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Formulation and Evaluation of Simvastatin Controlled Release Pellets by Extrusion Spheronozation Technique

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ABSTRACT

Simvastatin (SIM) is an antihyperlipidemic drug used in treatment of hypertension. This research was carried out to design oral controlled release matrix pellets of water insoluble drug Simvastatin, using blend of Sodium Alginate (SA), Eudragit RSPO and Eudragit RSPO as rate controlling polymers, micro crystalline cellulose (MCC) as spheronization aid and calcium carbonate to enhance sodium alginate matrix strength. *SIM* formulations were developed by the Extrusion and spheronization technique and characterized with regard to the drug content, size distribution, Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), other physicochemical parameters and drug release studies. Stability studies were carried out on the optimized formulation for a period of 90 days at 40 ± 2°C and 75 ± 5% relative humidity. 2^3 full factorial design was applied for optimization of formulation considering Sodium alginate, Eudragit RSPO and Spheronization speed as variables. The drug content was found to be in the range of 88 to 97 %. The particle size of the drug loaded pellets was in the range 750 to 1700µm. The compatibility between drug and polymers in the drug loaded pellets was confirmed by DSC and FTIR studies. Stability studies indicated that different ingredients used in formulation of pellets shows no interaction with the drug. Pellets prepared from batch P13 demonstrated good physical properties and also good drug release profile so considered as optimized batch.

KEYWORDS

Simvastatin, Extrusion-Spheronization, Sodium alginate, Eudragit RSPO, Eudragit RLPO.

INTRODUCTION

The extrusion-spheronization technique which was first developed by Nakahara in 1966 is one of the most popular methods of producing microspheres (Hellen et al., 1993a). Because of the advantages of microspheres compared to single unit dosage forms, they are well accepted in the pharmaceutical industry. These advantages may be summarized as: (a) good reproducibility of transport through the gastrointestinal tract (GIT), (b) minimization of local damage to the GIT mucosal membrane because of their wide distribution over a large area, (c) feasibility of a controlled release dosage form due to their smooth gastric emptying, (d) good content uniformity and (e) producing beads with drug loadings up to 90% (Eskilson, 1985; Mesiha and Valles, 1993).[1]

Simvastatin, a hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor (statin) is an antilipedemic agent. Simvastatin lowers the lipid level in blood and thereby prevent cardiovascular disease.[2] It is used in treatment of hypercholesterolemia, as it reduces levels of low-density lipoproteins and triglycerides, and raises high-density lipoprotein levels. Simvastatin is a BCS clsss-II drug. It is very sensitive to oxidization and having very short

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half life of about 2 to 3 hrs. Daily dose of Simvastatin ranges from 10 to 80 mg/day. So, it requires multiple administrations per day. Because of these properties simvastatin is a better candidate for controlled release formulation. Pellets are to be filled in capsules so this will protect it from oxidation.[3]

Alginates, a group of anionic polysaccharides, are linear polysaccharides extracted from brown seaweed. They contain varying amounts of (1–4)-linked b-D-mannuronic acid (M) and a-L-guluronic acid (G) residues. The residues may vary widely in composition and sequence and are arranged in a pattern of blocks along the chain. The homopolymeric regions of M and G blocks are interspersed with regions of alternating structure (MG blocks). The composition and extent of the sequences and the molecular weight determine the physical properties of the alginates. One of the most important and useful properties of alginates is the ability to form gels in the presence of some multivalent metal ions such as calcium. The controlled addition of these ions technically leads to insoluble alginate gel formation. The affinity of alginates for calcium ions and their gel forming properties is mainly related to the overall fraction of G residues, the molecular weight of the polymer, and the calcium ion concentration at the time of gelation. When two G residues are adjacent in the polymer, they form a binding site for calcium Alginates are of pharmaceutical interest because of their non-toxicity, biodegradability and biocompatibility. Alginate hydrogels have the potential to be used as either controlled release membrane or matrix systems for therapeutic drugs. In the membrane system, alginates could be applied as a coating material.[4]

There are a few reports on the production of matrix pellets by extrusion–spheronization based on pH-dependent acrylic polymers such as Eudragit S (Krogars et al., 2000) or Eudragit L100 55 and S100 (Mehta et al., 2001). pH-independent acrylic polymers such as Eudragit RL30D and RS30D have been used in preparation of granules by spraying or fluidized bed method (Tsai et al., 1998; Radtke et al., 2002).[5] However, there is no report on production of pellets by extrusion–spheronization using this kind of acrylic polymers. In the present work, the application of Eudragit RSPO, Eudragit RLPO or their combination was studied for production of pellets.[6]

MATERIALS AND METHODS

Simvastatin (Gift sample from Zydus Cadila healthcare limited), Sodium alginate (SD Fine Chemicals.) Eugragit RSPO, Eudragit RLPO (Gift sample from Evonic), Micro Crystalline Cellulose (FMC Corporation, USA) Polyvinyl Pyrrolidone (SD Fine Chemicals), Calcium carbonate (SD Fine Chemicals).

