Atorvastatin calcium formulation development followed by pharmacokinetic with in vitro and in vivo correlation (IVIVC) with employing soluplus and hydroxy propyl methyl cellulose with optimization

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Objectives
The goal of this study was to evaluate different proportions of solid dispersions and formulations by employing various carriers in order to improve solubility of poorly soluble atorvastatin calcium.
Materials and methods
Solid dispersions can be created using the Solvent Evaporation technique. In comparison to pure drug, (Hydroxy propyl methyl cellulose) HPMC (1:1) indicated as (Solid dispersion) SD1, HPMC E5 (1:2), HPMC E5 (1:4), HPMC (1:1.5) designated as SD2, SD3, SD4, drug caffeine (1:0.5) and caffeine (1:1), denoted as SD5, SD6. The Design Expert software used to 2 level factorial design, the three independent components of X1: are ratios of solid dispersion equivalent (drug: HPMC:soluplus), X2:Superdisintegrant (Primellose), and X3:Surfactant (Sodium lauryl sulphate) was used to do analysis of variance (ANOVA), 3D surface plots, counter plots, optimization, and desirability. Fourier-transform infrared spectroscopy was used to investigate drug-excipient compatibility. Marketed tablets (uncoated tablets manufactured by 'Revat Laboratories limited) with optimized tablet composition were used in the comparative trials (A2) and Pharmacokinetics.
Results and discussion
The solid dispersion approach greatly increased the amount of atorvastatin calcium released. The values of f1 and f2 were determined to be 1.89 and 77.78, respectively, and the dissolution profiles of the optimized formulation (A2) and the market tablet were found to be significance. The optimized formula did better on the desirability level (0.975), indicating that it was a good fit. To determine dose bioavailability and to see if there is an in-vitro-in-vivo link.
Conclusion
The formulations were successfully developed using factorial design, and can be further used for oral delivery of antilipidemic agents is atorvastatin calcium. The model's predictability and validity were demonstrated when the experimental values matched the expected values. The in vitro-in vivo correlation was good in pharmacokinetic experiments, indicating a significant improvement.

Keywords:
atorvastatin calcium, design expert, in vitro-, in vivo correlation, percent drug release, solid dispersions

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Introduction

One of the most extensively utilized antilipidemic agents is atorvastatin calcium (ATR). It is an inhibitor of hydroxyl methyl glutaryl- CoA (HMG-CoA) reductase1 and a Biopharmaceutical classification system (BCS) Class II drug with limited solubility and high permeability. Recent approach, arotvastatin formulations, evaluate liquid and solid self-emulsifying drug delivery systems for atorvastatin [1], solid dispersions of atorvastatin with different drug:polymer ratios and different polymers polyethylene glycol 6000, Pluronic F-68 and chitosan to improve its solubility [2], Oral bioavailability development, including establishing an improved oral nano structured lipid carrier formulation of poorly soluble atorvastatin Ca and analyzing it's in vitro release [3], Using a combination of anti-solvent and probe sonication methods, a novel oral chitosan-based ATR nanocrystals formulation was effectively developed [4], Different forms of chitosan were used to make gel formulations, and the gels' viscosity, bioadhesivity, and syringeability, as well as in vitro drug release properties, were examined [5].

The mannitol and lactose were used as water-soluble carriers, while Sylysia 350 and Aerosil 200 were used as water-insoluble carriers to create a solidified [6], atorvastatin nano structured lipid carriers were synthesized and studied [7]. To design, optimize, and evaluate a self-nano emulsifying drug delivery system to improve the solubility and dissolution rate of the Atorvastatin/Ezetimibe(ATV/EZT) combination, which is weakly water soluble [8]. The study was to see if floating spheroids of Atorvastatin Calcium loaded nanostructure lipid carriers could be useful self-administrable eye drops, atorvastatin is put into solid lipid nanoparticles (SLNs) [9], solid dispersion of atorvastatin calcium was made using the solvent evaporation method with hydrophilic carriers poloxamer 188 [10], glyseryl tri palmitate was used as lipid carrier, poloxamer 407 as a surfactant and soya lecithin as an emulsifier to make solid lipid nanoparticles [11], amorphous solid dispersion technology create by spray drying process was used to increase water solubility enhancement, atorvastatin calcium co-crystals were made utilizing a liquid-assisted grinding process using citric acid and nicotinamide as co-formers [12]. The develop and test an atorvastatin trihydrate calcium porous tablet [13], potential of stearic acid conjugation with gelatin in the formulation of new atorvastatin loaded nanoparticles. To improve in vitro solubility and dissolution, formulations with amphiphilic carriers were designed as hard capsules [14], emulsion-diffusion-evaporation process, atorvastatin was encapsulated in poly (D,L-lactide-co-glycolide) (PLGA) utilizing a sustainable method [15], ATR encapsulated eudragit RSPO nanoparticles could be used as a drug delivery method to improve medication bioavailability [16], delivery strategy for atorvastatin calcium, created an oleic acid–reinforced PEGylated poly methacrylate trans dermal film [17], in-vitro disintegration and in-vivo performance, lyophilized orally disintegrating tablets made with the dry emulsion process were developed [18], processing methods affect the physic chemical and pharmacokinetic features of co-amorphous materials [19]. A biodegradable poly (lactic-co-glycolic acid) nanoparticle loaded with atorvastatin calcium to improve oral bioavailability [20], ATV-eluting tubular mesh covered with poly (D, L-lactide-co-glycolisde) acid for perivascular application was developed [21]. Lipid bilayer of the vesicle, different non-ionic surfactants (NISs) (Spans, Tweens, Cremophor RH 40, and Brij 52) was combined with lecithin [22]. The various approach by using soluplus as carrier and additive used weakly water-soluble indomethacin, hot-melt extrusion processing could change the interactions between medicines, cyclodextrins, and polymers, altering the microstructure and characteristics of supra molecular gels, mixtures that included amphiphilic polymers Soluplus, develop a topical nano micellar formulation of the immune suppressant drug ever olimususing Soluplus, a grafted copolymer of polyvinyl caprolactam-polyvinyl alcohol-polyethylene glycol (PVCL-PVA-PEG) for improved permeation through ocular epithelia with minimal or no irritation, resulting in increased ocular bioavailability [23–37]. The aim of this study was to make ATR solid dispersions and investigation of formulations with many parameters such as flow parameters, physical features, in vitro, Fourier-transform infrared spectroscopy (FTIR), and comparative examinations with commercially available tablets and (A2), pharmacokinetics and in vitro- in vivo correlation. The Design Expert software was used to do analysis of variance (ANOVA), 3D surface plots, counter plots, desirability, and optimization.

Materials and methods

Materials

Atorvastatin calcium A gift sample by VKT Pharmaceuticals Pvt Limited, HPMC (Hydroxy propylmethyl cellulose): Purchased sample from Otto Chemie Pvt.ltd., Mumbai. India, SuperTab 11 SD (Spray dried lactose) a gift sample from IMDC Private limited, Mumbai, India. Primellose a Gift sample from IMDC Private limited, Mumbai, India. Soluplus a gift sample from IMDC Private limited, Mumbai, India. Camphor was purchased from Loba cheme pvt ltd Mumbai, India. Sodium lauryl sulphate was purchased sample from Loba cheme pvt ltd Mumbai, India. Talc was purchased from Loba chemie pvt ltd. Mumbai, India. Magnesium stearate was purchased sample from Loba Chemie Pvt Ltd Mumbai, India. Acetone was purchased sample from Thermo fisher scientific, Mumbai, India. Dichloromethane was purchased from Emplura Merk Life Science Pvt. Ltd.Mumbai, India.

