken before spray drying [16].

$$\text{Drug loading} = \frac{\text{Weight of drug loaded in microcapsule}}{\text{Total weight of microcapsule}} \times 100$$

2.2.4.6 Encapsulation efficiency

To estimate linezolid content, drug loaded microcapsule were weighted and crushed properly in mortar and pestle. Briefly 200 mg of each batch of linezolid-loaded microcapsule were crushed and then dissolved in 100 ml of phosphate buffer 7.2 pH. The above solution was kept on sonicator for 3 to 4 hours to get maximum drug released from microcapsule into solution. Then phosphate buffer containing drug was filtered through whattman filter paper to remove any polymer debris. The clear solution obtained was analyzed using UV spectrophotometer at ƛmax value of 251 nm using pure phosphate buffer as blank [17]. The % Encapsulation efficiency of linezolid microcapsule was calculated using formula as follows

$$\% \text{ Encapsulation efficiency} = \frac{\% \text{ Drug loading}}{\% \text{ Theoretical loading}} \times 100$$

2.2.4.7 Drug Content Uniformity

Weight accurately the 200mg microcapsule which contains 100mg equivalent weight of linezolid and then transferred to 100ml of 7.2 pH Phosphate Buffer containing volumetric flask and kept on sonicator for 3-4 hours to get maximum drug release from microcapsule into solution. The solution was analyzed at 251nm using double beam UV-Visible spectrophotometer after suitable dilution. The content of drug was calculated from calibration curve [18].

2.2.4.8 *In-vitro* drug release study

The *In-vitro* drug release was performed using USP 24 type II paddle apparatus using 700 ml of 0.1 N HC1 at 50 rpm at 37±0.5°C for first two hours. The samples were withdrawn at predetermined time intervals for period of 2 hr and replaced with the fresh medium. After 2 hours that add the 200 ml solution of tri-sodium phosphate to replace the pH 1.2 to 7.2 and sample are withdrawn at predetermined time intervals for remaining 10 hrs. The samples were filtered through whattman filter paper; suitably diluted and analyzed at 251nm using double beam UV-Visible spectrophotometer. The content of drug was calculated using calibration curve.

2.2.5 Evaluation Parameter of Reconstitutable Suspension

2.2.5.1 Organoleptic property

Prepared formulation with different excipient was observed for colour, odour and appearance and it was found properly mixed.

2.2.5.2 pH

The pH of reconstitutable suspension was determined by using digital pH meter (Welltonix digital pH meter PM100).

2.2.5.3 Viscosity

The viscosity of suspension was determined by Brookfield viscometer (Brookfield Eng. Lab). In adapter 40 ml of suspension was taken and the adapter is set over the viscometer by a stand such a way that spindle is completely immersed in the suspension. Spindle number 3 was used.

2.2.5.4 Sedimentation volume

Take 10 ml of each suspension was taken in 50 ml stopper graduated measuring cylinder. The suspension was dispersed thoroughly by moving upside down for three times. Later, the suspension was allowed to settle for three minutes and the height of sediment was noted. This was the original height of sediment (H_0). The cylinder was kept undisturbed for 7 days. The height of sediment read at every 24 hr for 7 days was considered as final height of sediment (Hu).

Sedimentation volume (F) = Hu/H_0

The ultimate height of the solid phase after settling depends on concentration of solid content. To obtain an acceptable suspension, F should be at least 0.9 for 1hour but a longer period was preferred for our purpose and F value means sedimentation volume was measured to check the physical stability of the suspension. It can have values nearly 1.

2.2.5.5 Redispersibility

Fixed volume of each suspension (10 ml) was kept in stoppered cylinder which was stored at room temperature for 7 days. The redispersibility was determined by studying number of stocks to redisperse the formed sediment at the end of 7 days of storage of the formulation [19, 20].

2.2.5.6 Accelerator Stability Study

The purpose of stability testing is to provide evidence on how the quality of drug substance or drug product varies with time under the

influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test for the drug substance or a shelf life for the drug product and recommended storage condition. The storage condition used for stability studies were accelerated condition 40^0 C ± 2^0 C / 75 % ± 5% RH for the optimized formulation of reconstitutable sustained release suspension [21].

3. Result and discussion

3.1 Drug Excipient Compatibility Study

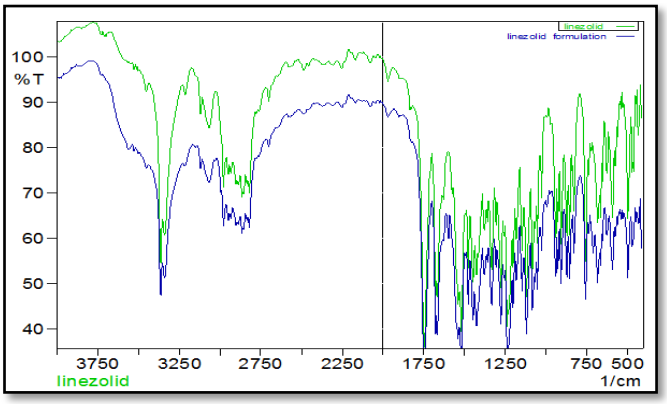

Fig. (1). Compatibility study of drug with excipients

Fourier transform infrared spectroscopy has been used to study the physical and chemical interactions between drug and Excipients used in the formulation. Fourier transform infrared (FTIR) spectra of Linezolid, Eudragit RS100, Sucrose, Xanthan gum, citric acid and sodium benzoate were recorded using Potassium bromide (KBr) mixing method and there was not found any kind of interaction between drug, polymer and other excipient and it spectra of drug and excipient compatibility are showed in the Figure 1 and Table 6.

Table 6: Functional Group and Frequency of Drug with Excipient

Functional group	Frequency of Pure Drug (cm^{-1})
C-H	680.89, 756.12
R-CH=CH2	906.57
N-H	1516
C-N	1357
C=O	1143.83, 1274.99

FTIR peaks observed in the linezolid and excipient sample mixture were found to be 1274.99 cm^{-1}, 1143.83 cm^{-1}, 1357cm^{-1}, 1516 cm^{-1}, 906.57 cm^{-1}, 756.12 cm^{-1}, 680.89 cm^{-1}.

3.2 Characterization of Microcapsule

3.2.1 Physical Characterization of Microcapsule

The angle of repose for the microcapsule was carried out after spray drying and results were reported that the batches F1, F2,F3,F6 has a value between 20° to 30°, which shows good flow property and batches F4, F5, F7, F8, and F9 shows range between 30^0 to 34^0, Which shows the passable flow property.

Compressibility index for the microcapsule was carried out after spray drying and results were reported that the batches F1, F2, F5 have a range between 11-15 so, it shows good compressibility index, batches F3, F4, F6, F7, F9 have a range between 16-20 so, it shows fair compressibility index and batches F8 have a range between 21-25 so, it shows the passable compressibility index.

Hausner's ratio for the microcapsule was carried out after spray drying and results were reported that the batches F1, F2, F3, F5 have a range between 1.12-1.18 so, it shows good flow property, batches F4, F6, F7, F8, F9 have a range between 1.19-1.25 so, it shows a fair flow property.

In the preliminary screening of the batches F1 to F9 have a physical characteristics of microcapsules in the acceptable range and all the result of Physical Characterization of Microcapsules of preliminary batches (F1-F9) are depicted in Table 7.

Table 7: Physical Characterization of Microcapsule (F1-F9)

Batch	Bulk density (g/cm^3)	Tap density (g/cm^3)	Carr's Index	Hausner's ratio	Angle of repose
F1	0.36	0.42	14.28	1.16	27.97
F2	0.38	0.44	13.63	1.15	26.56
F3	0.39	0.46	15.21	1.17	26.24
F4	0.37	0.45	17.87	1.21	34.99
F5	0.38	0.43	11.62	1.13	34.45
F6	0.39	0.49	20.40	1.25	29.62
F7	0.34	0.41	17.07	1.20	34.11
F8	0.36	0.45	21.01	1.25	33.66
F9	0.37	0.46	20.20	1.24	30.32

3.2.2 Evaluation of Microcapsule

In the preliminary study, the microcapsule batches were evaluated for % practical yield, encapsulation efficiency, % drug loading, mean particle size and surface morphology. The % practical yield, encapsulation efficiency and mean particle size are increased with increase to drug to polymer ratio and drug loading are decreased with increase to drug to polymer ratio. Hence, batch F3 show high % practical yield, encapsulation efficiency and particle size. Sustained release suspension was prepared for the 12 hours so, F1 batch are optimized for further factorial analysis with different polymer ratio and different feed flow rate (Table 8).