FORMULATION OF CONTROLLED RELEASE PELLETS[7]

Accurately weighed amount of solid materials shown in table 2 were transferred to a clean bowl. Accurately weighed amount of drug geometrically mixed with above powder blend**.** To the prepared powder blend water was added till wet mass of acceptable plasticity was obtained. Above prepared wet mass was then extruded using a radial piston type extruder. The screen was 1 mm thick and the apertures were 1 mm in diameter. Prepared extrudates were then cut manually with small cutter to get extrudate size approximately 1 mm in length. Extrudates prepared were then spheronized at 2000 rpm for 10 to 15 min. Prepared pellets were then dried below 60^{o}C for 2 hours**.**

2^3 Full Factorial Design

Table 1: Variables, Coded Value and Actual Values

Variables level	Low (-1)	High (+1)
Spheronization Speed (RPM) (X_1)	1500	2000
Concentration of Sodium Alginate % (X_2)	25%	30%
Concentration of Eudragit RSPO % (X_3)	10%	15%

Table 2: Composition of Pellets Prepared Using Sodium alginate, Eudragit RSPO and Eudragit RLPO

Ingredients	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**
Drug	10%	10%	10%	10%	10%	10%	10%	10%	10%
MCC	55%	55%	55%	55%	55%	55%	52%	52%	52%
Sodium Alginate	30%	-	-	15%	15%	-	30%	15%	15%
Eudragit RLPO	-	30%	-	15%	-	15%	-	15%	-
Eudragit RSPO	-	-	30%	-	15%	15%	-	-	15%
PVA	5%	5%	5%	5%	5%	5%	5%	5%	5%
Cal.carbonate	-	-	-	-	-	-	3%	3%	3%

Table 3: Protocol for Batches as per 2^3 Full Factorial Design

Batch Code	**X_1**	**X_2**	**X_3**
P10	-1	-1	-1
P11	1	-1	-1
P12	-1	1	-1
P13	1	1	-1
P14	-1	-1	1
P15	1	-1	1
P16	-1	1	1
P17	1	1	1

Table 4: Composition of Simvastatin Pellet as per 2^3 full factorial Design

Batch No.	**Drug**	**MCC**	**Sod. Alginate**	**Eudragit RSPO**	**PVA**	**Calcium Carbonate**	**Spheronization speed**
P10	10%	50%	25%	10%	5%	3%	2000.00
P11	10%	50%	25%	10%	5%	3%	1500.00
P12	10%	45%	30%	10%	5%	3%	2000.00
P13	10%	45%	30%	10%	5%	3%	1500.00
P14	10%	50%	25%	15%	5%	3%	2000.00
P15	10%	50%	25%	15%	5%	3%	1500.00
P16	10%	45%	30%	15%	5%	3%	2000.00
P17	10%	45%	30%	15%	5%	3%	1500.00

EVALUATION OF PELLETS

Drug –Excipients Compatibility Study By FTIR

Fourier-transform infrared **(**FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The samples (Simvastatin and Excipients) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample:KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm-1, from 4000 to 400 cm-1.[8]

Drug –Excipients Compatibility Study DSC study

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The samples (drug and excipients) were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.[9]

Particle Size and Size Distribution

The size and size distribution of the pellets produced was determined by agitation for 10 min with a sieve shaker fitted with a progression of standard sieves. From the weight retained on each sieve particle size is determined from standard sieve aperture size as per Indian Pharmacopeia.[10]

Bulk Density[11]

Apparent bulk density was determined by placing prepared pellets into a graduated cylinder and measuring the volume and weight as it is. That was calculated by formula

$$D_b = W/V_b$$

Where, W = Weight of Pellets taken, V_b = bulk volume.

Tapped Density[6]

Tapped density was determined by USP method II. Pellets were filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum. That was calculated by formula

$$D_t = W/V_t$$

Where, W = Weight of pellets taken, V_t= tapped volume.