Preparation solid dispersions by solvent evaporation method by using different carriers

Using various Carriers, solid dispersions can be made using the Solvent Evaporation technique. HPMC (1:1) by using acetone and denoted as SD1, HPMC E5 (1:2),HPMC E5 (1:4), HPMC (1:1.5) by using Dichloromethane and denoted as SD2, SD3, SD4. Solid dispersion of atorvastatin calcium with varied weighted ratios of polymers such as HPMC (1:1) by using acetone and denoted as SD2. By employing

Dichloromethane and acetone, the drug caffeine (1:0.5) and caffeine (1:1), designated as SD5, SD6, were produced using the solvent evaporation method.

In the mortar and pestle, a precise weighed amount of drug and polymer was triturated well, and acetone and dichloromethane (1:3) solution was added drop by drop and triturated to achieve the surface modification. The solvent was extracted using a hot air oven at 50–60°C, the solid residue was dried for 24 h, the product was sieved using # 22, and the sample was stored in a desiccator at room temperature for further research.

Preparation of tablets

The tablets were made utilizing the direct compression approach, which was based on an experimental design that included 2^3 factorial designs (see Tables 1 and 2). The ratios of solid dispersion equivalent (drug: HPMC: Soluplus) (X1) high (+): (40:10:4) (mg), low (–) (40:7:4) (mg), mix with diluent Super tab 11 SD and other excipients to make a solid dispersion corresponding to 40 mg of medication. The higher (+) (8%) lower (–) (4%) Primellose (superdisintegrant) (X2) and Sodium lauryl sulphate (X3) higher (+) (1%) lower (–) (0.25%) were added, and talc and magnesium stearate were mixed and blended. Single punch tablet compression machine was used to compress the constituent blend into tablets.

Evaluation of the tablets

All tablets prepare were evaluated for

Active ingredient content

The 5 tablets were precisely weighed and pulverized. In a boiling test, the tablet powder equivalent to 40 mg of atorvastatin calcium was extracted with 6 –10ml of methanol. The methanolic extract was collected into a 100 ml volumetric flask, diluted to 100 ml with pH6.8phosphate buffer, and the drug content was determined using a UV spectrophotometric technique.

Hardness

Monsanto hardness tester, SISCO, India used to determine the tablet's hardness.

Friability

Labindia Tablet Friability Tester model- FT 1020, India was used to test friability.

Disintegration time

The Labindia, Model- DT 1000, India, tablet distentegrating Tester was used to determine the disintegration time.

Dissolution study

The dissolution rate of atorvastatin calcium from tablets was determined using a USP Type II (Paddle technique) dissolution test apparatus LABINDIA, Model- DS 8000, India, with phosphate buffer pH6.8 as the dissolution fluid at 37±1°C and a stirrer speed of 50 rpm throughout the investigation. Each test sample (5 ml) was taken at different intervals, such as 10 min, 20 min, 30 min, 40 min, 50 min, and 60 min Using a UV-Vis Spectrophotometer, ELICO Double beam, Model- SL210, India. The samples were examined at 246 nm. Each time a sample of dissolving fluid was extracted, it was replaced with new fluid. The dissolution of each produced tablet was replicated four times (n=4).

Comparative studies

The comparative studies of optimized formulation (A2) with market product (Atorvastatin calcium uncoated tablet containing 10 mg of atorvastatin calcium manufactured by 'Revat Laboratories limited, India), Batch no: RAST-9004, Mfg.date:1/2020, Mfg.Licno:129/PS/AP/96/F/G, Exp date: 12/2022.

Table 2 Design as per 2^3 factorial design distributions of factors

Formulation	X1	X2	X3
A1	-	-	-
A2	+	-	-
A3	-	+	-
A4	+	+	-
A5	-	-	-
A6	+	-	+
A7	-	+	+
A8	+	+	+

Table 1 Experimental design by 2^3 factorial designs

S. No.	Factor	High (mg) (+)	Low (mg) (–)	Central Point (mg)
1	X1;Drug;(HPMC: Soluplus)	20:4	14:4	17:4
2	X2; Primellose	16	8	12
3	X3;SLS	2	0.5	1.25
4	Dependent Variables	Target		
a)	Y1 (Percentage drug dissolve in 20 min (PD_{20})	83.9879%		
b)	Y2 (Time required to drug release 90%) (Q_{90})	23.5 min		

Drug-excipient compatibility studies

The Fourier Infrared Spectroscopy (FTIR) spectra of samples was obtained on a Bruker ALPHA II FTIR system (Bruker OPTIK GmbH, Rudolf-Plank-Str, Germany) by using Kbr disc method (2 mg sample in 300 mg of Kbr) the scanning range was 4000–600 $cm^{-1}$and the resolution was 1 cm^{-1}.

High-performance liquid chromatography (HPLC) method

A mobile phase was utilized to elute the concentration in plasma samples using the HPLC method by using Waters Alliance HPLC System, Model: e2695, Germany at 235 nm equipped (with an Inertsil ODS (150×4.6 mm) and a flow rate of 1.0 ml/min. In a 60/40 volume ratio, acetonitrile and phosphate buffer pH3.0 were used as the mobile phase. The injection volume was 15 µl, and the atorvastatin and valsartan (internal standard) retention times were 4.676 min and min 3.713 min, respectively.

Pharmacokinetics

Following the approved protocol, Institutional Animal Ethics Committee authorized the in vivo experimental protocol (Regd. No. CPCSEA/SVCP/ORG/2021-03), 18 healthy albino rats (300-500 g) were used in this study. The rats were separated into three groups of six (n=6) and fed a regular meal. Using heparinized syringes, blood samples (0.3 mL) were taken from the right femoral artery of each cannulated rat at specified intervals and emptied into heparinised micro tubes. Each blood sample was centrifuged for 10 min at 9000 rpm, and the plasma was separated. Following that, the samples were evaluated using the HPLC method as indicated.

Data analysis

By using Design Expert software.

In vitro- in vivo correlation

For a possible in vitro – in vivo correlation, the cumulative percentage of dug released in-vitro from the optimized tablet formulation was compared to the extent of absorption, i.e., AUC $^{(0-\infty)}$ of product.

Results and discussion

The three independent components, X1: HPMC concentration, X2: Primellose (super disintegrant) concentration, and X3: SLS (Sodium lauryl sulphate) concentration, were examined in a two-level factorial design with varied levels and an experimental trail to execute eight alternative combinations. Table 1 and Table 2 depicted the combination of X1, X2, and X3.

