INCREASING THE ORAL BIOAVAILABILITY OF POORLY WATER-SOLUBLE ATORVASTATIN USING NON-ORDERED MESOPOROUS SILICA MICRO PARTICLES

Abstract

The aim of the study was to increase dissolution rate of Atorvastatin by the use of mesoporous silica SYLOID® 244 FP. The poorly soluble drug Atorvastatin was adsorbed on &/or into SYLOID® 244 FP in the ratio1:1,1:1.1.5, 1:2, 1:2.5,& 1:3, 1:3.5 into a tablet by the use of wetness impregnation method. The absence of crystalline form & presence of hydrogen bond interaction between them is done by FTIR. The flowability and wettability of the atorvastatin loaded powder were evaluated by bulk & tapped density & by angle of repose, respectively. The atorvastatin loaded matrix containing lack of atorvastatin in the crystalline form & large surface area of the SYLOID® 244 FP showed improvement in the dissolution rate. Physical stability of atorvastatin & atorvastatin- SYLOID® 244 FP matrix was satisfactory observed when it is kept over a 1 month storage at 40°C and75% ± 5% humidity. Correspondingly, the solubility of Atorvastatin-loaded matrix was increased upto 2.83 times. So Atorvastatin tablet prepared from drug-loaded silica may provide a feasible approach for development of an oral formulation for this poorly water-soluble drug.

Keywords: Non-ordered mesoporous silica; Atorvastatin; wetness impregnation method;3^2 factorial design; bioavailability.

1. Introduction

Pharmaceutical scientists are constantly developing new strategies to improve drug dissolution rate so as to enable the effective oral delivery of poorly water soluble drugs. Various strategies have been widely investigated to enhance the dissolution of poorly water soluble drugs such as solid dispersions, emulsion based drug delivery, hydrotropy, Inclusion complexation, solid lipid nanoparticles, and so on [1-5]. In recent years considerable research efforts have been directed towards the development of porous carriers for increasing the dissolution of relatively insoluble drugs[6]. One of the pharmaceutically exploited porous adsorbent includes mesoporous silica. Porous silica is a porous material that has been commonly used as a pharmaceutical excipient. Several grades of porous silicate having different characteristics such as particle size, pore size, specific surface area are commercially available. Since the discovery of mesoporous (2-50 nm) silica materials in the 1990s, the synthesis and application of mesoporous silica have received substantial attention due to their unique features such as, inert nature, high surface area, large pore volume, good compatibility and high physicochemical stability[7].

Mesoporous silica as a drug carrier was first evaluated by Vallet –Regi et al[8]. Adsorption onto mesoporous silica (MS) is a new enabling technology that improves the performance of poorly water soluble drugs by improving their dissolution rate and solubility and thereby enhancing oral bioavailability [9,10]. A concentrated drug solution is loaded into pores through capillary forces.

In the present study we selected SYLOID® 244FP (S244) silica as a carrier due to its unique particle structure and morphology. It has a highly developed network of pores that provide access to the ultra high surface area an adjustable pore size in the range of 2.5 to 3.7 µm, and a high drug-loading capacity[11-13] which defines it's performance as a suitable dissolution

enhancement agent. SYLOID® 244 FP was combined with excipients to develop modified tablet using direct compression method.

Statins are a class of cholesterol lowering drugs which have low dissolution rate and bioavailability, warranting the preparation of novel formulations. Atorvastatin calcium (ATC) a BCS Class II drug, one of the world's top-selling statin, has an absolute oral bioavailability of 12% (% F) from a 40 mg oral dosage form. The oral bioavailability of ATC is mainly limited by, solubility and dissolution rate. Hence it was porposed to enhance the dissolution of ATC using mesopororus silica as a carrier .

The main objective of the present work was to develop a Atorvastatin calcium tablet formulation with improved drug dissolution by using adsorption based drug loading on or into SYLOID® 244 FP mesoporous silica. Additional objective was to find out minimum effective quantity of S244 required to enhance solubility. This work is also expected to expand the use of silica-based non-ordered mesoporous materials as drug delivery systems.

Materials and Methods

Materials

Atorvastatin pure drug was provided by Accent Pharma Ltd, Jammu, India as a gift sample. Xtor-20 tablets were manufactured by IPCA laboratories Ltd., India. SYLOID® 244 FP silica was gifted by Grace Davison Discovery Sciences, Germany. Microcrystalline cellulose & crospovidone, sodium lauryl sulphate and ethanol were obtained from Research-Lab Chem industries, Mumbai, India. Lactose, Potassium dihydrogen phosphate (monobasic) & Sodium hydroxide were obtained from SD fine chemicals. All other chemicals and reagents used were of high analytical grade.

Method

Loading Atorvastatin on and/ or into SYLOID® 244 FP silica

A wetness impregnation method[11] was used to load ATC on &/or into the SYLOID® 244 FP. SYLOID® 244 FP in varying quantity was added to a 1.5 ml ethanol solution containing (20 mg)ATC according to Table no. 1. Ethanol was used as the loading solvent because it is safe, nontoxic, and can dissolve large amounts of ATC. Further, the mixture was sonicated using probe sonicator (Sonapros PR-250, Oscar Ultrasonics, Mumbai).) in a closed vial for 10 mins and brought to adsorption equilibrium under magnetic stirring at room temperature for 24 h in order to achieve maximum drug loading in the SYLOID® 244 FP pore channels. Finally, the mixture was evaporated at 50°C on a rotary evaporator (Heidolph, UK) until dry in order to remove the ethanol completely.