Angle of Repose[12]

Angle of repose was determined by using funnel method. Pellets were poured from funnel, that can be raised vertically until a maximum cone height h was obtained diameter heap D, was measured. The repose angle Φ was calculated by formula

$$\Phi = \tan^{-1} h/r$$

Where, h = height of tip of funnel from horizontal ground surface and r = the radius of base of conical pile.

Compressibility Index[8]

Compressibility index was calculated by following equation

Carr's index = (Tapped density - Bulk density / Tapped density) X 100

Hausner's Ratio[8]

Hausner's ratio was calculated by following equation

Hausner's ratio = Bulk density / Tapped density

Where, Dt = tapped density; Do = bulk density.

Friability[7]

Friability was measured with an Electrolab Tablet friabilitor apparatus for 30 min at 20 rpm. 20 g of pellets was mixed with 30 g of glass beads. Friability was estimated as the increase in the percentage of sampling weight due to pellets or pellet fragments.

Drug Content[13]

Accurately weighed 100 mg of prepared pellets are transferred to a 100 ml volumetric flask and 5 ml Methanol was added to above flask to extract out drug from pellets. Phosphate buffer pH 7.4 was added to above flask. The flask is then sonicated for 5 min. Volume will be then made up to 100ml with phosphate buffer pH 7.4. Above solution will be filtered through wahtman paper and absorbance will be measured at 238 nm.

In-vitro Drug Release Study[10]

The dissolution test was performed using Apparatus - I (basket type) at 100 rpm in 900 ml HCl buffer solution pH 1.2 for 2 hr and in 900 ml Phosphate buffer pH 7.4 for 12 hrs at 37±0.5°C. 5 ml samples were withdrawn at time intervals of 1 hr replaced with 5 ml of fresh dissolution media each time. Collected samples were then analyzed by UV-visible spectro-photometer at 238 nm.

Stability Study of Optimized Batch[14]

Stability studies were performed according to ICH and WHO guidelines. Batch F25 was packed in an airtight amber glass bottles. The bottles were kept at 25ºC ± 2ºC / 60% RH ± 5% RH and 40ºC ± 2ºC / 75% RH ± 5% RH tested at 1 month. The sample of pellets was than evaluated for stability by determining drug content and physical appearance.

RESULT AND DISCUSSION

In the present work, an antihyperlipidemic drug Simvastatin and various types of polymers like sodium alginate, Eudragit polymers were selected for formulation of pellets and their different concentrations were studied to get desired matrix retention and drug release profile. Sodium alginate was used as matrix forming polymer and different grades of Eudragit were used as rate controlling polymers. Calcium carbonate was added to increase gel strength of sodium alginate to retain polymer matrix till whole dose of drug was released.

The IR spectra of pure drug shows characteristic functional peaks at 2929.1, 1709.8, 1369.1, 1269.0, and 1055.6 cm^{-1}, while physical mixture shows characteristic peaks at 2928.5, 1712.7, 1366.0, 1268.4, 1062.7 cm^{-1} with negligible shift in wave umbers. The negligible shift in wave numbers might be due to presence of amorphous nature of polymers and excipients used. The IR spectra of optimized formulation show characteristic functional peaks at 2928.5, 1692.8, 1372.0, 1268.4 and 1057.1 cm^{-1}. The similarity in the peaks indicated that the compatibility of drug with excipients. The obtained results from FTIR studies were also proved by DSC analysis.

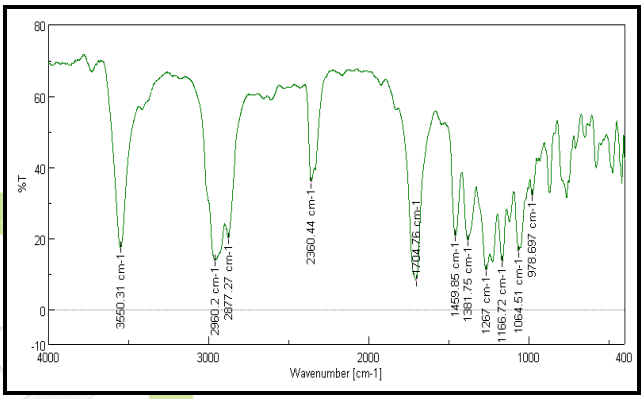

Figure: 1 FT-IR Spectra of Simvastatin (Pure Drug)