Table 8: Evaluation of Microcapsule (F1-F9)

Batch	Practical yield (%)	Drug loading (%)	Encapsulation efficiency (%)	Mean Particle Size (µm)
F1	85.37	58.82	97.98	14.66
F2	86	38.75	98.11	14.79
F3	87	28.73	98.64	15.89
F4	77.8	64.26	93.01	16.24
F5	83.73	39.80	94.41	15.38
F6	84.7	29.51	97.46	17.23
F7	79	63	94.04	14.98
F8	82	40.65	96.75	15.82
F9	84	29.76	97.46	16.72

3.2.3 *In-Vitro* Drug Release of Preliminary Batches of Microcapsule

In the present research work, formulation of preliminary batches F1 to F3 use Eudragit RS100 in varying concentration, (1:1, 1:2, 1:3) for preparation of microcapsule by spray drying technique and it was reveal that as concentration of drug to polymer is increases with increase the drug release. F1 batches shows drug release up to 98.94 % within 10 hours whereas the formulation batches F2 and F3 shows the drug release up to 96.89 % and 83.98 % within 12 hours, respectively. Results were depicted in table 9 and figure 2.

Table 9: *In-Vitro* Drug Release of Preliminary Batches (F1-F9) of Microcapsule.

Time (Hours)	CPR								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	36.88	23.75	22.55	47.89	39.09	36.18	36.08	35.75	33.47
2	47.32	27.19	23.25	59.09	44.02	42.07	44.67	42.71	39.47
3	57.42	35.99	27.31	61.07	53.66	49.44	53.61	47.24	43.79
4	64.66	46.81	30.73	77.97	59.85	55.23	62.55	51.67	49.33
5	76.96	53.45	34.40	86.97	63.51	59.11	73.28	58.46	55.99
6	81.46	67.84	38.09	91.84	76.68	64.89	85.08	63.11	59.94
7	87.80	74.95	46.48	98.89	79.66	67.81	91.49	69.55	64.45
8	92.51	79.21	57.48		89.07	73.55	98.71	73.26	67.45
9	97.21	83.78	66.67		91.02	77.61		77.41	73.31
10	98.94	88.10	72.87		96.23	84.97		83.70	78.28
11		93.83	76.77		98.91	89.80		87.29	83.68
12		96.89	83.98			93.74		92.37	89.14

In formulation batches F4 to F6 use the Eudragit RL100 in varying concentration, (1:1, 1:2 and 1:3) for preparation of microcapsule it was justify that as concentration of polymer is increases with increase the drug release. F4 batches shows drug release up to 98.89% within 7 hours while the formulation batches F5 and F6 shows the drug release up to 98.91% and 93.74% within 11 and 12 hours, correspondingly. Results were depicted in table 9 and figure 2.

In formulation batches F7 to F9 using ethyl cellulose in varying concentration, (1:1, 1:2 and 1:3) for preparation of microcapsule it was justify that as concentration of polymer is increases with increase the drug release. F7 batches shows drug release up to 98.71% within 8 hours even as the formulation batches F8 and F9 shows the drug release up to 92.37% and 89.14%, in that order. Results were depicted in table 9 and figure 2.

From all the batches of microcapsule (F1 to F9), F1 batch exhibit excellent and uniform drug release up to 98.94 % within 10hours, So Eudragit RS100 (1:1) ratio was use for optimization of flow rate.

In the preliminary study other batches are also show drug release at 11 and 12 hours. Here F5 batches show drug release at the 11 hours 98.91% but here drug to polymer ration are 1:2. So, finally bulky volume of reconstitutable suspension are increased and it not comfortable to the patient.

Hence main goal to prepare reconstitutable sustained release suspension is, in the low drug to polymer ratio it give a sustained action till to 12 hours and it may too comfortable to the patient to take orally. So, here F1 batches are optimized for further factorial design to using 1:1.1, 1:1.2 and 1:1.3 drug to polymer ratio and 5, 10, 15 ml/min feed flow rate.

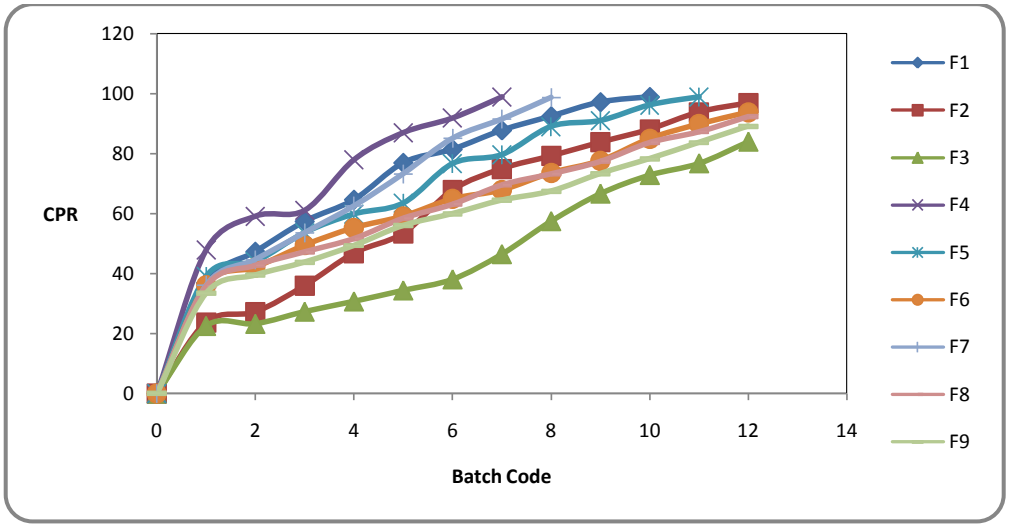

Fig. (2). CPR of the preliminary batches (F1-F9) batches

This figure 2 indicates that with increase the drug to polymer ratio drug release rate are decreased.

3.3 Evaluations of Factorial Batches of Microcapsule

3.3.1 Physical characterization of factorial batches of Microcapsule

Cars index of factorial batches are showed in the table 10. Here batches S1, S2, S3, S4, S5, S6 and S9 has a range between 11 to 15 so, it show good compressibility index and S7 and S8 has a range between 16 to 20 so it show a fair compressibility index.

Hausner's ratio of factorial batches are showed in table 10 and here batches S1, S2, S3, S4, S5, S6, S7 and S9 has a range of hausner's ratio between 1.2 to 1.8 so, it show a good flow property and batch S8 show a range between 1.19 to 1.25 so, it show a fair flow property.

Table 10: Physical characterization of factorial batches (S1-S9)

Batch	Bulk density (g/cm³)	Tap density (g/cm³)	Carr's Index	Hausner's ratio	Angle of repose	Drug loading (%)
S1	0.3816	0.4424	13.76	1.15	25.24	55.55
S2	0.3848	0.4347	11.47	1.12	24.36	52.63
S3	0.3875	0.4424	13.57	1.14	22.68	49.50
S4	0.3787	0.4347	12.90	1.14	25.19	56.17
S5	0.3848	0.4347	11.47	1.12	24.83	53.70
S6	0.3921	0.4504	12.95	1.14	22.68	50.50
S7	0.3636	0.4310	15.64	1.18	30.21	57.60
S8	0.3676	0.4424	16.92	1.20	27.14	53.76
S9	0.3737	0.4347	14.81	1.17	26.56	50.96

Angle of repose of a factorial batches showed in the table 10. here batches S1, S2, S3, S4, S5, S6, S8 and S9 has a range of angle of repose between 20 to 30 so, it show a good flow property and batch S7 show a range between 30 to 34 so, it show a passable flow property.

3.3.2 Evaluations of Factorial Batches of Microcapsule

Ideal values of the percentage practical yield, percentage encapsulation efficiency and mean particle size are showed in the table 11. The practical yields are increase with the increase the polymer ratio, but it may be decrease with increase the feed flow rate. But the percentage encapsulation efficiency is also increase with increase the polymer ratio, where as it may also decrease with increase the feed flow rate. Particle sizes of the factorial batches are increase with increase the polymer ratio and the feed flow rate.