The ATC loading in the matrix was determined by FT-IR, DSC & phase solubility studies.

Table no.1: Composition of binary mixture

S.No.	**Amount of drug**	**Amount of SYLOID® 244 FP (mg)**	**Amount of ethanol**
1	20	20(1:1)	1.5ml
2	20	30(1.:1.5)	1.5ml
3	20	40(1:2)	1.5ml
4	20	50(1:2.5)	1.5ml
5	20	60(1:3)	1.5ml
6	20	70(1:3.5)	1.5ml

Characterization of binary mixture (ATC- S244)

Fourier Transform Infra-Red Spectroscopy(FTIR)

Fourier Transform Infra-Red spectroscopy is used to estimate the interaction between ATC and S244. The scans were evaluated for the presence of principal peaks of ATC, shifting and masking of drug peaks due to S244 and appearance of new peaks .

Differential Scanning Calorimetry Analysis (DSC)

Thermogram of the binary mixture recorded. An empty aluminium pan used as a reference. DSC measurement were perfomed at a heating rate of 10^0C/min from 30 to 350^0C. During the measurement, the sample was purged with nitrogen.

Phase solubility study

The most widely used approach to study binary mixture is the phase solubility method which examines the effect of a SYLOID®244 FP on the solubility of drug. Solubility measurements were performed according to method reported by Higuchi and Connors [14,15]. 20 mg of Atorvastatin dissolved in ethanol solution was prepared in five beakers. To each beaker SYLOID® 244 FP was added as indicated in Table. 10 ml of 6.8 pH phosphate buffer was added in beaker and solution was stirred for 24 h and further filtered through Whatman grade 41 filter paper. Absorbance was measured at 250 nm using UV Visible Spectrophotometer (SHIMADZU, V-630, Japan) and solubility was calculated and compared with plain ATC solubility in pH 6.8 phosphate buffer. As shown in Table no. 2

Table no. 2: Phase Solubility Values

Conc. of SYLOID® 244FP(mg)	Solubility (mg/ml)
20	$2.90\times10^{-1}\pm0.038$
30	$3.30\times10^{-1}\pm0.047$
40	$4.033\times10^{-1}\pm0.061$
50	$5.42\times 10^{-1}\pm 0.042$
60	$5.\ 26\times10^{-1}\pm0.042$
70	$5.13\times10^{-1}\pm0.052$
Plain ATC	$1.9\times10^{-1}\pm0.076$

Formulation of Atorvastatin tablet

Conventional Atorvastatin tablet prepared by direct compression method without SYLOID® 244 FP

(20mg) Atorvastatin was taken as a drug, microcrystalline cellulose as a binder, crosspovidone as a disintegrant, and lactose as a diluent. All ingredients were mixed thoroughly and then passed through sieve no. 100 & then disodium lauryl sulphate was added as lubricant just before compression & then tablet was compress by direct compression method.

Atorvastatin tablet prepared by direct compression method with SYLOID® 244 FP

Atorvastatin (20 mg) was dissolved in ethanol (1.5 ml) at room temperature. Add SYLOID® 244 FP (55 mg) and then suspension was shaken for at least 1.5 h using mechanical shaker. Next, the solvent was evaporated under reduced pressure in a water bath at 45-50 °C for 15 min using a rotavapor. The samples were dried under vacuum at room temperature.

Mix thoroughly microcrystalline cellulose as a binder, crosspovidone as a disintegrant & lactose as a diluent with above dried sample & then pass this mixed powder through sieve no. 100. Add sodium lauryl sulphate as lubricant just before punching & then punch the tablet using direct compression method.As shown in Table no 3

Table No.3: **Formula of tablet with SYLOID® 244 FP**

Sr. No.	Ingredients(mg)	With S244	Without S244
1	Atorvastatin	20	20
2	SYLOID® 244 FP	50	-
3	MCC	20	50
4	Crosspovidone	4.5	4.5
5	SLS	1.5	1.5
6	Lactose (q.s)	120	120

*** Quantities are for one tablet**

Comparison between tablets prepared with & without SYLOID® 244 FP:

In vitro drug release of the tablets were carried out using IP – type I dissolution apparatus (Basket type). The dissolution medium, 900 ml of phosphate buffer (pH 6.8) solution, was placed into the dissolution flask maintaining the temperature of 37±0.5ºC and rpm of 75. One tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 2 hrs. Samples measuring 2 ml were withdrawn after every 0, 15, 30,45,60,90 and 120 min. Samples were filtered through 10 µm filter. The fresh dissolution medium was replaced every time to maintain sink condition. The collected samples were analysed at 250 nm using dissolution medium as blank**.** Results obtained from in vitro dissolution graph, comparison of tablets release profile was done.

4.1 Optimisation by 3^2 full factorial design from preliminary study

In 3^2 randomized full factorial design, amount of SYLOID® 244 FP (X_1) and Volume of ethanol(X_2) were selected as independent variables, solubility & % cumulative release were selected as dependent variables. In this design 2 factors was evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. For each batch, 20 mg of atorvastatin as a drug component was same.