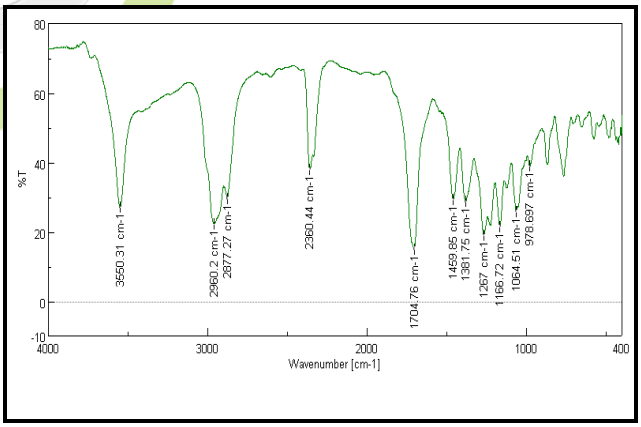

Figure: 2 FT-IR Spectra of Simvastatin (Pure Drug) + Excipients

DSC thermogram of simvastatin, polymers, physical mixture and formulation was carried out to study change in thermal properties of drug. Pure simvastatin thermogram was a single, sharp melting endotherm at 141.06 °C. In the physical mixture, the sharp peak was observed at 139.43°C with negligible change in

endotherm. It indicates that, the excipients used to formulate pellets had no effect on thermal properties of drug. The slight change in melting temperature of drug may be attributed due to addition of amorphous excipients.

Particle size

Particle size of pellets was determined by sieve analysis. Set of standard sieves were arranged with progression of their sieve number. Based on fraction retained on each sieve average particle size was calculated that is described in table 5. From the results it can be concluded that particle size of pellets is higher than pellets prepared from Eudragit RSPO and Eudragit RLPO. It can also be concluded that pellet size increased with increased in sodium alginate concentration.[15]

Density and Flow Properties

Pellets prepared with Sodium alginate (Batch P1) offered very good physical characteristics and flow properties. Density values for pellets shows that pellets prepared using sodium alginate as per batch P1 produced dense pellets. Pellets prepared from batch P2 and P3 containing Eudragit RLPO and Eudragit RSPO repectively have low density compared to Batch P1. Combination of sodium alginate with Eudragit produced pellets with higher density. Due to sphericaal shape pellets showed smaller angle of repose that is indicative of excellent Flowability. Pellets have also very good compressibility.

Friability

Friability is a very essential parameter for any drug formulations especially for a potent drug. Pellets prepared with sodium alginate (Batch P1) demonstrated less friability compared to Eudragit polymers (Batch P2, P3). This is due to good matrix forming properties of sodium alginate. Pellets produced with batch P2 and P3 containing Eudragit RLPO and Eudragit RSPO have higher friability and low product yield because of loss of material during spheronization process due to drying of pellets and high speed rotational movement that lead to dust formation.

Drug Content

From results shown in table 6 it can be concluded that pellets prepared from Sodium alginate (P1), and also in combination with Eudragit polymers has shown high Drug content about 90%. Pellets prepared from Eudragit RLPO (P2) or Eudragit RSPO (P3) had low drug content and also low product yield this is because loss of material occurred during spheronization as Eudagit polymers failed to produce strong matrix that can withstand frictional forces due to high speed rotational movement of pellets in spheronization phase.

In-vitro Drug Release Study

From results of *in-vitro* drug release study of pellets prepared according to batch P1, P2 and P3, it can be observed that sodium alginate, Eudragit RLPO and Eudragit RSPO does not show much difference in drug release profiles. Batch P1 containing sodium alginate shows somewhat high drug release at acidic pH than batch P2 and P3 containing Eudragit polymers. Batch P2 and P3 containing Eudragit was not able to produce dense matrix as compare to sodium alginate. So, Eudragit failed to control the drug release from pellets for 12hrs as shown in Figure 3.

From result and discussion, it was concluded that Sodium alginate pellets failed to comply with acid resistance test as they released more than 10% drug at acidic pH. This is due to channeling effect that is property of sodium alginate. To reduce these channeling effect hydrophobic polymers like Eudragit RSPO and Eudragit RLPO were combined with sodium alginate.

Batch P4 containing combination of sodium alginate (15%) with Eudragit RLPO (15%) has shown similar drug release at acidic pH compare to Batch P1 containing sodium alginate (Figure 4). This combination demonstrated poor control on drug release at both acidic and alkaline pH. Pellets containing sodium alginate and Eudragit RLPO released about 85% drug in just 5 hrs that is not desirable.