In present research work,S3 batch are optimized for preparation of the reconstitutable sustained release suspension because it has a high percentage yield (87.82) and percentage encapsulation efficiency (99.07), 16.06 µm mean particle size and smooth surface and spherical shape.

Table 11: Evaluations of factorial batches of Microcapsule

Batch	Practical Yield (%)	Encapsulation Efficiency (%)	Mean Particle size(µm)	Drug loading (%)
S1	85.71	97.87	13.17	55.55
S2	86.36	98.68	15.67	52.63
S3	87.82	99.07	16.06	49.50
S4	84.80	96.71	15.97	56.17
S5	85.91	97.69	16.91	53.70
S6	86.08	98.67	19.01	50.50
S7	82.67	95.89	17.54	57.60
S8	84.51	97.70	18.76	53.76
S9	85.30	98.09	20.21	50.96

3.3.3 *In-Vitro* Drug Release of Factorial Batches of Microcapsule

In the factorial batches Eudragit RS 100 are used in the different concentrations with the different feed flow rate. *In-vitro* drug release profile of the factorial batches are showed in the table 12 and result indicate that drug release time are increased with increase the drug to polymer concentration and feed flow rate. From the study of factorial design, batch S3 are optimized for the preparation of reconstitutable suspension because it show maximum cumulative percentage drug release up to 99.12% within 12 hours as compare to other batches.

Table 12: *In-vitro* drug release of factorial batches of Microcapsule

Time (hrs)	S1	S2	S3	S4	S5	S6	S7	S8	S9
0	0	0	0	0	0	0	0	0	0
1	41.58	38.76	36.35	40.34	37.25	35.67	39.75	37.34	35.09
2	48.37	45.37	42.56	46.53	45.83	43.55	45.63	44.21	41.05
3	56.42	51.78	48.33	54.35	52.64	47.35	50.64	49.67	46.53
4	64.82	58.67	54.21	63.45	60.37	54.64	62.53	58.37	55.28
5	71.89	66.31	60.45	71.53	67.25	63.64	70.46	64.86	61.48
6	79.82	73.49	66.89	77.59	73.56	72.18	75.34	67.58	65.48
7	87.35	81.64	73.09	82.69	79.38	77.68	80.45	72.58	69.87
8	95.37	87.33	79.24	89.55	84.37	83.57	86.66	77.34	74.95
9	98.64	93.86	85.11	94.36	91.65	89.08	93.56	83.49	79.32
10		98.91	91.56	98.10	95.34	92.14	97.09	89.57	86.11
11			95.89		98.34	94.53		92.67	89.46
12			99.12			96.32		94.48	92.56

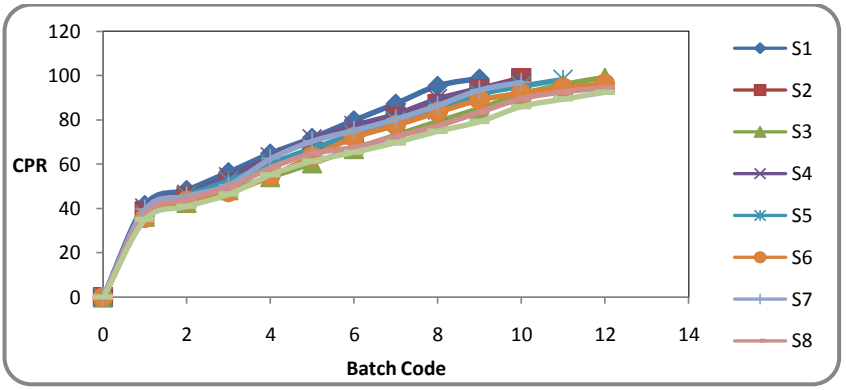

Fig. (3). CPR of the factorial batches S1 to S9

This figure 3 indicates that drug release rate are decreased with increase the drug to polymer ratio and feed flow rate.

3.3.4 Statistical Analysis of Factorial Batches

All batches contained microcapsule which contains drug (linezolid) and polymer (Eudragit RS100) in a different ratio. In 3^2 full factorial design here takes independent variable X1 (polymer ratio like 1:1.1, 1:1.2, 1:1.3) and X2 (feed flow rate 5, 10, 15 ml/min). A 3^2 full factorial design was designed to study the effects of the polymer ratio and feed flow rate (ml/min) of spray dryer on the percentage yield, mean particle size, encapsulation efficiency, Q_6, Q_8, t_{90}, diffusion exponent (n) and release rate constant (k) of microcapsule. The result of analysis of variance test for all three effects indicated that the test is significant (Table 13).

Table 13: Result of dependent variables

Batch code	Variable levels		% Yield	Mean Particle Size (µm)	% Encapsulation Efficiency	Q_6 (%)	Q_8 (%)	t_{90} (hr)	Diffusion Exponent (n)	Release Rate constant (k)
	X1	X2								
S1	-1	-1	85.71	13.17	97.87	79.01	93.88	7.47	0.4159	0.3809
S2	0	-1	86.36	15.67	98.68	73.04	86.79	8.465	0.428	0.349
S3	1	-1	87.82	16.06	99.07	66.43	78.25	9.988	0.4317	0.3223
S4	-1	0	84.80	15.97	96.71	75.85	89.71	8.040	0.4082	0.3715
S5	0	0	85.91	16.91	97.69	71.44	83.18	8.999	0.4245	0.3483
S6	1	0	86.08	19.01	98.67	68.91	79.64	9.766	0.441	0.3238
S7	-1	1	82.67	17.54	95.89	69.96	81.41	9.49	0.3893	0.3627
S8	0	1	84.51	18.76	97.70	66.69	77.26	10.40	0.3965	0.3444
S9	1	1	85.30	20.21	98.09	63.78	74.34	10.96	0.4137	0.3194

A statistical model incorporating interactive and poly nominal terms used to evaluate the response.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of 9 runs, and b_1 is the estimated coefficients for the factor X_1.The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the responses changes when two factors are change simultaneously. The polynomial terms (X_1X_1, X_2X_2) are included to investigate nonlinearity.

Analysis of variance (ANOVA) was performed to identify insignificant factors. Data were analyzed using Microsoft Excel software. The reduced models were developed for response variables by removing the insignificant terms with P more than 0.05. The terms with P less than 0.05 were considered statistically significance and retained in the reduced model.

3.4 Full and reduced model for % yield

$$Y_1 = 85.72 + 1.00X_1 - 1.23X_2 - 0.19X_1X_1 - 0.20X_2X_2 + 0.13X_1X_2$$

Response plot indicate that the positive effect of polymer ratio on the percentage yield. The response observed for this effect is of linear type. With increase in the polymer ratio, the percentage yield also increases due to the increase throughput of the polymer slurry and rapid evaporation of the solvent. Response surface plot also indicates the negative effect of feed flow rate on the percentage yield. The response observed for this effect is also of linear type. With increase in the feed flow rate, the value of percentage yield increases due to the incomplete atomization and drying, resulting in the deposition of a large amount of microcapsules on the walls of the desiccating chamber and the cyclone separator.

The significance level of coefficients b_{11}, $b_{22}$and b_{12} was found to be greater than P=0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in table 14. The coefficients b_1 and b_2 were found to be significant at P <0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_1 and b_2 contribute significant information for the prediction of % Yield. The results of testing the model in portions are shown in Table 15 and figure 4. Polymer ratio at higher level (X1, +1) and feed flow rate at lower level (X2, -1) yielded microcapsules with higher percentage yield.