Table no.5: Formulation of the factorial batches (F1 to F9)

Batches	Independent Variables		Actual Values	
	X_1	X_2	X_1 (%)	X_2(%)
F 1	-1	-1	45	1.25
F 2	-1	0	50	1.5
F 3	-1	1	55	1.75
F 4	0	-1	45	1.25
F 5	0	0	50	1.5
F 6	0	1	55	1.75
F 7	1	-1	45	1.25
F 8	1	0	50	1.5
F 9	1	1	55	1.75

X_1- Amount of SYLOID 244 FP,X_2- Volume of ethanol

Each factor was evaluated at three levels and experimental trials were performed for 9 different formulations, as shown in Table no.6

Table no.6: Formulation of Tablet for optimization

Ingredients	Formulations and Quantity in (mg per tablet)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Atorvastatin	20	20	20	20	20	20	20	20	20
SYLOID	45	50	55	45	50	55	45	50	55
MCC	20	20	20	20	20	20	20	20	20
Crosspovidone	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
SLS	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Lactose(q.s)	120	120	120	120	120	120	120	120	120

All the nine formulations were subjected to evaluation for drug content, drug release, in vitro dissolution studies.

5.1 Dissolution kinetic studies [16]

To analyze the mechanism of drug release from the *tablet,* data obtained from the drug release studies from optimized batch was subjected to different kinetic model treatments (Zero order, First order, Hixson-Crowell and Korsemeyer - Peppas.). The correlation coefficient (r^2) was used as an indicator of the best fitting for each of the models considered.

6.1 STABILITY PROFILE OF OPTIMIZED BATCH

Quantitative analysis:

The stability of optimized formulation batch(F8) were observed in physical parameters, when stored at temperature and humidity conditions of 40_+ 20C /75 +_5 % RH.(Climatic zone IV condition for accelerated testing) to access their long-term stability.

RESULTS AND DISCUSSION

Evaluation of atorvastatin- SYLOID® 244 FP matrix

I. FT-IR

The FT-IR Spectrum of atorvastatin pure drug was found to be similar to the standard spectrum. The spectrum of atorvastatin showed following functional groups at their frequencies. As shown in Figure No.

Fig. 1.FTIR spectrum of (a) SYLOID® 244 FP (b) Atorvastatin & (c) Atorvasatin-SYLOID® 244 FP matrix

II. Differential Scanning calorimetry (DSC)

Figure No. 17 Overlay of A .Mixture(Atorvastatin+ SYLOID® 244 FP),B. Excipient (SYLOID® 244 FP) and C. Drug (Atorvastatin).

As compared with atorvastatin pure drug, DSC spectra of atorvastatin-loaded SYLOID® 244 FP matrix shows changes in melting point, peak onset and appearance of peak which ultimately confirmed that atorvastatin was loaded on &/or in to SYLOID® 244 FP.

IV. Phase solubility

Atorvastatin pure drug show solubility in pH 6.8 phosphate buffer was found to be

$0.19\times10^{-1}\pm0.037$ mg/ml.

Table no.17 Phase solubility values

Conc. of SYLOID® 244FP(mg)	Solubility (mg/ml)
20	$2.90\times10^{-1}\pm0.038$
30	$3.30\times10^{-1}\pm0.047$
40	$4.033\times10^{-1}\pm0.061$
50	$5.42\times 10^{-1}\pm 0.042$
60	$5.\ 26\times10^{-1}\pm0.042$
70	$5.13\times10^{-1}\pm0.052$
Plain ATC	$1.9\times10^{-1}\pm0.076$

Value expressed as mean ±SD, n=3

Fig. 4.Phase solubility graph

The phase solubility study was conducted in phosphate buffer pH 6.8 show rise in solubility up to $5.42\times 10^{-1}\pm 0.042$. From this, it was confirmed that atorvastatin was loaded on &/or in to SYLOID® 244 FP.

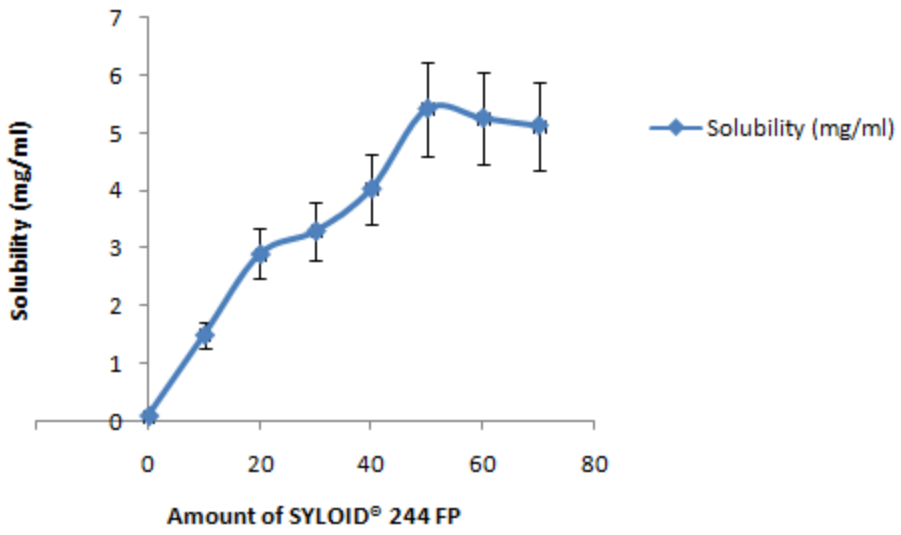

Figure no.4: Phase Solubility graph

Formulation of tablet by direct compression method

In vitro dissolution study of trial batches

Table no.20: % cumulative drug release of trial batches

TIME (min)	A1	A2	A3	Mean	B1	B2	B3	Mean
0	0.0038	0.0020	0.0025	0.0027±0.005	0.0842	0.1058	0.0982	0.287±0.0109
5	2.88595	1.4455	2.782	2.36±0.8014	7.427	5.785	3.7873	5.66±1.82
10	5.7233	3.7524	4.593	4.68±0.988	15.412	16.2561	13.14	14.802±1.60
15	5.9946	4.035	5.9806	5.33±0.970	21.159	23.06	29.21	23.429±4.26
20	10.47	8.5737	10.0899	9.71±0.833	35.161	31.48	36.96	34.53±2.79
25	18.3	12.487	14.087	14.95±3.006	41.253	46.01	48.75	45.33±3.79
30	19.39	15.957	16.049	17.132±1.960	54.150	55.49	54.68	54.77±0.677

Where A1, A2, & A3- Prepared atorvastatin tablet without SYLOID® 244 FP

B1,B2,& B3- Prepared atorvastatin tablet with SYLOID® 244 FP.