Table 5: Physical Properties of Pellets

Batch No.	Mean Particle Size (µm)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's ratio	Carr's Index	Angle of Repose	% Friability
P 1		1.1	1.52	0.72	7.63158	13.5	0.78
P 2	800	1.04	1.072	1.030	2.985075	18.12	1.21
P 3	950	0.958	1.06	1.10	9.622642	19.22	1.08
P 4	1100	0.842	0.88	1.045	4.318182	14.02	0.83
P 5	1050	1.053	1.078	1.023	2.319109	12.22	0.91
P 7	1300	0.963	1.03	1.069	6.504854	15.21	0.81
P 8	1000	1.03	1.09	1.058	5.504587	14.44	0.96
P 9	1050	1.05	1.086	1.034	3.314917	13.15	0.92
P 10	900	0.921	1.121	1.121	2.763158	12.23	0.98
P 11	1100	0.898	0.994	0.994	26.579	14.44	0.78
P 12	1050	0.873	0.899	0.899	2.8921	15.19	0.89
P 13	1150	0.913	1.121	0.121	3.1232	12.12	0.81
P 14	900	0.898	1.002	1.002	1.03792	17.34	0.93
P-15	1000	0.933	1.203	1.289	2.7032	11.87	0.91
P-16	850	0.872	0.917	1.051	4.9073	10.34	0.89
P-17	1000	0.843	0.899	1.066	6.22	12.08	0.82

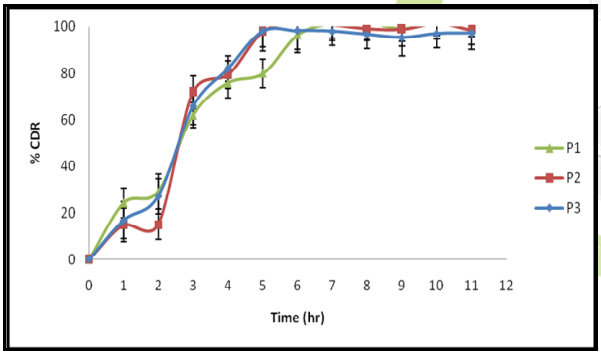

Figure 3: Comparison of Dissolution Profile of Batch P1; Batch P2 and Batch P3

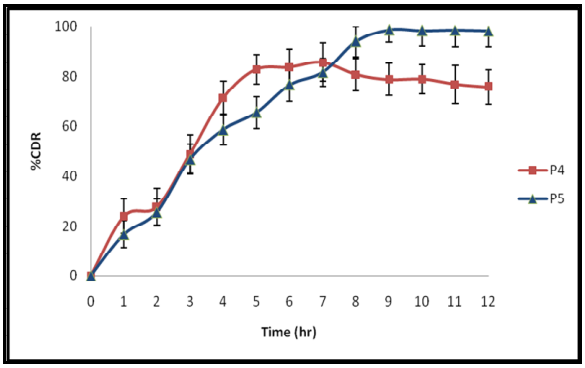

Figure 4: Comparison of *In-Vitro* Drug Release Profiles of Batch P4 and P5

Table 6: Drug Content and % Yield of Pellets

Batch No.	% Yield of Pellets	% Drug Content
P1	93.32%	95.10%
P2	77.59 %	81.50%
P3	79.23%	83.55%
P4	92.87%	90.32%
P5	88.87%	92.74%
P7	91.76%	90.87%
P8	90.90%	85.14%
P9	87.41%	91.82%
P10	90.76%	93.82%
P11	91.12%	89.43%
P12	88.76%	92.92%
P13	93.44%	94.89%
P14	91.58%	92.09%
P15	90.12%	89.64%
P16	89.45%	91.54%
P17	80.43%	90.73%

Batch P5 containing combination of sodium alginate (15%) with Eudragit RSPO (15%) has shown less drug release at acidic pH compare to Batch P1 containing sodium alginate (Figure 4). This combination of polymers also demonstrated good drug release pattern at alkaline pH as shown in figure 4.

Addition of calcium salt increases strength of sodium alginate matrix and that is clearly demonstrated by drug release pattern of pellets prepared according to batch P7 to P9 shown in figure 5. Calcium carbonate gets ionized at acidic pH to give up Ca^{++} ions. These calcium ions react with G sub unit of sodium alginate chain structure and improve cross linking to enhance matrix strength. Because of increased matrix strength, at acidic pH drug release was reduced to about 10%.