Table 14: Summary of results of regression analysis for % Yield

Response % yield	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	85.72	1.00	-1.23	-0.19	-0.20	0.13	0.953	0.033
P Value	1.84E-07	0.0163	0.0092	0.6188	0.6103	0.6409	-	-
RM	85.46	1.00	-1.23	-	-	-	0.939	0.00022

Table 15: Calculation for testing the models in proportions for % Yield

	DF	SS	MS	F	
Regression					
FM	5	15.4177	3.083	12.187	
RM	2	15.191	7.595	46.252	F_{cal}=0.2981
Residual					F_{cri}= 9.2766
FM	3	0.7590	0.2530	-	(DF= 3,3)
RM	6	0.9853	0.1642	-	

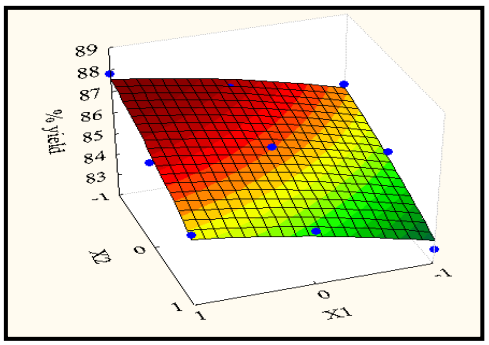

Fig. (4). Response surface plot of % yield

3.5 Full and reduced model for Mean particle size (µm)

$$Y_2 = 17.37 + 1.43X_1 + 1.93X_2 - 0.12X_1X_1 - 0.395X_2X_2 - 0.055X_1X_2$$

When considering second response in term of particle size (Y_2), interaction terms are insignificant. Response surface plot indicates the negative effect of drug to polymer ratio the particle size. The particle size of the microcapsule decreases with decrease the drug to polymer ratio or increase with increase the drug to polymer ratio and it may be increased due to increased viscosity of the feed solution which influence the interaction between disperse phase and dispersion medium that affects the size distribution of particle.

Response surface plot indicates negative effects of feed flow rate. This may be due to a higher feed flow rate the atomizing air may not be able to penetrate the stream of liquid. As a result, incomplete atomization may lead to wider droplet size distribution.

The significance level of coefficients b_{11}, b_{22} and b_{12} was found to be greater than P=0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 16. The coefficients b_1 and $b_2$were found to be significant at P <0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_1 and b_2 contribute significant information for the prediction of particle size (µm). The results of testing the model in portions are shown in Table 17 and figure 5. Drug to polymer ratio at lower level (X1, -1) and feed flow rate at lower level (X2, -1) yielded microcapsule with smaller particle size.

Table 16: Summary of results of regression analysis for Mean particle size (µm)

Response Particle size (µm)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	17.37	1.43	1.93	-0.12	-0.395	-0.055	0.973	0.014
P Value	3.19E-05	0.0085	0.0036	0.7847	0.3980	0.8588	-	-
RM	17.033	1.433	1.935	-	-	-	0.963	4.9E-05

Table 17: Calculation for testing the models in proportions for Mean particle size (µm)

	DF	SS	MS	F	
Regression					
FM	5	35.144	7.028	21.765	F_{cal}=0.3643
RM	2	34.792	17.396	78.966	F_{cri}= 9.2766
Residual					(DF= 3,3)
FM	3	0.9688	0.3229	-	
RM	6	1.3217	0.2202	-	

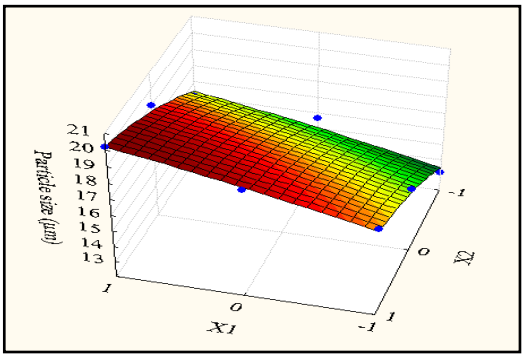

Fig. (5). Response surface plot of Mean particle size

3.6 Full and reduced model for Encapsulation efficiency (%)

$$Y_3 = 97.89 + 0.89X_1 - 0.656X_2 - 0.306X_1X_1 + 0.1933X_2X_2 + 0.25X_1X_2$$

When considering the response term of encapsulation efficiency, the response surface plot indicates the positive effect of drug to polymer ratio on the response term. The encapsulation efficiency of the microcapsule increase with increase in the drug to polymer ratio, due to amount of drug remaining and available for encapsulation increases as theoretical drug loading increases. Consequently, the actual drug loading increases. As the molecular weight of the polymer increased, its hydrophobicity increased, leading to better precipitation of polymer at the boundary phase of the droplets.

Response surface plot indicates negative effect of feed flow rate on the encapsulation efficiency; it may be due to that the high pumping rates during the spray drying process result in large volumes of nebulized solutions to be dried. Owing to this heated air may not instantaneously transform the liquid droplets into solid microcapsules, leading to the formation of larger, irregular particles that are not completely dried and hence resulting in decrease in encapsulation efficiency. The results of testing the model in portions are shown in Table 18 and 19 and figure 6. Drug to polymer ratio at higher level (X1, +1) and feed flow rate at lower level (X2, -1) yielded microcapsule with higher percentage encapsulation efficiency.

Table 18: Summary of results of regression analysis for Encapsulation efficiency (%)

Response Encapsulation efficiency (%)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	97.89	0.89	-0.656	-0.306	0.1933	0.25	0.975	0.0012
P Value	1.67E-08	0.0034	0.0083	0.1915	0.3672	0.1481	-	-
RM	97.81	0.893	-0.656	-	-	-	0.911	0.00068

Table 19: Calculation for testing the models in proportions for Encapsulation efficiency (%)

	DF	SS	MS	F	
Regression					
FM	5	7.888	1.577	23.675	F_{cal}=2.566
RM	2	7.375	3.6877	31.04	F_{cri}= 9.2766
Residual					(DF= 3,3)
FM	3	0.199	0.0666	-	
RM	6	0.7127	0.1187	-	

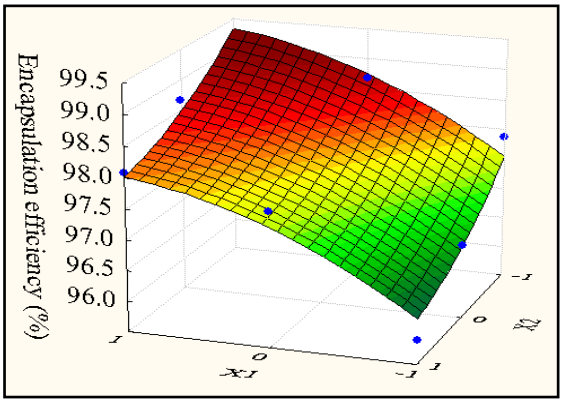

Fig. (6). Response surface plot of Encapsulation efficiency (%)

3.7 Full and reduced model for the Q_6 (%)

$$Y_4 = 71.88 - 4.28X_1 - 3.00X_2 + 0.266X_1X_1 - 2.24X_2X_2 + 1.6X_1X_2$$

Here negative value of the X1(drug: polymer ratio) variable indicate that the $Q_6$is decrease with respect to increase the polymer ratio.

Here negative value of the X2(feed flow rate) variable indicate that the Q_6 is decrease with respect to increase the feed flow rate.

When drug to polymer ratio and feed flow rate are increase, so there is increase size of particle and with respect to increase the particle size there is increase the time of cumulative percentage drug release with respect and According to Noyes Whitney equation the rate of dissolution is directly proportional to surface area of powdered drug that means higher surface area (very small the particle size), higher the rate of dissolution. If surface area of powdered drug is lower that means lower the rate of dissolution of powdered drug and higher the time of cumulative percentage drug release. Increase the particle size there is increase the time of drug release that means quantity of drug release is increase with increase in the drug to polymer ratio and feed flow rate. The results of testing the model in portions are shown in Table 20 and 21 and figure 7.

Table 20: Summary of results of regression analysis for Q_6 (%)

Response Q_6 (%)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	71.88	-4.28	-3.00	0.266	-2.24	1.6	0.986	0.005
P Value	1.89E-06	0.0014	0.0040	0.708	0.040	0.039		
RM	72.06	-4.283	-3.00	-	-2.248	1.6	0.985	0.0006

Table 21: Calculation for testing the models in proportions for Q_6 (%)

	DF	SS	MS	F	
Regression					
FM	5	184	36.97	43.99	F_{cal}=0.169
RM	4	184.73	46.18	69.35	F_{cri}= 10.12
Residual					(DF= 1,3)
FM	3	2.512	0.840		
RM	4	2.663	0.66		

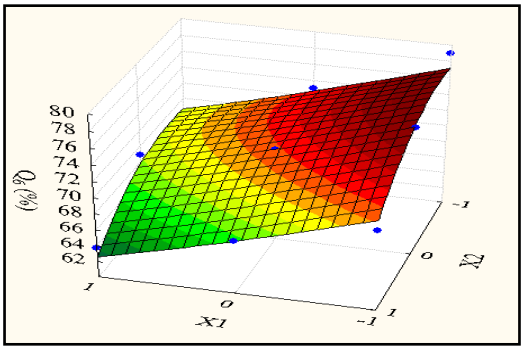

Fig. (7). Response surface plot of the Q_6 (%)

3.8 Full and reduced model for the Q_8 (%)

$$Y_5 = 83.86 - 5.46X_1 - 4.31X_2 + 0.46X_1X_1 - 2.18X_2X_2 + 2.14X_1X_2$$

Here negative value of the X1(drug: polymer ratio) variable indicate that the Q_8 is decrease with respect to increase the polymer ratio.