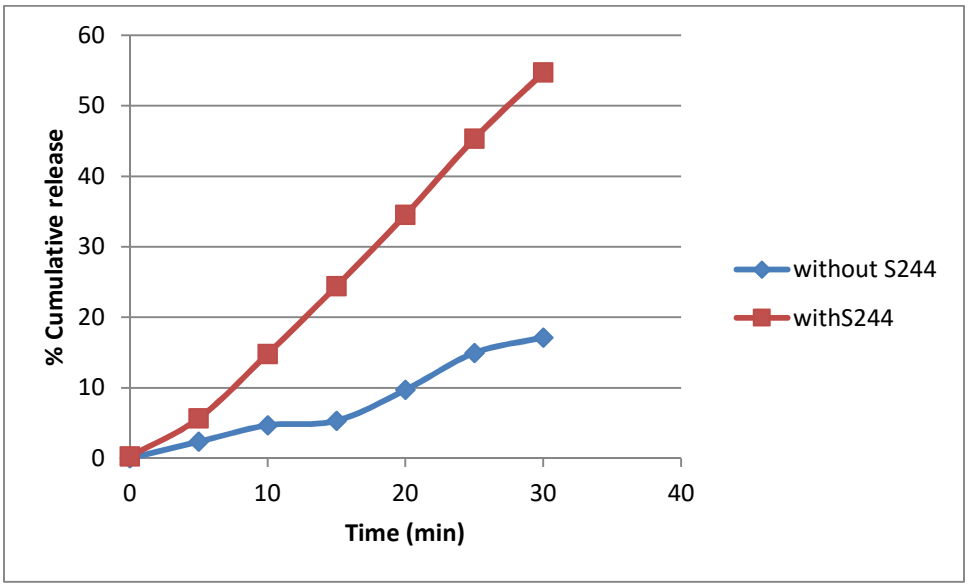

Figure No: 5 Time vs. % DRUG RELEASE

Average values of cumulative release Atorvastatin tablet without SYLOID® 244 FP and average values of cumulative release atorvastatin tablet with SYLOID® 244 FP were plotted in. Graph indicates that the % cumulative release of tablet contains SYLOID® 244 FP was increased & greater than that of the tablets without SYLOID® 244 FP, So ultimately results in the enhancement of the dissolution rate.

Optimisation by 3^2 full factorial design

Solubility optimisation

Table No. 21: Solubility optimisation by full factorial design

Sr.no.	Batch Code	Amount of ethanol (ml)	Amount of SYLOID® 244 FP (mg)	Solubility (mg/ml)
1	F1	1.25	45	$3.02\times10^{-1}\pm0.0040$
2	F2	1.25	50	$4.24\times10^{-1}\pm0.0057$
3	F3	1.25	55	$4.86\times10^{-1}\pm0.0084$
4	F4	1.5	45	$5.40\times10^{-1}\pm0.0071$
5	F5	1.5	50	$5.46\times10^{-1}\pm0.0061$
6	F6	1.5	55	$6.00\times10^{-1}\pm0.0039$
7	F7	1.75	45	$6.14\times10^{-1}\pm0.0087$
8	F8	1.75	50	$8.15\times10^{-1}\pm0.0057$
9	F9	1.75	55	$7.48\times10^{-1}\pm0.0049$

*Value expressed as mean ±SD, n=3

In vitro study of factorial batches:

Table No.27: % Cumulative release of factorial design batches

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.0402± 0.22	0.3021± 0.10	0.0512± 0.17	0.0404± 0.16	0.0842± 0.26	0.7386± 0.25	1.0281± 0.22	0.9550± 0.15	0.8182± 0.11
5	16.885± 1.03	14.445± 1.16	13.782± 1.22	10.8011± 1.53	7.427± 2.56	16.0261± 1.26	15.789± 1.25	15.7856± 1.26	10.427± 2.45
10	22.723± 2.08	26.752± 2.56	22.593± 2.65	14.031± 3.025	15.412± 3.25	19.0686± 2.58	33.133± 2.45	35.145± 3.151	23.145± 3.548
15	33.994± 3.16	36.035± 3.42	32.9806± 3.46	16.79± 2.15	21.159± 3.14	25.35± 3.45	49.21± 3.17	53.06± 3.15	35.152± 3.76
20	45.47± 4.15	47.5737± 4.25	42.0899± 4.12	23.724± 4.52	35.161± 5.516	33.957± 5.59	69.96± 4.52	71.48± 4.25	49.140± 4.56
25	56.32± 5.15	54.487± 5.23	50.087± 6.12	54.91± 5.42	41.253± 6.51	52.905± 6.54	81.75± 6.15	85.01± 5.97	61.125± 5.23
30	59.39± 6.35	65.957± 6.13	62.049± 7.16	69.481± 7.580	54.150± 6.84	65.215± 6.59	91.39± 6.15	**95.68± 7.26**	74.147± 7.11

Value expressed as mean ±SD,n=3

ANOVA for response surface quadratic Model

Table No. 22: Analysis of variance

Source	Sum of squares	Df	Mean square	F value	p-value	
Model	3.52	3	1.17	9.53	0.0165	Significant
A-Amount of Syloid	0.81	1	0.81	6.56	0.0506	
B- Amount of ethanol	1.26	1	1.26	10.22	0.0241	
AB	1	1.45	11.80	0.0185		
Residual	0.62	5	0.12			
Cor Total	4.13	8	-			

The Model F-value of 9.53 implies the model is significant.There is only a 1.65% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case B, AB are significant model terms.

Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy),model reduction may improve your model.

Table No. 23: Different R^2 Values

Std. Dev.	0.35	R-Squared	0.8511
Mean	4.21	Adj R-Squared	0.7618
C.V. %	8.34	Pred R-Squared	0.3342

PRESS	2.75	Adeq Precision	9.068

The "Pred R-Squared" of 0.3342 is not as close to the "Adj R-Squared" of 0.7618 as one might normally expect. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc."Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 9.068 indicates an adequate signal.

This model can be used to navigate the design space

Graphical Representation:

The 3D Respone Surface Plot and contour plot of both variables are mentioned below which are represemting the effects of independent variables on dependent variables.

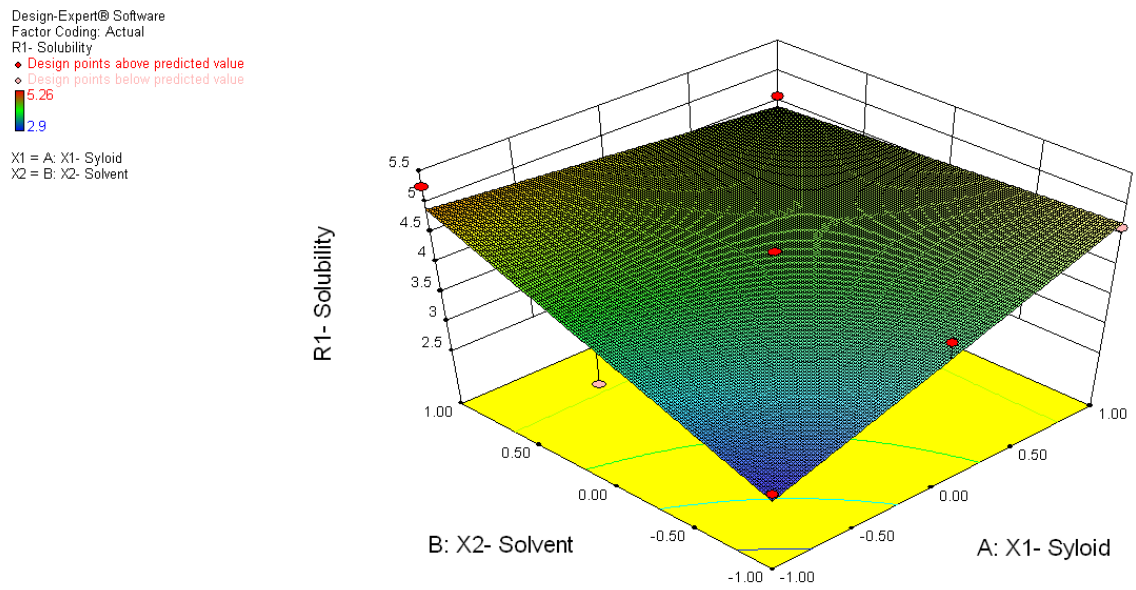

Figure No.24: Three-Dimensionl surface graph for solubilty

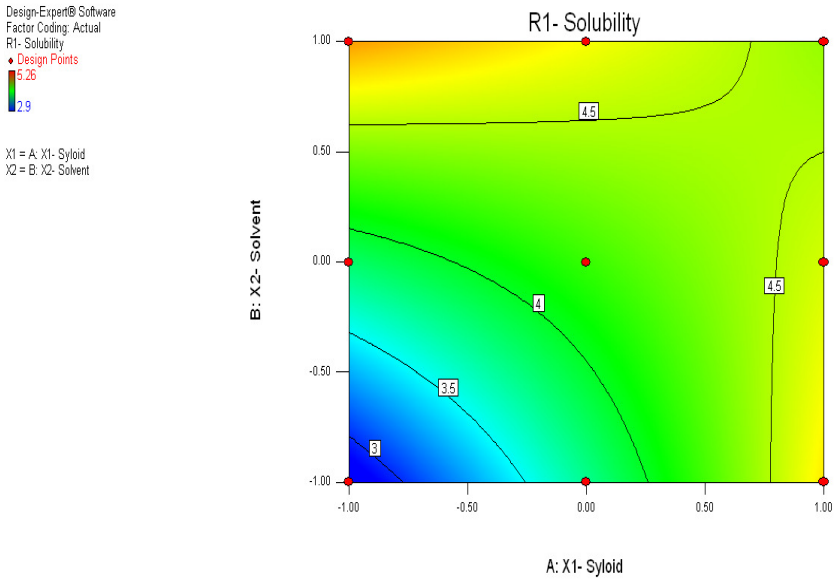

Figure No.25: Counter plot graph

Polynomial equation for response surface :

$$R_1 \text{ (Solubility)} = +4.21 + 0.37\ X_1 + 0.46\ X_2 - 0.60\ X_1X_2$$

ANOVA for Response Surface Quadratic Model

Table No.28: Analysis of variance table

Source	Sum of squares	Df	Mean square	F value	p-value	
Model	8085.44	5	1617.09	134.34	0.0010	Significant
A-Amount of Syloid	6666.67	1	6666.67	553.85	0.0002	
B- Amount of ethanol	468.17	1	468.17	38.89	0.0083	
AB	1	121.00	10.05	0.0505		
A2	1	826.89	68.70	0.0037		
B2	1	2.72	0.23	0.6669		
Residual	36.11	3	12.04			
Cor Total	8121.56	8	-			