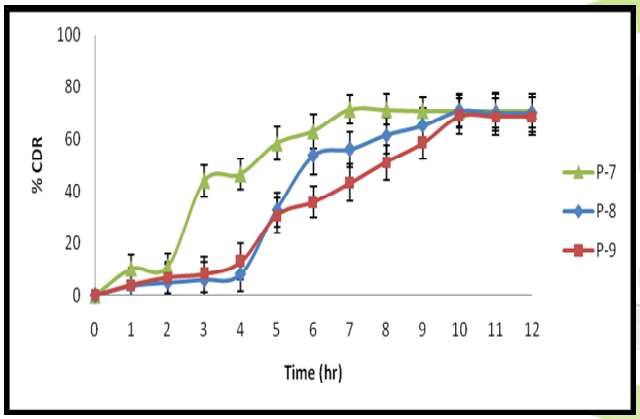

Figure 5: Comparison of *In-vitro* Drug Release Profiles of Batch P7, P8 and P9

In-vitro Drug Release Study of Batch P10 to P17 Prepared According to 2^3- Factorial Design

Results of drug release for Batch P10 to P13 containing 10% Eudragit RSPO has shown in figure 6. All these batches were prepared to study effect of concentration of sodium alginate and different spheronization speed. Drug release of batch P11 containing sodium alginate 25% and spheronized at 2000 rpm was found to be higher compared to that of P10 containing sodium alginate 25% spheronied at 1500 rpm. Results of batch P12 containing 30% sodium alginate and spheronized at 1500 rpm had shown less drug release compared to batch P13 spheronized at 2000 rpm. From above findings it can be concluded that drug release from pellets increased with increased in sodium alginate concentration and also with increased in spheronization speed. Batch P13 shows drug release about 96% in 12 hr.

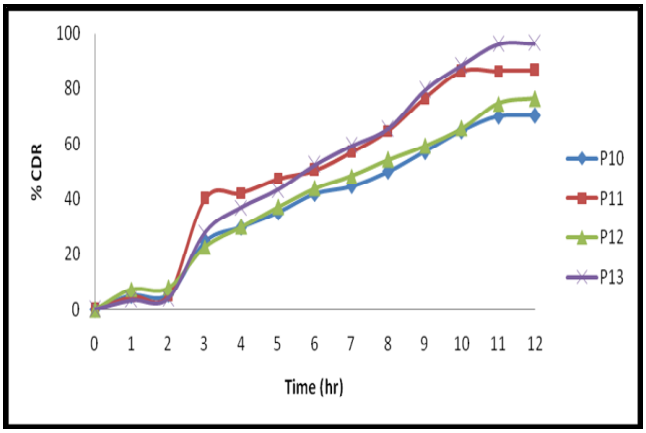

Figure 6: Comparison of drug release profiles of Batch P10 to P13

Drug release profiles for Batches P14 to P17 are shown in figure 7. Batches P14 to P17 were designed to study effect of Eudragit RSPO on drug release from pellets. From drug release of all batches P10 to P14, it can be concluded that drug release from pellets decreases with increase in Eudragit RSPO concentration. From above findings it can be concluded that batch P13 shows about 96% drug release in 12 hrs, so can be selected as optimized formulation.

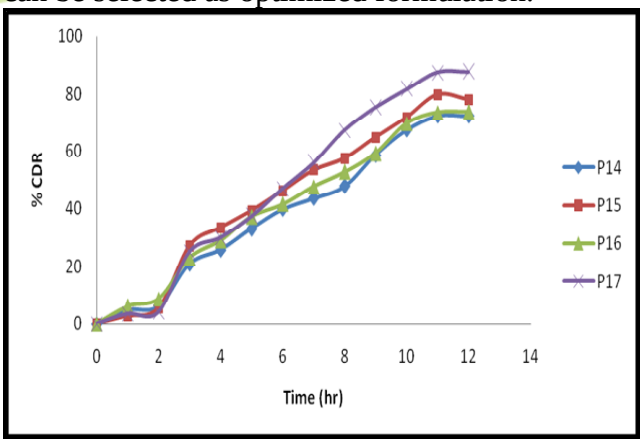

Figure 7: Comparison of drug release profiles of Batch P10 to P13

Data Analysis

The polynomial equations for full model relating to the response, % drug release, the

transformed factor are shown in the Table 7. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive). Table 7 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Since the values of r^2 are quite high, i.e., 0.9311, the polynomial equations form best fit to the experimental data and are statistically valid.