Here negative value of the X2(feed flow rate) variable indicate that the Q_8 is decrease with respect to increase the feed flow rate.

When drug to polymer ratio and feed flow rate are increase, so there is increase size of particle and with respect to increase the particle size there is increase the time of cumulative percentage drug release with respect and According to Noyes Whitney equation the rate of dissolution is directly proportional to surface area of powdered drug that means higher surface area (very small the particle size), higher the rate of dissolution. If surface area of powdered drug is lower that means lower the rate of dissolution of powdered drug and higher the time of cumulative percentage drug release. Increase the particle size there is increase the time of drug release that means quantity of drug release is increase with increase in the drug to polymer ratio and feed flow rate. The results of testing the model in portions are shown in Table 22 and 23 and figure 8.

Table 22: Summary of results of regression analysis for Q_8 (%)

Response Q_8 (%)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	83.86	-5.46	-4.31	0.46	-2.18	2.14	0.993	0.0019
P Value	9.8E-07	0.0005	0.0011	0.502	0.036	0.015	-	-
RM	84.17	-5.46	-4.318	-	-2.18	2.14	0.991	0.000201

Table 23: Calculation for testing the models in proportions for Q_8 (%)

	DF	SS	MS	F	
Regression					
FM	5	319.18	63.83	86.56	F_{cal}=0.578 F_{cri}= 10.12 (DF= 1,3)
RM	4	318.76	79.69	120.80	
Residual					
FM	3	2.212	0.7374		
RM	4	2.63	0.6596		

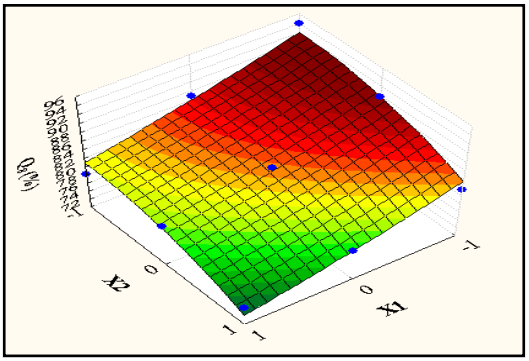

Fig. (8). Response surface plot of the Q_8 (%)

3.9 Full and reduced model for the t_{90} (hr)

$$Y_6 = 8.93 + 0.950X_1 + 0.823X_2 - 0.001X_1X_1 + 0.531X_2X_2 - 0.260X_1X_2$$

Here positive value of the X1(drug: polymer ratio) variable indicate that the t_{90} (hr) is increase with respect to increase the polymer ratio.

Here positive value of the X2(feed flow rate) variable indicate that the t_{90} (hr) is increase with respect to increase the feed flow rate.

When drug to polymer ratio and feed flow rate are increase, so there is increase size of particle and with respect to increase the particle size there is increase the time of cumulative percentage drug release with respect and According to Noyes Whitney equation the rate of dissolution is directly proportional to surface area of powdered drug that means higher surface area (very small the particle size), higher the rate of dissolution. If surface area of powdered drug is lower that means lower the rate of dissolution of powdered drug and higher the time of cumulative percentage drug release. Increase the particle size there is increase the time of drug release that means quantity of drug release is increase with increase in the drug to polymer ratio and feed flow rate. The results of testing the model in portions are shown in Table 24 and 25 and figure 9.

Table 24: Summary of results of regression analysis for t_{90} (hr)

Response t_{90} (hr)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	8.93	0.950	0.823	-0.001	0.531	-0.2607	0.990	0.0030
P Value	7.5E-06	0.0010	0.0015	0.9912	0.025	0.062		
RM	8.935	0.9504	0.8236	-	0.5319	-0.260	0.990	0.00026

Table 25: Calculation for testing the models in proportions for t_{90} (hr)

	DF	SS	MS	F	
Regression					
FM	5	10.32	2.065	63.48	F_{cal}=7.044E-05 F_{cri}= 10.12 (DF= 1,3)
RM	4	10.32	2.58	105.80	
Residual					
FM	3	0.0976	0.3253		
RM	4	0.0976	0.0244		

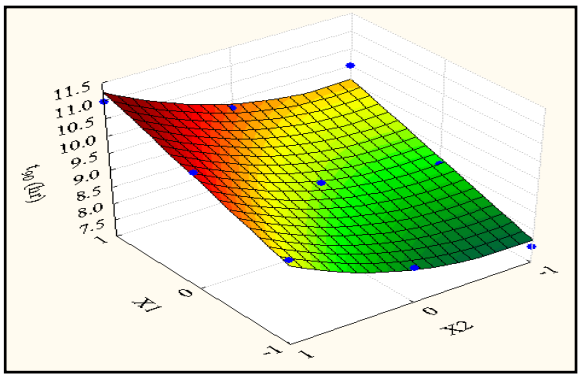

Fig. (9). Response surface plot of the t_{90} (hr)

3.10 Full and reduced model for the diffusion exponent (n)

$Y_7 = 0.4243 + 0.012X_1 - 0.012X_2 + 0.0003X_1X_1 - 0.012X_2X_2 + 0.00215X_1X_2$

Here positive of the X1(drug: polymer ratio) variable indicate that the diffusion constant is increase with respect to increase the polymer ratio.

Here negative value of the X2(feed flow rate) variable indicate that the diffusion constant is decrease with respect to increase the feed flow rate.

The significance level of coefficients b_{11} and b_{12} was found to be greater than P=0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in table 26. The coefficients b_1, b_2 and b_{22} were found to be significant at P <0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_1, b_2 and b_{22} contribute significant information for the prediction of diffusion exponent (n). The results of testing the model in portions are shown in Table 27. The critical value of F for α = 0.05 is equal to (DF=2, 3). Since the calculated value (F=0.341) is less than the critical value (F=9.55), it may be concluded that the omitted term do not contribute significantly to the prediction of diffusion exponent (n). The results are shown in the form of response surface plot in figure 10.

Table 26: Summary of results of regression analysis for diffusion exponent (n)

Response diffusion exponent (n)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	0.4243	0.012	-0.01	0.0003	-0.012	0.00215	0.963	0.0229
P Value	1.71E-06	0.0107	0.009	0.940	0.0471	0.4711		
RM	0.4245	0.012	-0.01	-	-0.012	-	0.955	0.00085

Table 27: Calculation for testing the models in proportions for diffusion exponent (n)

	DF	SS	MS	F	
Regression					
FM	5	0.0021	0.00043	15.81	F_{cal}=0.341 F_{cri}= 9.55 (DF= 2,3)
RM	3	0.0021	0.00071	35.48	
Residual					
FM	3	8.2E-05	2.73E-05		
RM	5	0.00010	2.01E-05		

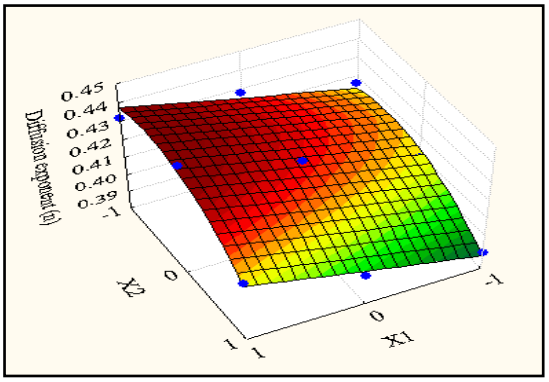

Fig. (10). Response surface plot of the diffusion exponent (n)

3.11 Full and reduced model for the release rate constant (k)

$Y_8 = 0.3481 - 0.024X_1 - 0.004X_2 - 0.0004X_1X_1 - 0.0014X_2X_2 + 0.0038X_1X_2$

Here negative value of the X1(drug: polymer ratio) variable indicate that the release rate constant is decrease with respect to increase the polymer ratio.