Dissolution behavior of different solid dispersions

Weight ratios were established for six proportions of solid dispersion of Drug: HPMCE5 (1:2, 1:4) (SD2, SD3), Drug: HPMC (1:1, 1:1.5) (SD1, SD4), and Drug: Caffeine (1:0.5, 1:1) (SD5, SD6), and dissolution was assessed according to dissolution profile. Under phosphate buffer pH 6.8, the in vitro performance of solid dispersions up to drug polymer ratios of Drug: HPMC (1:1) (SD1) and Drug: Caffeine (1:0.5) (SD5) was judged satisfactory. Both solid dispersions extend the release of atorvastatin calcium to more than 30 min, while Drug: Caffeine 1:0.5 produces a 100% release in less than10 minutes. In comparison to pure drugs, 80% of the substance is released in60 minutes. The dissolution behavior of pure drug was release 100% in 60 min, SD1 release 30 min, SD2 and SD3 was release greater than 2 h's, SD 4 was release with in 50 min SD5 and SD6 release greater than 1 hr. shown in Fig. 1

Flowability and compressibility

Angle of repose, bulk density, tapped density, hausner's ratio, and Carr's index were used to determine the flow parameters of the preparation blend. The bulk density ranges from 0.301 to 0.378 gm/cc, actual density from 0.356 to 441 gm/cc, angle of repose from 10 to 12, Carr's index from 10 to 17, and Hausner's ratio from 1 to 1.25. The above characteristics of the preparation blend show good to exceptional flow qualities and are appropriate for direct compression.

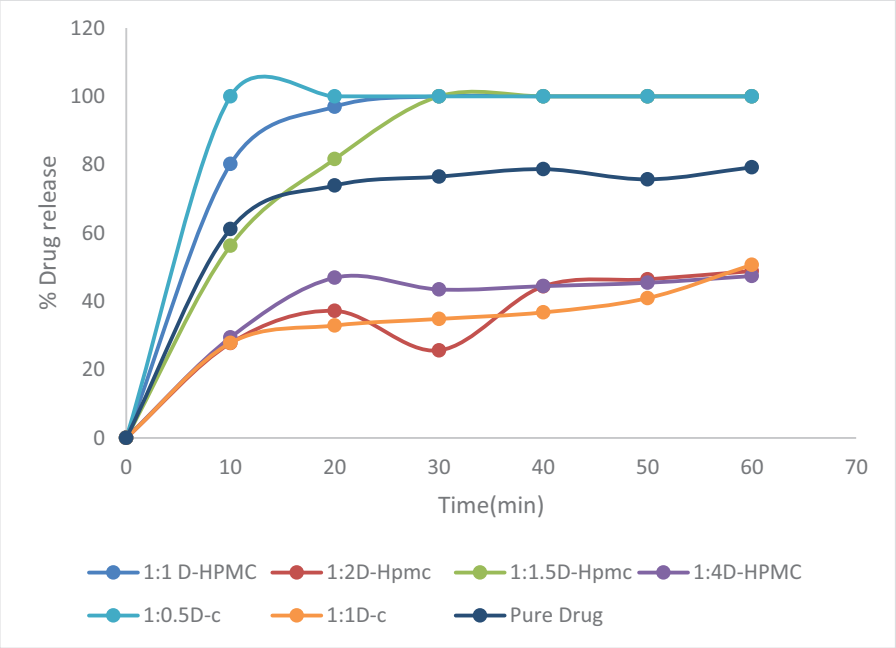
Drug-excipients compatibilities

The FTIR spectrum of atorvastatin calcium shown in characteristic peaks observed at 884 cm^{-1} 842 cm^{-1}, 746 cm^{-1}, 916 cm^{-1}, 639 cm^{-1} (Due to C-N Rocking), 884 cm^{-1}, 842 cm^{-1},746 cm^{-1} (Due to N-H Rocking),1368 cm^{-1},1216 cm^{-1},1159 cm^{-1}, 1056 cm^{-1} (Due to C-F Stretch), 1422 cm^{-1}, 1368 cm^{-1}, 1216 cm^{-1} (Due to O-H Bending),1422 cm^{-1}, 1368 cm^{-1} (Due to C-N bending plane)), 1650 cm^{-1}, 3363 cm^{-1} Due to C=O Stretch), 1650 cm^{-1}, 1551 cm^{-1} Due to N-H Bending), 3363 cm^{-1} (Due to N-H Stretch), 3363 cm^{-1} (Due to O-H Stretch), confirming the drug structure. Pure drug FTIR spectrum with different excipients HPMC, Primellose, and SLS all have sharp peak. The FTIR spectra of pure drug and combinations with diverse excipients were comparable, indicating that the drug and excipients have no chemical interaction. Figure 3 and Figure 4 shows the distinctive peaks.

Tablet properties

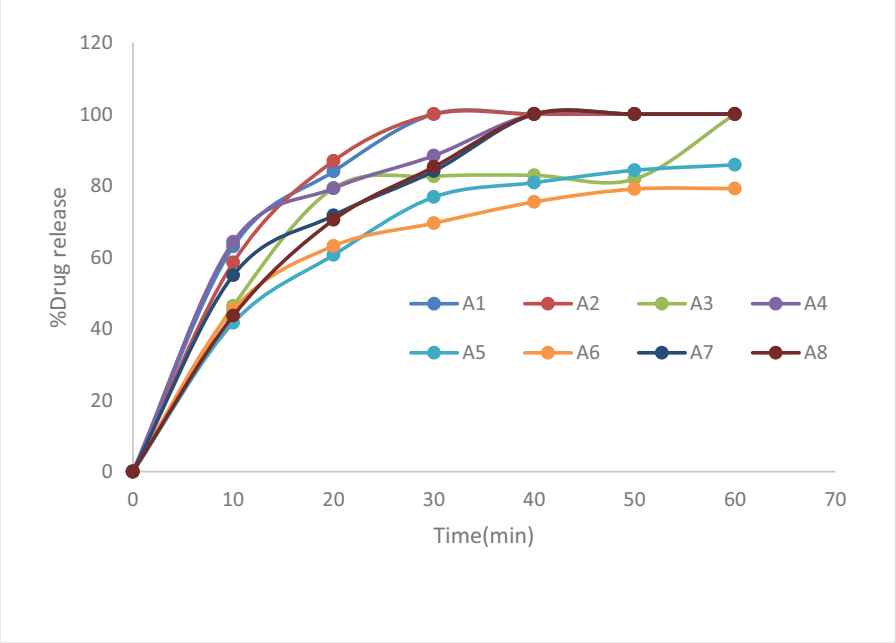
The hardness of all tablet formulations was found to be between 4 and 4.5 kg/cm^2, with the highest hardness in

Figure 1



Dissolution profile of atorvastatin calcium pure drug and its solid dispersions.