Coefficients with one factor represent the effect of that particular factor on responses while the coefficients with more than one factor and those with second order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively.[16] Positive sign in front of the terms indicates synergistic effect while negative sign indicates antagonistic effect upon the response.[17] So from above data it can be observed that Spheronization speed and concentration of sodium alginate concentration have synergistic effect on drug release from pellets and concentration of Eudraagit have negative coefficient value that indicates antagonistic effect on drug release. From the equation of the model as shown, it can be qualitatively concluded that X1 had the largest agonistic effect on the response Y1, which indicated that X1 was a more important parameter to regulate drug release.

Table 7: Statastical Data from ANOVA test for 2^3 Factotrial Design

Regression statistics		
Multiple R	0.954871	
R Square	0.9311	
Adjusted R square	0.8392	
Mean Standard error	0.9836	
Observations	8	
Coefficients		
Coefficient	**Coefficient value**	**P-value**
b0	80.12	0.0434
b1	6.98	0.0123
b2	3.35	0.0802
b3	-2.23	0.0818
b12	1.48	0.1818
b13	-2.06	0.1268
b23	-0.62	0.1342
Abc	0.56	-
Equation: Full Model		
$\mathbf{Y = 80.12 + 6.98X_1 + 3.35X_2 - 2.23X_3 + 1.48X_1X_2 - 2.06X_1X_3 - 0.62X_2X_3 + 0.56X_1X_2X_3}$		

Contour Plots

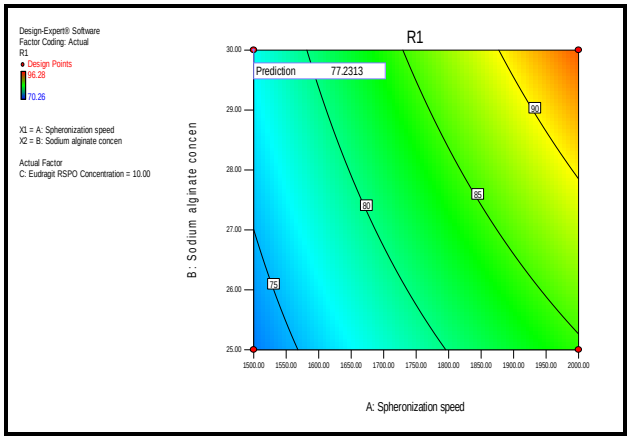

Figure 8: Effect of Sodium alginate and Spheronization Speed on Drug release

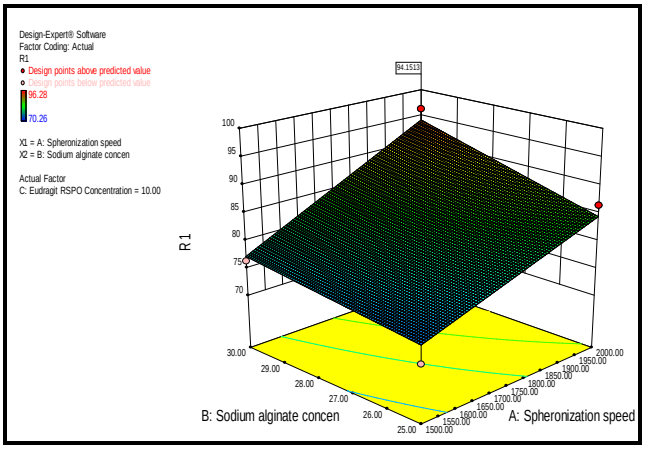

Figure 9: 3D Surface Curve: Effect of Sodium alginate and Spheronization Speed on Drug release

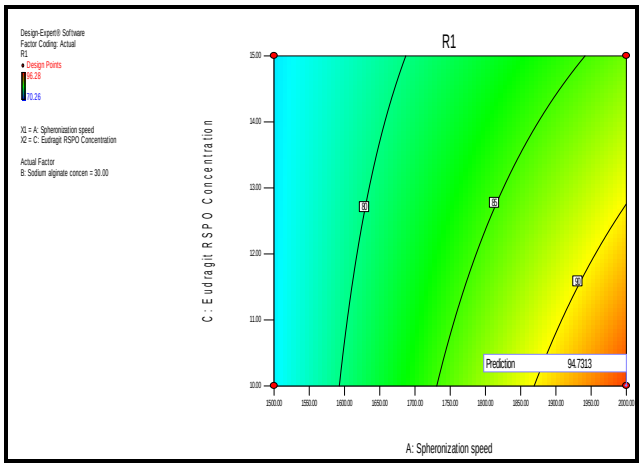

Figure 10: Contour Plot : Effect of Eudragit RSPO and Spheronization Speed on Drug release