Here negative value of the X2(feed flow rate) variable indicate that the release rate constant is decrease with respect to increase the feed flow rate.

The significance level of coefficients b_{11} and b_{22} was found to be greater than P=0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in table 28. The coefficients b_1, b_2 and b_{12} were found to be significant at P <0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_1, b_2 and b_{12} contribute significant information for the prediction of release rate constant (k). The results of testing the model in portions are shown in Table 29. The critical value of F for α = 0.05 is equal to (DF=2, 3). Since the calculated value (F=0.434) is less than the critical value (F=9.55), it may be concluded that the omitted term do not contribute significantly to the prediction of release rate constant (k). The results are shown in the form of response surface plot in figure 11.

Table 28: Summary of results of regression analysis for release rate constant (k)

Response release rate constant (k)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	0.3481	-0.024	-0.004	-0.0004	-0.0014	0.0038	0.996	0.0008
p Value	2.51E-07	0.0001	0.0188	0.789	0.441	0.043	-	-
RM	0.3469	-0.024	-0.004	-	-	0.003	0.994	3.69E-06

Table 29: Calculation for testing the models in proportions for release rate constant (k)

	DF	SS	MS	F	
Regression					
FM	5	0.0039	0.00078	152.511	F_{cal}=0.434 F_{cri}= 9.55 (DF= 2,3)
RM	3	0.0038	0.0013	328.08	
Residual					
FM	3	1.54E-06	5.12E-06		
RM	5	1.98E-05	3.96E-06		

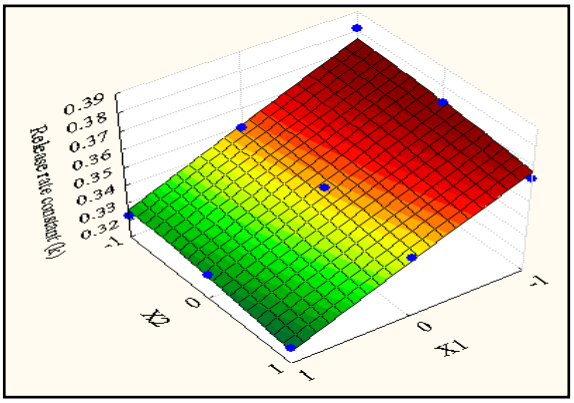

Fig. (11). Response surface plot of release rate constant (k)

3.12 Kinetic Modeling of Dissolution Data

The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Korsemeyer-Peppas model as evident from regression coefficients (table 30). The value of diffusion exponent (n) for S1 to S9 factorial formulations was between 0.3585 to 0.4317 so it indicates Fickian diffusion of the drug from formulation which corresponds to diffusion, erosion and swelling mechanism. Kinetic model Higuchi indicating that R^2 value of S1 to S9 was between 0.981 to 0.998 shows that drug release type was diffusion type from gel network and extended drug release for longer period of time. Kinetic Model Zero order indicating that R^2 value of S1 to S9 was in range 0.981 to 0.999 that near about 1.000 clearly mentioned that drug release from stiff gel networking was Zero order drug release that not depend on concentration of drug. Kinetic Model First order indicating that R^2 value of S1 to S9 was between 0.956 to 0.986 that having less than Zero order release R^2 value, mentioned that drug release type was not first order release from gel network (Table 30).

Table 30: Kinetic Modeling of Dissolution Data

Parameters	S1	S2	S3	S4	S5	S6	S7	S8	S9
Zero order									
S	7.529	6.71	5.90	7.18	6.11	5.54	5.48	4.81	4.80
I	36.56	35.44	30.98	39.32	36.01	36.60	37.49	36.50	34.31
R^2	0.998	0.991	0.998	0.984	0.992	0.981	0.998	0.995	0.995
First order									
S	0.047	0.043	0.0394	0.044	0.039	0.036	0.035	0.032	0.033
I	1.61	1.600	1.564	1.638	1.607	1.606	1.621	1.604	1.580
R^2	0.971	0.967	0.986	0.967	0.972	0.956	0.989	0.978	0.977
Higuchi									
S	30.98	28.89	27.06	29.66	27.28	5.546	24.16	22.23	22.17
I	7.750	7.442	3.42	11.62	8.72	36.60	13.73	13.59	11.46
R^2	0.994	0.998	0.990	0.994	0.996	0.981	0.990	0.996	0.996
Hixon Crowell									
S	-2.50	-2.23	-1.96	-2.395	-2.036	-1.84	-1.827	-1.605	-1.600
I	21.14	21.51	23.00	20.22	21.32	21.13	20.83	21.16	21.89
R^2	-0.98	-0.991	-0.998	-0.984	0.992	-0.981	-0.998	-0.995	-0.995
Korsemeyer and Peppas									
N	0.424	0.428	0.431	0.400	0.411	0.414	0.358	0.363	0.376
I	-0.40	-0.439	-0.491	-0.386	-0.440	-0.456	-0.414	-0.446	-0.471
R^2	0.991	0.995	0.982	0.991	0.992	0.990	0.981	0.990	0.990
S= slope, I= intercept, R^2= square of correlation coefficient, n= diffusion exponent									

3.13 Comparison of Dissolution Profiles For Selection of Optimum Batch

The values of Dissimilarity factor (f_1) for batches S2, S3, S5, S6, S7, S8, and S9 were less than 15 compared with theoretical dissolution profile indicating good similarity in dissolution. The batch S3 showed minimum value of f_1 (2.90). The values of similarity factor (f_2) for batches S2, S3, S5, S6, S7, S8, and S9 were greater than 50 compared with theoretical dissolution profile indicating good similarity in dissolution. The batch S3 showed maximum value of f_2 (82.35). Similarity Factor (f_2) and Dissimilarity factor (f_1) for S1-S10 are showed in table 31.

Table 31: Similarity Factor (f_2) and Dissimilarity factor (f_1) for S1-S9

Batch	Similarity factor (f_2)	Dissimilarity factor (f_1)
S1	44.56	21.85
S2	54.50	12.83
S3	82.35	2.90
S4	49.71	16.46
S5	57.93	10.54
S6	66.62	5.75
S7	62.79	8.25
S8	73.32	4.315
S9	75.92	3.18

3.14 Validation of Experimental Design

1. Percentage relative error or bias

Reliability of the generated models was studied by comparing the experimental and predicted values in terms of % bias. Low values of % bias for all responses shows a good agreement between the experimental and predicted values (Table 32, 33 and 34). The result of analysis of variance test for both effects indicated that the test is significant.

Table 32: Actual response, predicted response and % bias obtained for the studied parameters percentage yield, mean particle size, encapsulation efficiency

Code	% Yield			Mean particle size			% Encapsulation efficiency		
	Predicted	Actual	% Bias	Predicted	Actual	% Bias	Predicted	Actual	% Bias
S1	85.69	85.71	0.02	13.44	13.17	2.00	97.79	97.87	0.08
S2	84.29	86.36	2.45	15.04	15.67	4.18	98.73	98.68	0.05
S3	87.69	87.82	0.14	16.41	16.06	2.13	97.76	99.07	1.34
S4	84.53	84.80	0.31	15.82	15.97	0.94	96.88	96.71	0.17
S5	85.72	85.91	0.22	17.37	16.91	2.64	97.89	97.69	0.20
S6	88.53	86.08	2.76	18.68	19.01	1.76	98.47	98.67	0.20
S7	85.43	82.67	3.23	17.41	17.54	0.74	95.92	95.89	0.03
S8	84.29	84.51	0.26	18.90	18.76	0.74	97.42	97.70	0.287
S9	85.23	85.30	0.08	20.16	20.21	0.24	98.26	98.09	0.17

Table 33: Actual response, predicted response and % bias obtained for the studied parameters Q_6, Q_8, t_{90}