The Model F-value of 134.34 implies the model is significant.There is only a 0.10% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant.In this case A, B, A^2 are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.If there are many insignificant model terms (not counting those required to support hierarchy),model reduction may improve your model.

Table No. 29 Different R^2 Values

Std. Dev.	0.44	R-Squared	0.9970
Mean	66.49	Adj R-Squared	0.9920
C.V. %	0.65	Pred R-Squared	0.9741
PRESS	4.88	Adeq Precision	44.194

Polynomial equation for response surface quadratic model

$$R_2 \text{ (DR2h)} = +35.44 - 33.33\ X_1 + 8.83\ X_2 - 5.50\ X_1 X_2 + 20.33\ X_1^2 - 1.166\ X_2^2$$

Graphical Representation

The 3D response Surface Plot and Contour Plot of both variables are mentioned below which are representing the effects of independent variables on dependent variables.

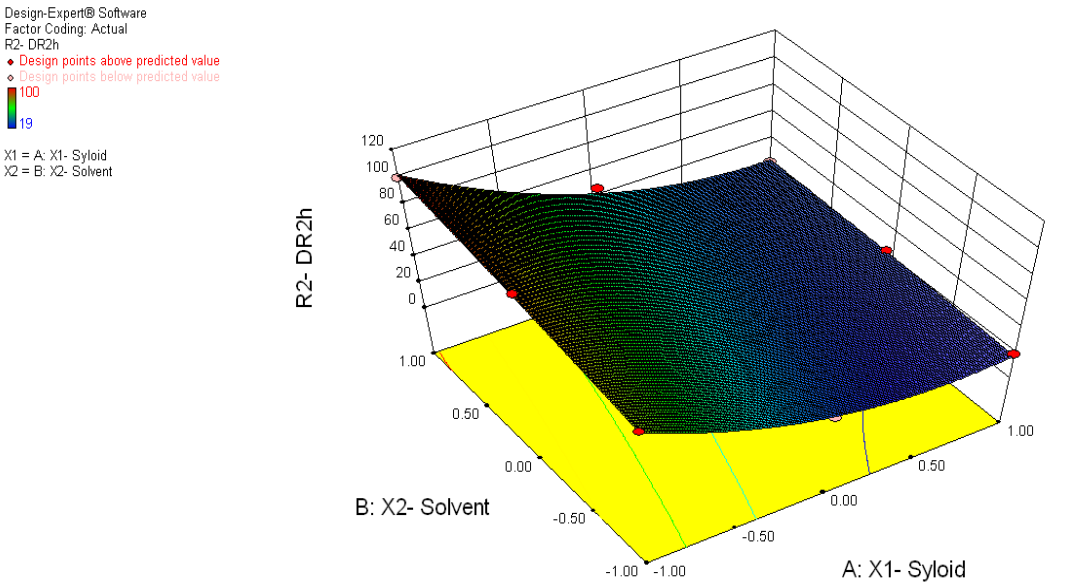

Figure No: 27. Three Dimensional surface Area for % cumulative release

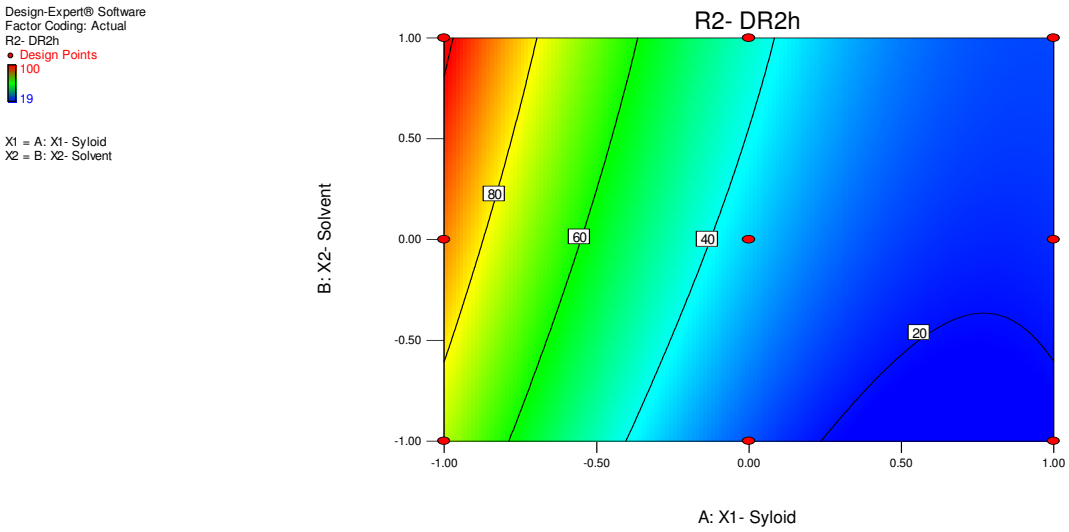

Figure No.28 Counter plot graph

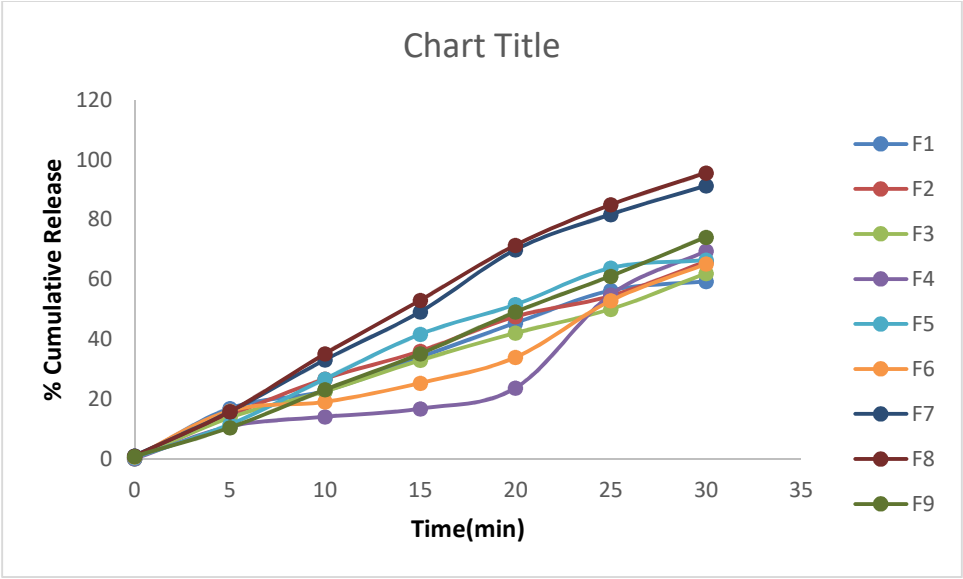

Figure No.28: Time Vs. % Cumulative release (Batch F1 to F9)

In Batch F1,F4, & F7, low level of SYLOID® 244 FP amount i.e. 45 mg (-1) was used and, the amount of ethanol varies to 1.25 ml (-1), 1.5 ml (0) & 1.75 ml (+1).

From figure 28 and Table no. 21, it was evident that on increasing amount of ethanol solubility of ATC increases, it was further observed that the formulation F7 showed maximum cumulative