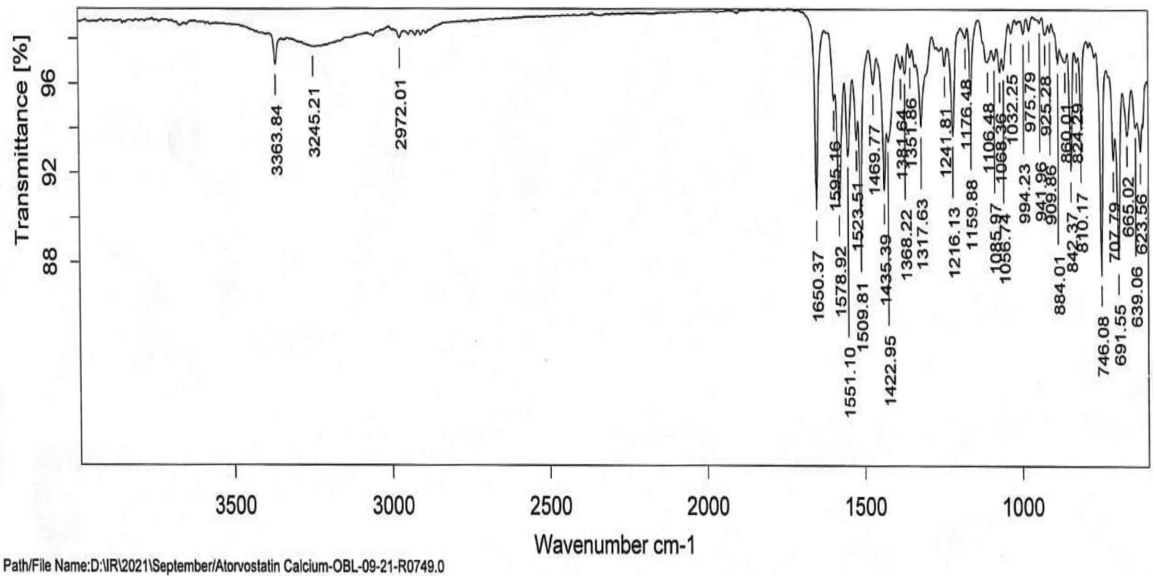
Figure 2



Mean dissolution profiles of atorvastatin tablet formulation prepared A1-A8.

(A7), indicating an enhancement in hardness-related binding properties of atorvastatin calcium tablets. The friability test is effective for determining the physical strength of all prepared formulations with a percentage weight loss of less than 1% in accordance with pharmacopeial requirements. All of the formulation tablets disintegrate within a short period of time. A1 takes 3 min and 13 seconds to disintegrate, A2 takes 2 min and 22 seconds to disintegrate, A3 takes 4 min and 5 seconds to disintegrate, A4 takes 3 min and 20 seconds to disintegrate, A5 takes 8 min and 10 seconds to disintegrate, A6 takes 8 min and 20 seconds to

Figure 3



FTIR of atorvastatin calcium pure drug.

disintegrate, A7 takes 4 min and 5 seconds to disintegrate, and A8 takes 3 min and 4 seconds to disintegrate. All produced tablets disintegrated in between 2 and 8 min and 20 s. High disintegration was seen in formulations A5, A6, which had greater quantity of SLS, Primellose. The effect of HPMC, Primellose, and SLS concentrations on the disintegration time of a tablet formulation. The disintegration time increase and decreased with a higher level of three polymers concentration and a lower level of three polymers concentration. The HPMC were unable to form gels in the disintegration medium. The combination of a high polymer concentration SLS and a low

Polymer concentration Primellose has a negative effect on tablet disintegration, requiring the formulation of a strong barrier to prevent more disintegration medium penetration.

Active ingredient in the content

The medication concentration of all manufactured pills was between 96 and 98%. According to IP, the above quality control criteria of the prepared tablets meet the standard specification of uncoated tablets.

In vitro dissolution

Figure 2 demonstrate the in vitro dissolving characteristics of preparation tablets. In comparison to other formulations, formulation A1, A2 has the fastest and greatest drug release of 100% at 30 min The A1 formulation, which contains 7% HPMC, 4% primellose, and 0.5% SLS (Sodium lauryl sulphate), has much higher dissolving performance. The A2 formulation, which contains 10% HPMC, 8% primellose, and 1% SLS, has a much superior dissolving performance. The camphor 1% that allows for faster water uptake and dissolution of tablets. The A3 formulation provides 100% drug release in 60 min The A4 formulation provides 100% drug release in 40 min The A5 formulation has a medication release rate of 85% in 60 min The A6 formulation has a medication release rate of 79% in 50 minutes.The A7 formulation provides 100% drug release in 40 min The A8 formulation provides 100% drug release in 40 min The formulations A6, A5, and A4 result in less dissolving, which is used to reduce variability shown in A6<A5<A3<A7<A8<A4< A1<A2.

Model dependent

Zero order and first order drug release kinetics were used. Table 3 shows the correlation coefficient (r-value). The correlation coefficient values in all situations were greater first order release kinetics rather than zero order release kinetics. Table 3 shows the dissolution parameters $t_{1/2}$, dissolution efficiency (DE_{30},) PD_{10}, PD_{30}, MDT (mean dissolution time), and Dissolution rate constant (K_1) [38–40].

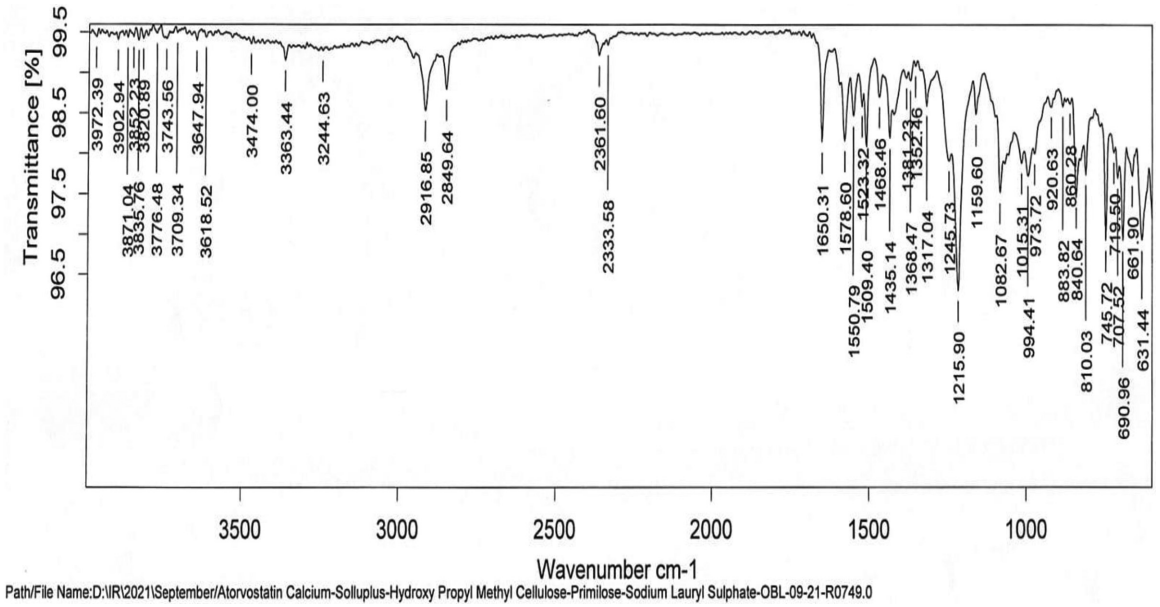
Comparative studies

The studies compared the optimized Atorvastatin calcium tablet formulation (A2) to the commercially available tablet (Atorvastatin calcium, Revat laboratories, India). The value of f1 was determined

Table 3 Dissolution parameters of prepared atorvastatin calcium tablet formulations