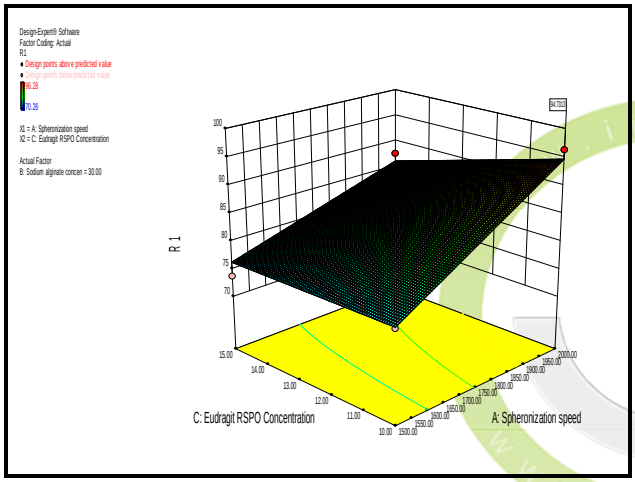

Figure 11: Surface 3D Plot: Effect of Eudragit RSPO and Spheronization Speed on Drug release

Above contour plot (Figure 8) and surface 3D plot (Figure 9) shows the effect of Spheronization speed (X1) and concentration of Sodium alginate (X2) on % drug release (Y). As value of X1 and X2 increases, the value of response Y increases.

Contour plot (Figure 10) and 3D surface plot (Figure 11) shows effect of Spheronization speed (X1) and Eudragit RSPO concentration (X3) on % Drug release (Y). From above plot it can be said that as concentration of Eudragit increases % drug release decreases.

Stability Study of Optimized Batch[18]

The selected batch P13 was evaluated for stability studies which were stored at 25ºC ± 2ºC / 60% RH ± 5% RH and 40ºC ± 2ºC / 75% RH ± 5% RH tested at 1 month, and were analyzed for their drug content at that interval. The drug release of formulation was found to be within the permissible limits and the results of 1 month's duration are shown in the Table 8.

CONCLUSION

Aim of present study was to prepare controlled release pellets of simvastatin that can deliver simvastatin for about 12 hr. From different polymers used, sodium alginate was found to produce pellets with good spherical shape, and flow properties. Pellets prepared with Eudragit RSPO and Eudragit RPLO had high friability that was because of poor matrix formulation ability of Eudragit polymers.

Table 8: Stability Study of Simvastatin Pellets

Time	Initial drug content of batch P 13	Batch F25 stored at 25ºC ± 2ºC / 60% RH ± 5% RH			Batch F25 stored at 40ºC ± 2ºC / 75% RH ± 5% RH		
		Physical appearance*	% DC	%Drug Release	Physical appearance *	% DC	%Drug Release
1 month	94.68%	+++	93.32 %	94.01	+++	91.72%	91.91

*+++ = Same as on zero day
% DC - % Drug Content

In combination with sodium alginate Eudragit RSPO and Eudragit RLPO produced pellets with acceptable physical and flow properties.

From the FTIR, DSC Study and physical compatibility study it can be concluded that there is no significant Drug- Excipient interaction. So it can be concluded that drug and other excipients used in the formulation of pellets were physically compatible.

From results of *in-vitro* drug release study of pellets it can be concluded that sodium alginate failed to control drug release for 12 hr because of channeling effect associate with it. Eudragit RSPO and Eudragit RLPO also failed to control drug release due to poor matrix forming property. But combination of sodium alginate and Eudragit polymers showed good control on drug release. Type of Eudragit polymer, RSPO or RLPO, does not significantly affect drug release from pellets. Spheronization speed is also a key factor affecting drug release profile. From results of 2^3 factorial design pellets prepared from Batch P13 produced pellets with better physical and drug release properties, so selected as optimized batch. The optimized batch was subjected to one month stability study and did not show any significant physicochemical changes so considered to be stable.

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