Code	Q_6 (%)			Q_8 (%)			t_{90}(hr)		
	Predicted	Actual	% Bias	Predicted	Actual	% Bias	Predicted	Actual	% Bias
S1	78.78	79.01	0.29	94.05	93.88	0.18	7.42	7.47	0.67
S2	69.64	73.04	4.88	85.99	86.79	0.93	8.63	8.465	1.96
S3	67.02	66.43	0.88	78.85	78.25	0.76	9.84	9.988	1.42
S4	76.42	75.85	0.74	89.78	89.71	0.07	7.97	8.040	0.87
S5	71.88	71.44	0.61	83.86	83.18	0.81	8.93	8.999	0.67
S6	67.86	68.91	1.54	78.86	79.64	0.98	9.87	9.766	1.11
S7	69.58	69.96	0.54	81.15	81.41	0.32	9.59	9.49	1.04
S8	66.64	66.69	0.07	77.37	77.26	0.14	10.28	10.40	1.16
S9	64.22	63.78	0.68	74.51	74.34	0.22	10.97	10.96	0.09

Table 34: Actual response, predicted response and % bias obtained for the studied parameters Diffusion Exponent (n) and Release Rate constant (k)

Code	Diffusion Exponent (n)			Release Rate constant (k)		
	Predicted	Actual	% Bias	Predicted	Actual	% Bias
S1	0.4147	0.4159	0.289	0.3781	0.3809	0.74
S2	0.4243	0.428	0.87	0.3507	0.349	0.48
S3	0.4344	0.4317	0.62	0.3225	0.3223	0.06
S4	0.4126	0.4082	1.06	0.3717	0.3715	0.05
S5	0.4243	0.4245	0.04	0.3481	0.3483	0.05
S6	0.4366	0.441	1.00	0.3237	0.3238	0.03
S7	0.3864	0.3893	0.75	0.3701	0.3627	1.99
S8	0.4003	0.3965	0.94	0.3427	0.3444	0.379
S9	0.4147	0.4137	0.24	0.3221	0.3194	0.83

2. Check point batch

The 3^2 factorial designs were run with one check point composition of which is shown in Table 35. Batch CP1 was prepared to validate the derived equation for Evaluation parameter and *in-vitro* dissolution time of microcapsule with one check point composition. The data for Evaluation parameter and *in vitro* dissolution time for the predicted and observed values are shown in table 35.

It can be observed that the predicted value and observed value for CP1 for Evaluation parameter and *in-vitro* dissolution time of microcapsule were nearly similar with 3^2 factorial designs batches. It can be concluded that the evolved model can be used for prediction of response i.e. Evaluation parameter and *in-vitro* dissolution time of microcapsule within the simplex space. Comparative analysis of the predicted value and experimental value using paired *t*– test indicated that there was no significant difference between the two values thereby establishing validity of generated mode. In this research work between the t_{stat} (1.36) and t_{cri} (2.44) not significant difference and t_{cri} value very high as compare to $t_{stat.}$

In the present research work, no very much difference between factorial batches and one check point composition and percentage relative error small between predicted and experimental value.

Table 35: Composition and Evaluation parameter and *in-vitro* dissolution of check point batch

Check point batch (CP1)	Evaluation parameter					
	% yield		Mean particle size		% Encapsulation efficiency	
	P	O	P	O	P	O
X1 = -0.5; X2 = +0.5; X3 =7.5	84.5	84.6	17.5	18.1	97.02	96.31
Check point batch (CP1)	**In-vitro dissolution study**					
	Q_6		Q_8		t_{90}	
	P	O	P	O	P	O
X1 = -0.5; X2 = +0.5; X3 =7.5	71.95	67.41	83.98	78.83	9.1	9.95
Check point batch (CP1)	**In-vitro dissolution study**					
	Exponential constant (n)		Release rate constant (k)			
	P	O	P	O		
X1 = -0.5; X2 = +0.5; X3 =7.5	0.4249	0.4248	0.3467	0.3300		

*** P= Predicted value; O = Observed value**

3.15 Morphological Studies of Microcapsules

- **By simple microscope**

The surface topography of the microcapsule was investigated by simple binocular microscope. As seen in figure 12, they were spherical in shape and exhibited porous surface.

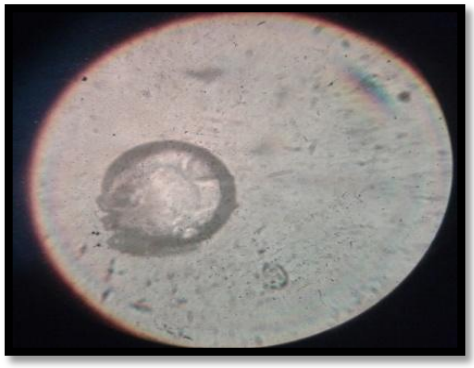

Fig. (12). Morphological Characteristics of Microcapule by simple microscope

- **SEM analysis of the microcapsule**

SEM of drugs loaded polymeric microcapsule reveals that the microcapsule possess rough, porous and rugged surface Figure 13. The surface porosity is crucial for drug release in microcapsule prepared, since the polymer is not biodegradable, the release of the drugs from microcapsule take place by dissolution and diffusion through the pores. The most part of microcapsule was small and had spherical shape, non-uniform surface and were coalesced.

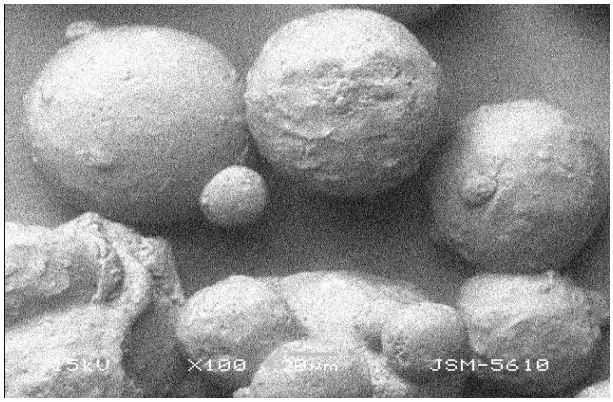

Fig. (13). SEM analysis of the microcapsule

Evaluation of Reconstitutable Suspension

1. *In-vitro* dissolution study

Reconstitutable suspension are prepared by using a various suspending agent like xanthan gum, acacia and guar gum and here suspending agent do not have a more effect of the drug release profile of the reconstitutable SR suspension. In the batches no N1-N3 there is use a xanthan gum (2, 3, 4 % w/w), N4-N6 uses acacia (2, 3, 4 % w/w) and in N7-N9 uses a gaur gum (2, 3, 4 % w/w) respectively (Table 36).

Table 36: Dissolution profile of Reconstitutable suspension

Time (hrs)	N1	N2	N3	N4	N5	N6	N7	N8	N9
0	0	0	0	0	0	0	0	0	0
1	37.04	35.67	34.21	36.91	36.67	35.76	37.79	36.46	38.76
2	42.34	40.98	39.83	40.64	45.25	43.68	41.35	42.44	43.68
3	47.55	47.69	43.65	44.61	51.73	47.56	44.51	49.21	48.56
4	55.64	53.45	51.93	48.53	58.39	53.51	48.94	54.29	54.51
5	61.09	59.15	59.86	53.82	62.37	59.41	53.34	62.13	59.58
6	67.88	65.32	64.72	59.18	66.58	65.77	61.89	68.49	64.77
7	72.49	72.42	71.86	64.32	72.86	71.53	69.44	74.59	70.37
8	78.91	78.64	76.53	72.56	77.56	76.52	77.61	78.64	76.81
9	86.47	84.39	82.14	81.86	83.67	84.61	82.81	85.46	82.89
10	90.55	90.79	87.64	89.43	89.46	93.82	89.75	92.58	92.56
11	96.18	93.85	92.58	95.46	95.47	97.67	94.81	96.33	95.46
12	98.71	98.34	98.15	98.23	98.11	98.07	98.43	98.31	98.11

2. Organoleptic property of all formulation

- Colour- White
- Odour- odourless
- Appearance –white amorphous dry mixture
- Flavor- cherry flavor

3. Sedimentation volume

The sedimentation volumes of all the formulations are depicted in table 37. F value means sedimentation volume was measured to check the physical stability of the suspension. It can have values nearly 1. The result showed that formulation batch (N3) having sedimentation of(0.928) after 7 days which is very nearer to the standard value of sedimentation volume 1, so that N3 formulation was better than other.