Formulation	(Percent Dissolved) PD_{20} (%)	PD_{30} (%)	$t_{1/2}$ (min)	t_{90} (min)	DE_{30} (%)	K (Min_{-1})	MDT (Mean dissolution time)	'r' value 1st order	'r' Zero order
A1	83.992	100	8	24	65.655	0.0838	19.34 1	0.998	0.944
A2	86.925	100	8.2	22	65.13	0.1156	8.653 8	0.996	0.954
A3	79.26	82.587	11.3	53	55.63	0.0951	35.30 92	0.922	0.854
A4	79.265	88.4	7	32	62.57	0.0545	7.022 0	0.987	0.900
A5	60.62	76.81	8.5	79	46.58	0.0393	36.05 29	0.970	0.893
A6	63.127	69.515	7.9	85	47.75	0.0188	35.33 39	0.944	0.858
A7	71.66	84.08	9	36	56.214	0.0462	24.95 3	0.993	0.941
A8	70.43	85.25	13	32	52.22	0.0647	25.68 04	0.999	0.969

Figure 4



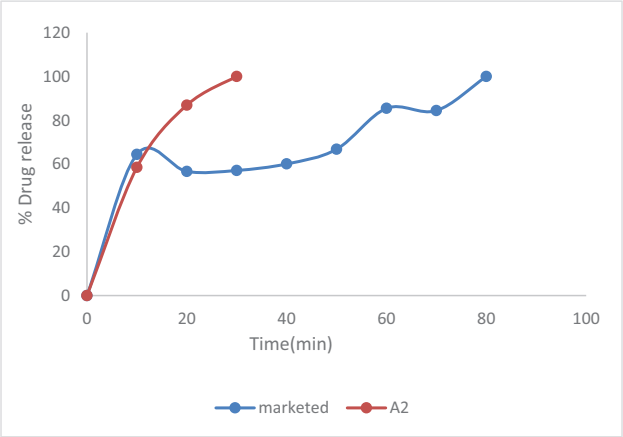
FTIR of atorvastatin calcium with Primellose +Soluplus +HPMC+SLS.

to be smaller than 15(1.89), indicating that the two curves are identical. The value of f2 was discovered to be more than 50 (77.7), indicating that two curves are equivalent. As a result, the dissolution characteristics of optimum formulation (A2) and market tablet are close or equal shown in Fig. 5.

Data analysis

The design expert software (design expert version 13 stat-Ease Inc.com, USA). After fitting these data, the Design expert generated a viable model equation. For statistical optimization, the two responses Y1 (PD20) andY2 (Q90) were chosen and fitted to a specified model. Table 4 and Table 5 shown in comparative R square, PRESS, std., provide a summary of statistical parameters. Design expert software was used to compute DEV, Mean, C.V percent, Adj R-squared,

Figure 5



Comparative Dissolution profile of optimised formulation (A2 and marketed tablet).

Table 4 Analysis of variance (ANOVA) of responseY1 and Y2

(Y1) Percentage drug dissolve in 20 min (PD20)						
Source	Sum of square	Df (degree of freedom	Mean square	F value	*P* value	Remarks
Model	2.18	5	0.44	1288.24	<0.0001	**Significant**
A-HPMC-Soluplus	7.575E-003	1	7.575E-003	22.42	0.0091	
Primelose	0.025	1	0.025	72.96	0.0010	
C-SLS	1.72	1	1.72	5079.73	≤0.0001	
AB	0.019	1	0.019	56.55	0.0017	
BC	0.41	1	0.41	1209.54	≤0.0001	
Curvature	0.74	1	0.74	2187.04	≤0.0001	
Residual	1.352E-003	4	3.379E-004			
Lack of fit	1.352E-003	2	6.758E-004			
Pure error	0.000	2	0.000			
Cor total	2.92	10				
(Y2)Time required to drug release 90% (Q90)						
Model	2546.48	3	848.83	18.70	<0.0019	Significant
B-Primellose	147.06	1	147.06	3.24	0.1002	
C-SLS	766.36	1	766.36	16.88	0.0063	
BC	1633.06	1	1633.06	35.98	0.0010	
Curvature	845.67	1	84.67	18.63	0.0050	
Residual	272.35	6	45.39			
Lack of fit	272.35	4	68.09			
Pure error	0.000	2	0.000			
Cor total	3664.50	10				

Table 5 Statistical parameters

Parameters	PD20	Q_{90}
Std. dev	0.018	6.74
Mean	8.77	37.92
C.V%	0.21	17.77
PRESS	0.022	1089.38
-2 log likeli hood	–67.83	66.52
R-Squared	0.9994	0.9034
Adj R-squared	0.9986	0.8551
Pred R-Squared	0.9901	0.6135
Adeqprecision	104.866	10.600
BIC	–53.44	76.11
AICc	–34.83	81.18

Pred R-square, Adeq accuracy, BIC, AICc,-2log likelihood, F values, and *P* values.

In order to validate the experimental design utilizing polynomial equation two parameters, the dependent responses PD20 and Q90 were evaluated. As a mathematical model, PD20, Q90 was used. Y= β0 +β1×1+ β2×2+ β1 β2 × 1 × 2+ β3×3+ β1 β3 ×1 × 3+ β3β2 ×2 × 3+ β1 β2 β3+ X1 X2 X3. Where Y= is the dependent variable, 0=is the mean response of 8 runs, and 1, 2, 3 is the estimated coefficient for the corresponding factor X1, each representing the average result of increasing one component at a time from a low to a high value. When three elements change at the same time, the interaction time (X1.X2, X1.X3, and X1.X2.X3) defeats the changes in the response.

Each tablet contains 40 mg of atorvastatin calcium, which was prepared using a 2^3factorial design to evaluate the individual and combined effects of three factors, includingX1 – HPMC high level (10%) low level (7%), X2 primellose (super disintegrant) high level (8%)low-level(4%), and X3 SLS high level 1% and low level 0.5%.

Responses PD20 (Y1)

The PD20 analysis of variance, a model with a $P<0.0001$ statistically significant result. Table 4 and Table 5 shows the results of the PD20 analysis of variance. The model equation can be used to describe the parameter PD20. PD20=+ 9.26300+0.059129×1 +5.22693E-003×2-1.52171×3-4.07268E-003 × 1 × 2-0.075342. The positive indication for X1 and X2 indicates that HPMC and Primellose (superdisintegrant) concentrations are increasing, as is the percent drug dissolve in 20 min (PD20). The negative sign for coefficient X3 implies that when the concentration of surfactant SLS increases, the percent drug dissolve in 20 min drops, or the R-square values for PD20 are 0.994, suggesting a high correlation between independent and dependent variables. The significance of $P<0.001$ was determined. The 'F' value for PD20 was found to be of model 1288.24, within dependent variables X1=22.42, X2=72.96, X3=5079.73, and other statistical parameters such as Adj.R2=0.9986, PRESS=0.022, Adeq precision= 104.866, BIC=-53.44, AICc=-34.83, –2log