drug release 91.39 % (Table 27)whereas formulation F1 and F4 showed 59.39 % and 69.049 % CDR respectively in 30 min. In these batches solubility increases on increase in amount of ethanol.

In Batch F2, F5& F8, medium level SYLOID® 244 FP amount i.e. 50 mg (-1) was used and the amount of ethanol varies to 1.25 ml (-1), 1.5 ml (0) & 1.75 ml (+1).

From figure 28 similar results were observed as that of batch F1,F4, & F7, that is on increasing amount of ethanol solubility of ATC increases, it was observed that the formulation F8 showed maximum cumulative drug release 95.68 % whereas formulation F2 and F5 showed 66.48% and 65.95 % CDR respectively in 30 min.

In Batch F3,F6 & F9,at high level SYLOID® 244 FP amount i.e. 60 mg (-1) was used and the amount of ethanol varies to 1.25 ml (-1), 1.5 ml (0) & 1.75 ml (+1).

From figure 28 it was observed that on increasing amount of ethanol solubility of ATC increases, the formulation F9 showed maximum cumulative drug release 74.147 % whereas formulation F3 and F6 showed 62.049% and 65.215 % CDR respectively in 30 min. Using design expert, optimisation was done & from that we found that batch F8 shows maximum % cumulative release i.e.95.68%. So we conclude that batch F8 was the optimised batch. From our results it is clear that a medium level of SYLOID® 244 FP(50mg) and higher level of ethanol (1.75ml), gives highest release. Increase of SYLOID® 244 FP from 50 mg to 55mg does not increase the release.

3.5.4.4 Kinetic modelling of dissolution data

The optimised formulation Batch F8 was subjected to various mathematical models to understand the release pattern. The study was carried out by using PCP-Disso-v3 software. The