Table 37: Sedimentation rate of the reconstitutable suspension

Formulations	Height of sediment(cm) after								Sedimentation Volume F = Hu/Ho
	Ho	1 Day (Hu)	2 Day (Hu)	3 Day (Hu)	4 Day (Hu)	5 Day (Hu)	6 Day (Hu)	7 Day (Hu)	
N1	7.0	6.7	6.6	6.5	6.5	6.4	6.3	6.2	0.885
N2	7.0	6.8	6.7	6.6	6.5	6.4	6.4	6.3	0.900
N3	7.0	6.8	6.7	6.7	6.6	6.6	6.5	6.5	0.928
N4	7.0	6.5	6.4	6.3	6.2	5.9	5.8	5.7	0.814
N5	7.0	6.6	6.5	6.4	6.4	6.2	6.0	5.9	0.842
N6	7.0	6.7	6.6	6.5	6.4	6.3	6.3	6.2	0.885
N7	7.0	6.1	5.8	5.7	5.5	5.2	4.9	4.7	0.671
N8	7.0	6.2	6.0	5.8	5.6	5.4	5.1	4.9	0.700
N9	7.0	6.4	6.2	6.1	5.9	5.8	5.8	5.7	0.814

4. pH

The pH of reconstitutable suspension was determined by using digital pH meter (Welltonix digital pH meter PM100). All the batches N1-N9 have a pH 7.0, which are neutral and it is show in the table 38.

5. Viscosity

Viscosity of different formulation is shown in table 38. Xanthan gum imparts its high viscosity at low concentration with good ranging flow characteristics, which increase with increasing concentration of suspending agent. In this formulation batch N3 has a high viscosity (697 cP) as compare to other batches.

Table 38: Viscosity, pH and Redispersibility of the reconstitutable suspension

Batch No.	Viscosity (cP)	pH	Redispersibility (No. of Strokes)
N1	672	7.0	7
N2	683	7.0	5
N3	697	7.0	4
N4	657	7.0	7
N5	664	7.0	6
N6	671	7.0	5
N7	623	7.0	8
N8	631	7.0	7
N9	636	7.0	6

Accelerator Stability Studies of Reconstitutable Sustained Release Suspension

Result showed accelerator stability parameter of the prepared formulation batch N3 is depicted in table 39. To obtain acceptable suspension, all parameter have minor differences.

Table 39: Accelerator stability studies of the reconstitutable suspension

Evaluation Parameters	Initial	After 15 days
Colour	White	White
Odour	Cherry	Cherry
pH	7.0	6.8
Sedimentation volume	7.0	6.3
Viscosity	697	703
Redispersibility	4	6
% Drug Release	98.15	96.84

4. Conclusion

In the present Research work, attempt has been made to design and develop reconstitutable sustained release (SR) suspension of linezolid using spray drying technique for decrease the dosing frequency and suitable for pediatric and geriatric patients.

Spray drying technique are used to prepare microcapsule for reconstitutable SR suspension of API (linezolid) and polymer (Eudragit RS100, Eudragit RL100 and Surelease), which are freely soluble in the dichloromethane so it is used as a solvent to prepare microcapsule in the preliminary and factorial batches.

From the preliminary study, Eudragit RS100 was exhibited the higher % practical Yield, more encapsulation efficiency, superior mean particle size, uniform drug release for prolong period up to 10 hrs. So, batch F1 are more suitable and used for the preparation further 3^2 factorial batches.

FTIR spectroscopy revealed that there was no chemical interaction between drug and polymer so; it is compatible with drug and polymers. Scanning electron Microscopy showed that microcapsules were spherical with smooth surface.

Results was clearly indicated that drug to polymer ratio and feed flow rate had significant influence on percentage yield, mean particle size, encapsulation efficiency, Q_6, Q_8, t_{90}, Diffusion coefficient (n) and Release rate constant (k). Form the study, the optimized formulation (S3) showed 99.12% cumulative drug release at the end of 12 hrs with drug to polymer ratio (1:1.3) and feed flow rate (5 ml/min) respectively for obtaining the higher percentage of yield, maximum encapsulation efficiency, Particle size of microcapsules which is found to be 87.82%, 99.07% and 16.06µm consequently.

6. Redispersibility

The Redispersibility of preliminary batches of reconstituted suspension is exhibited in table 38. Redispersibility is an important factor when one has to deal with suspension. As if there is no dispersion of suspension then it will lead to caching of solid content and if caking occurs then there must be chance of non-uniform dose of drug during medication because the drug remains in the cake. Result shows formulation batch N3 had minimum number of strokes 4 as compared to other formulation batch.

In 3^2 factorial designs batches were used two independent variable X1(drug to polymer ratio) and X2 (feed flow rate), while percentage yield, mean particle size, encapsulation efficiency, Q_6, Q_8, t_{90}, Diffusion coefficient (n) and Release rate constant (k) were taken as dependent variable and in the 3^2 factorial designs the positive coefficient of X1 in case Y_1,Y_2, Y_3, Y_6 and Y_7 refers to increase in percentage yield, particle size, encapsulation efficiency,t_{90} and diffusion exponent (n) with increase in drug to polymer ratio. Similarly, positive coefficient of X2 in case of Y_2 and Y_6 refers to increase mean particle size and t_{90} with increase in feed flow rate.

While in case of response term Y_4, Y_5 and Y_8, there is negative coefficient of X1 refers to decrease in Q_6,Q_8 and release rate constant (k) with increase to drug to polymer ratio. Whereas, In case of response term Y_3, Y_4, Y_5, Y_7 and Y_8, there is negative coefficient of X2 refers to decrease in encapsulation efficiency, Q_6, Q_8, diffusion exponent (n) and release rate constant (k) with increase to drug to polymer ratio.

Low values of % bias for all responses shows a good agreement between the experimental and predicted values. Comparative analysis of the predicted value and experimental value using paired *t* – test indicated that there was no significant difference between the two values thereby establishing validity of generated mode of Evaluation parameter and *in-vitro* dissolution time of microcapsule with one check point composition. The results from the estimated ridge of maximum response value of Y_1 (percentage yield), minimum response value of Y_2 (particle size) and maximum response value of Y_3 (Encapsulation efficiency) and cumulative percentage drug release in terms of desirability revealed that optimum drug to polymer ratio (X1) and feed flow rate (X2) were 1:1.3 and 5 ml/min respectively are desirable.

From the full factorial design and different graphical representation, it was finalized that batch S3 was found to be optimized batch having drug release up to 12 hr. More ever, the dissolution profile of optimized batch S3 was found to be similar with theoretical drug release profile having similarity factor more than 50 ($f2$= 82.35) and dissimilarity factor less than 15 ($f1$=2.90) which reflects the feasibility of the optimization procedure in successful development of sustained release microcapsule by using Eudragit RS 100.

Microcapsule prepared with 1:1.3 drug to polymer ratio were selected for SR suspension formulations since they have higher loading efficiency and suitable micrometric properties to disperse in aqueous medium. Reconstitutable SR suspensions were prepared using optimize batch of microcapsules with various suspending agent (xanthan gum, acacia, gaur gum), Sweetener (sucrose), preservative (Na benzoate), buffering agent (citric acid) and flavoring agent (cherry).

From the results of reconstitutable SR suspension, it can conclude that the high sedimentation volume and better redispersibility and high viscosity of the suspending agent xanthan gum in a low quantity which more suitable for the optimization of formulation.

As the viscosity of suspension was higher the particles or solid contents present in the suspension will not sediment for a longer time. So they will remain suspended in the suspension. Due to this effect the

sedimentation volume of suspension was higher and the sedimentation rate was slow.

Redispersibility of higher viscous suspension is also better. This was because of that as the lowest sediments of particles occur it will easily redisperse again. So in present work it was shown that due to high viscosity of xanthan gum (3% w/w), it's the sedimentation volume was highest and redispersibility and viscosity was better than other formulations.

Results clearly revealed that drug release studies of SR suspension formulation did not show any statistically significant differences (P>0.05) from the properties of microcapsule alone.

Results reported the release profiles of suspension prepared from microcapsules no significant difference (P>0.05) was observed in cumulative percentage drug release for sustained release suspension on 1day and after 15days which indicates the suspension stability.

Finally, it was concluded that the type of polymer and feed solution of the spray dryer had a major impact on the in vitro release of drug from microcapsules and suspensions and it can be precise dosing of drug, patient compliance and suitable for pediatric and geriatric intended sustained release of drug up to 12 hrs.

Conflict Of Interest

The author declares no conflict of interest.

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