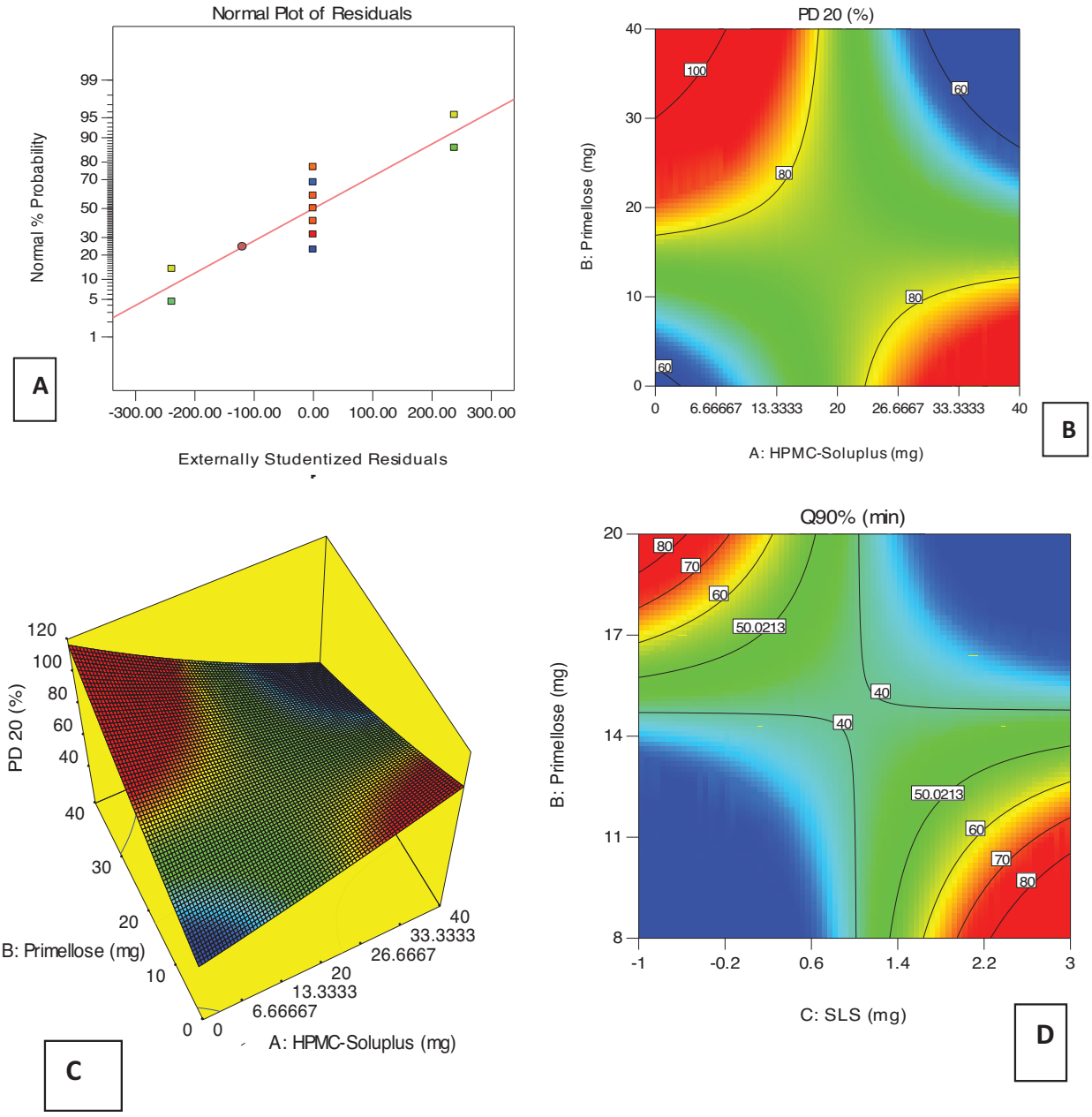
likelihood=-67.83, Mean=8.77, Std.DEV =0.018, C. V %=0.21, Pred R square.=0.9901.

Response Q90 (Y2)

The Q90 ANOVA model yielded a statistically significant result of $P<0.0019$. Tables 4 and 5 shows the Q90 analysis of variance. The model equation cans determine the attractiveness of the parameter Q90. Y2=-36.96932+4.88125 ×2 +70.20000 ×3 −4.76250 ×2 +X3. The presence of a positive indication for X2 implies that the concentration of Primellose (super disintegrant) in Q90 has increased by 90%. The presence of a positive sign for X3shows that the concentration of SLS has increased by 90% and that drug dissolution in Q90 has increased as well. The R^2 result of 0.9034 for Q90 indicates that the independent and dependent variables are well correlated. The significance of the phrase $P<0.0019$ was determined. Statistical metrics such as Std. DEV = 6.74, Mean =37.92, C.percent=17.77, PRESS=1089.38, -2 log likelihood =66.52, Adj R-squared=0.8551, Pred R-squared=0.6135, Adeq. Precision=10.600, BIC=76.11, AICc=81.18 were found.

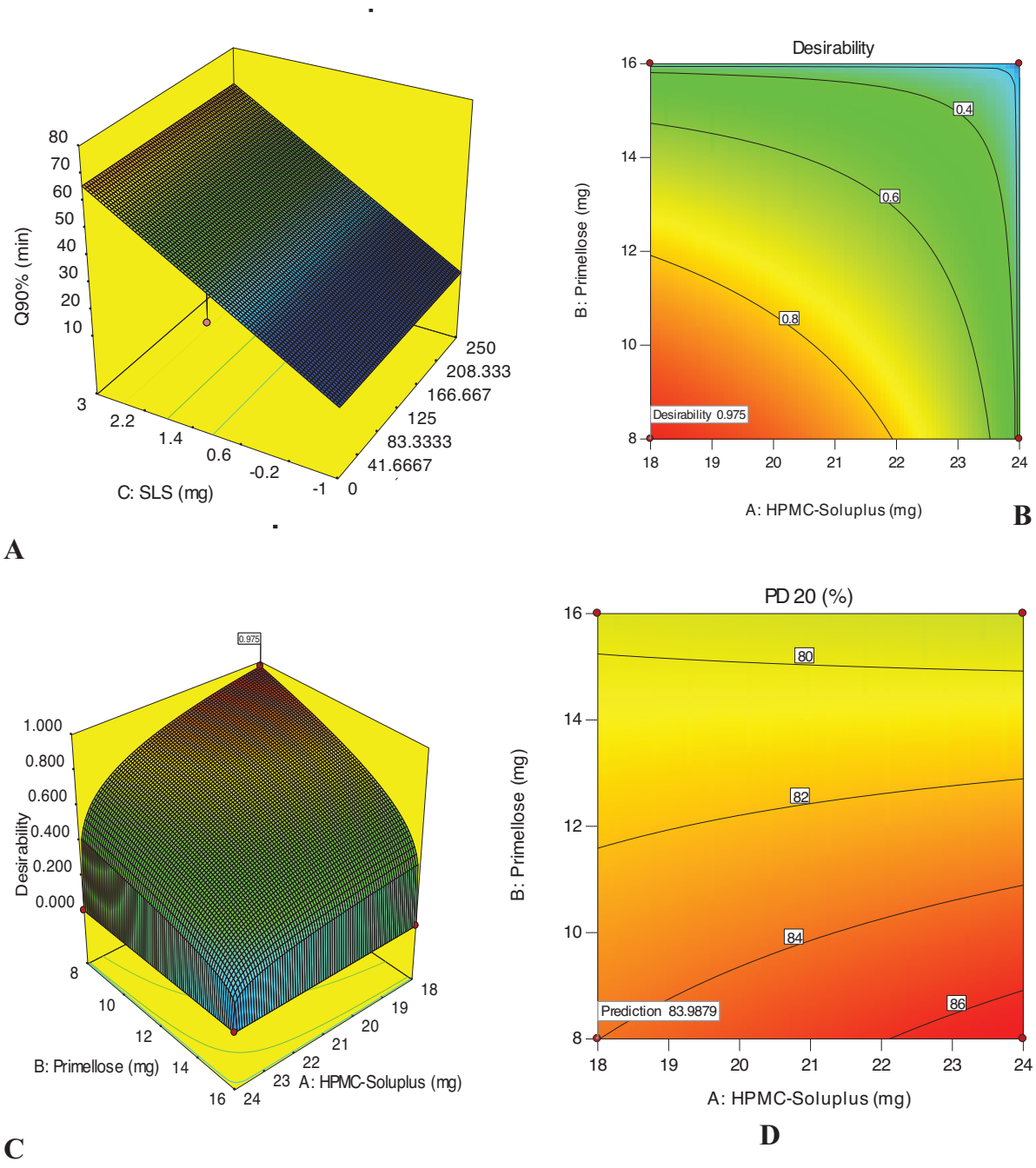
The contour and response surface as a function of three factors at a time, with all other parameters held constant, are more useful in analyzing the individual and interaction effects of three variables. Figures 6–8