value of coefficient of regression suggest the best fit kinetic model

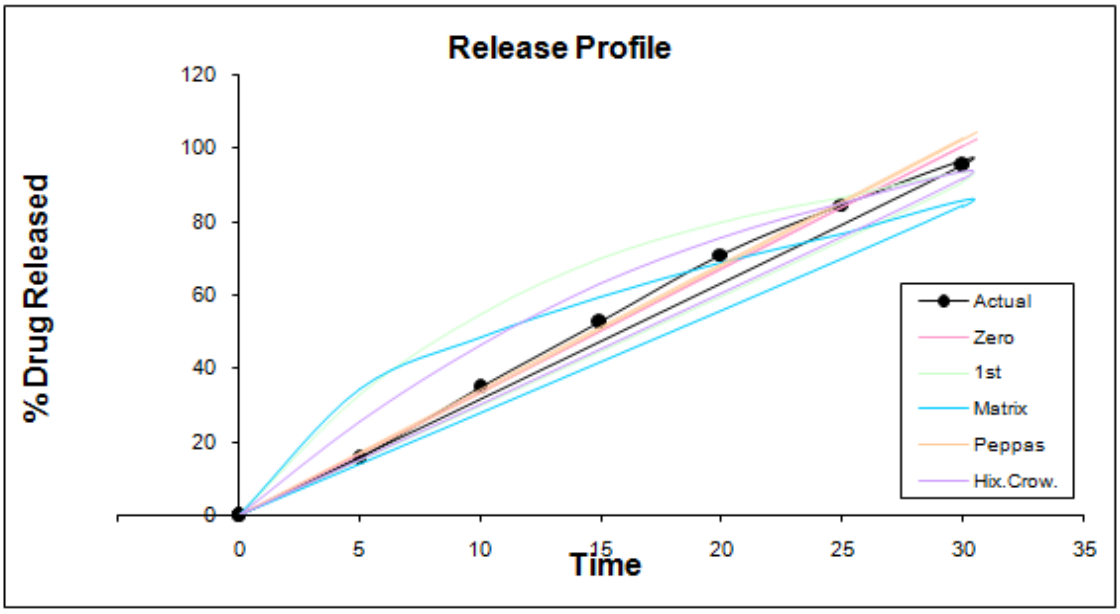

Fig. 30. Graphical representation of model fitting

Table No.31: Various model fittings for optimized batch formulation

Model	R2	K
Zero Order	0.9965	3.3511
1st order	0.9270	-0.0796
Matrix	0.9477	15.3757
Peppas	**0.9970**	3.1992
Hix. Crow. Model	0.9750	-0.0187

From interpretation, the best fitted kinetic model was found to be Peppas model, Peppas model shows value of coefficient of regression 0.9970, various dissolution kinetics parameters

computed for batch F8 . In our experiments, the *in vitro* release profiles of ATC could be best expressed by Peppas Eqn.

3.6 Comparison with conventional tablet & marketed tablet

Comparison study is done by taking % cumulative release as a factor & graphical representation was as follows in Table no. 32

Table No.32. Comparison with conventional tablet & marketed tablet

TIME(mins)	F8(Optimized Batch)	A(Without S244)	Z(Marketed Batch)
0	0.9550±0.3130	0.0027±0.005	0.4245±0.1244
5	15.785±2.7459	2.36±0.8014	10.4818±1.8627
10	35.145±3.1754	4.68±0.988	30.8121±1.0617
15	53.06±4.574	5.33±0.970	45.1678±2.4659
20	71.48±5.749	9.71±0.833	55.09724±3.5316
25	85.01±6.745	14.95±3.006	69.8149±4.897
30	95.68±6.0789	17.132±1.960	74.0654±3.0048

Where F8- Optimised batch,

A1-Conventional tablet without SYLOID® 244 FP

Z-Marketed tablet

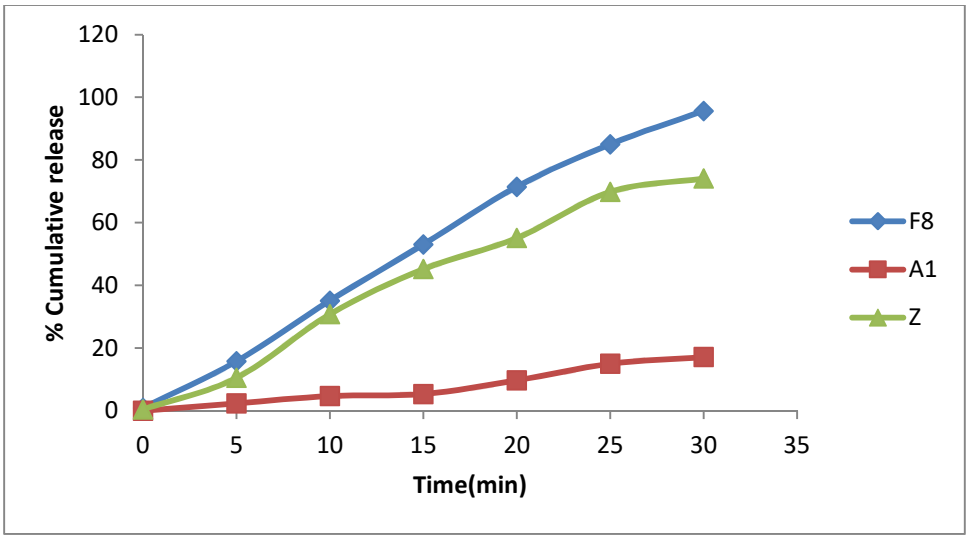

Figure No.31. Comparison with conventional tablet & marketed tablet

From table no.27 & figure no.26 , we found that % cumulative release profile was increased up to 95.68±6.0789% from conventional tablet & marketed tablet i.e. 17.132±1.960 & 74.0654±3.0048 % respectively.

3.7 Stability profile of optimized batch

Quantitative analysis

The stability studies of optimised formulation revealed that no significant changes were observed in the physical parameters, when stored at temperature and humidity conditions of 40 ± 2ºC / 75 ± 5% RH.(Climatic zone IV condition for accelerated testing) to access their long-term stability. Tablets were taken and retested for drug content after interval of 7, 15, 30 days. Percent drug content was found in ranged from 96.21 ± 0.41 to 99.61 ± 0.37 indicating no significant reduction in the content of the active drug was observed over a period of one month; the percent drug contained was found within a specified limit of IP. Therefore no evidence of degradation of drug quantity was observed.

CONCLUSION

Conclusively, the current study concluded the successful design, preparation and evaluation of SYLOID® 244 FP containing atorvasatin tablet. So atorvastatin tablet prepared from drug-loaded silica may provide a feasible approach for development of an oral formulation for this poorly water – soluble drug. This work is also expected to expand the use of silica- based non-ordered mesoporous materials as drug delivery systems.

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