Figure 6



A. Normal plot residual B.Counter plots of PD 20C. 3D Surface plots for PD 20 D. Counter plots for Q90.

Figure 7



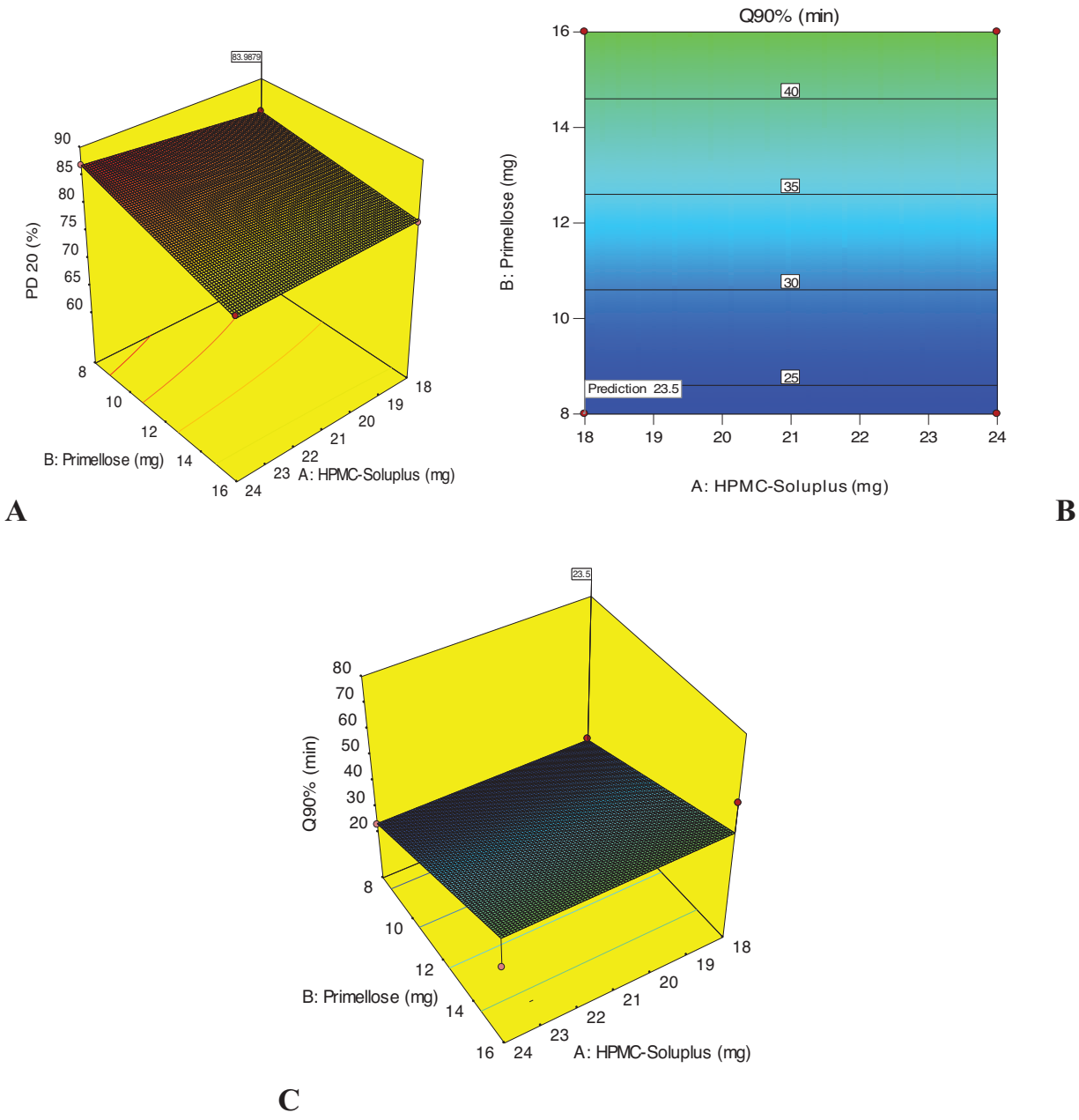
A.3D Surface plot Q90 B. Counter plots of Desirability C. 3D Surface plots for Desirability D. Counter plots for PD 20 Optimization.

shows the normal response, contour and response surface plots, as well as the normal plots of residual, desirability, and optimizes plots for all formulation components.

Optimization

The higher the desirability value, the better the formulation and the optimize formulae can be obtained directly from the desire function response surface plots. The optimal formula had a greater desirability concern (0.975), indicating that the formulation was suitable. To obtain product, each response was optimized with a desirable target adjust point PD20 (Y1) and Q90 (Y2) set to be minimized. The composition of the optimized formulation was provided in Table 6 as three independent variables for optimizing in accordance with the goals of responses by using a desirability function. With a corresponding desirability function of 0.975, X1, X2, and X3 were 24.0 mg, 5.0 mg, and 0.5 mg, respectively. To verify the theoretical prediction, statistical optimization was performed on the optimized formulation to satisfy

Figure 8



A.3D Surface plot PD 20 B. Counter plots of Optimization Q90C. 3D Surface plots Q90 Optimization

Table 6 Comparison of predicted and experimental response for optimized formulation

Parameter			
Independent Variables	X1	X2	X3
Composition	24.0 (mg)	5.0 (mg)	0.5 (mg)
Response	PD_{20}	$^{T}90$	
Predicted value	83.98%	23.5 min	
Experimental value	85.98%	22.93 min	
Predicted error (%)	−2.326	−5.165	

all of the dissolution parameters. Table 6 shows the in vitro percentage drug release PD20, which was found to be 85.98%, and Q90, which was found to be 24.78 min, as values for observed and close agreement with model prediction. For each answer, the relative errors percent between anticipated and experimental values were determined, and the values were found to be −2.326% and −5.165%, respectively. The experimental values matched the anticipated values, demonstrating the model's predictability and validity. The optimal formulation resulted in a PD 20 of 85.98% and a Q90 of 24.78 min The optimal formulation's drug release follows a first-order kinetic model. The percentage prediction error was

used to compare the predicted value to the experimental value in order to measure the prediction's dependability and accuracy [41–45].

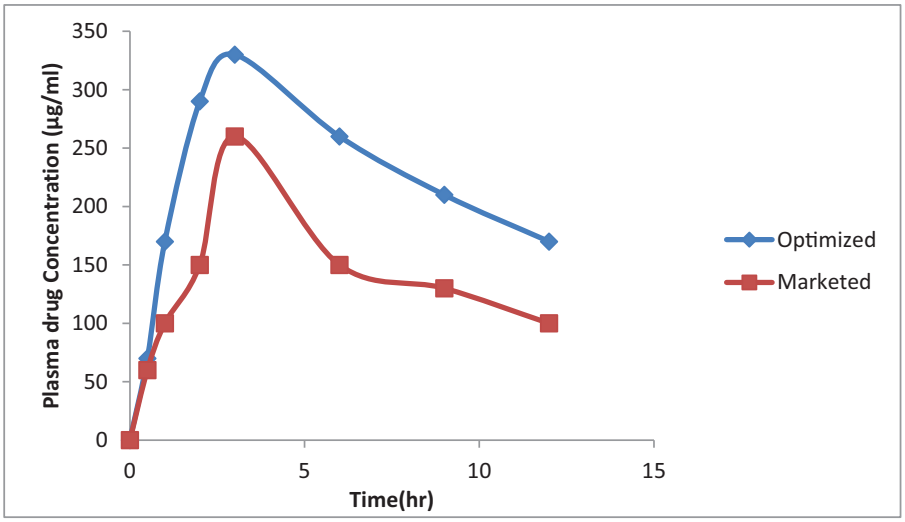
Pharmacokinetics

A comparison of the plasma concentration-time profiles for the Optimized and marketed tablets are shown in Fig. 9. The pharmacokinetic parameters for the optimized and marketed formulations are shown in Table 7. The C_{max} of was 343.450 (µg/ml) and 278.88 (µg/ml), respectively in optimized tablets and the market tablets. The $(AUC)_{0\text{-}12h}$concentration of optimized and market product 2923.433(µg/ml).h and 1232.766(µg/ml).h. However, the T_{max} of optimized tablets and market was 3.0±1.25 h and 2.211±0.123 h respectively. In consequence, the bioequivalence of the two preparations was shown by the C_{max}, $(AUC)_{0\text{-}12\,h}$.

In vitro and in vivo correlation

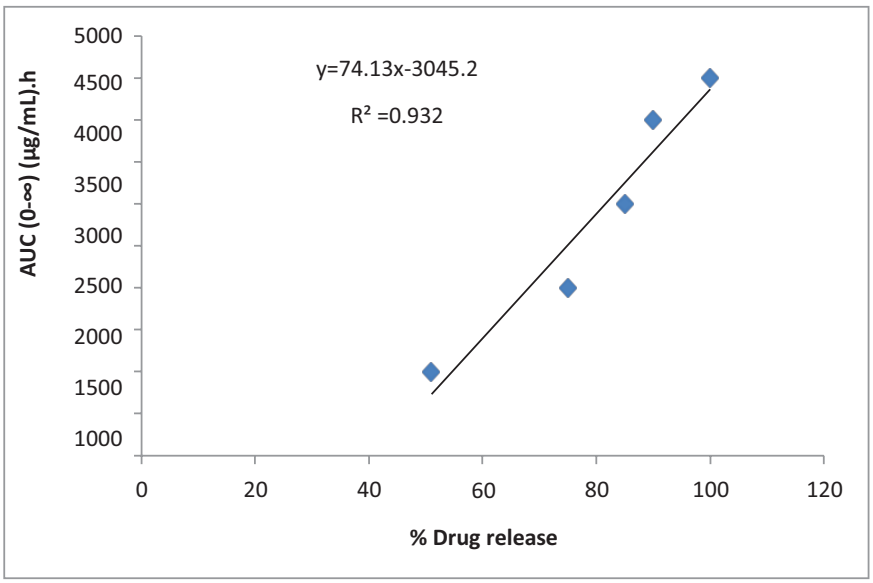
To demonstrate a link between cumulative percent drug release and cumulative AUC in vitro and in vivo. To obtain the level A correlation, a best fit line was created with a R^2 value of 0.932. This demonstrates how drugs are released in relation to their absorption in the lower gastro intestinal system (Fig. 10). According to the in vitro-in vivo association; the cumulative % of medication released in the control method was absorbed through the lower gastro intestinal tract.

Figure 9



Plasma Concentrations (µg/ml) v/s Time (hr) Profile of Optimized tablets and Marketed tablets.

Figure 10



In vivo-in vitro correlations of optimized tablets.

Table 7 Pharmacokinetic parameters

Parameter	Optimized	Marketed
C_{max}(μg/ml)	343.450	278.88
T_{max}(hr)	3.0±1.25	2.211
$t_{1/2}$(hr)	1.071	0.874
$AUC_{(0-12)}$(μg/mL).h	2923.433	1232.766
CL/F	0.002	0.0043
MRT(hr)	15.161	11.114
AUC $^{(0-\infty)}$(μg/mL).h	4442.855	1334.77

Conclusion

The current study successfully established and produced two level factorial designs to optimize atorvastatin calcium formulation. When solid dispersions were compared to pure medication with various carriers, the dissolution of the solid dispersions was dramatically improved. The produced mix has well to outstanding flow characteristics and is suitable for compression by direct compression. The FTIR spectra of pure drug and mixes with various excipients were identical, indicating no chemical interaction between the drug and excipients. HPMC, Primellose, and SLS exhibit characteristic peaks. The produced tablets' quality control criteria meet the official un coat specification. The manufactured tablets' quality control characteristics meet the standard IP specification for uncoated tablets. The A1 formulation contains 7% HPMC, 2% soluplus, 4% Primellose, and 0.5% SLS (Sodium Lauryl Sulphate) for much faster dissolving, 100% in 30 min, and A2 formulation containing 10% HPMC, 8% Primellose, 1%, and SLS as a considerably rapid dissolution performance. The increasing order of drug dissolution of various formulations are A6<A5 <A3 <A7 <A8 <A4 <A1 <A2. The dissolution characteristics of optimum formulation (A2) and market tablets are comparable or same. The ANOVA (analysis of variance) models for PD20 and Q90 are statistically significant at P <0.0001. The statistical optimization was performed on the optimized formulation to ensure that all of the dissolution parameters were met, allowing the theoretical prediction to be confirmed. The optimal formulation resulted in a PD20 of 85.98% and a Q90 of 24.78 min The optimal formulation's drug release follows a first-order kinetic model. The in vitro- in vivo correlation was good in pharmacokinetic experiments, indicating a significant improvement.

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Conflicts of interest

There are no conflicts of interest.

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