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FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLETS OF SIMVASTATIN USING LIQUISOLID TECHNOLOGY BY USING DOE APPROACH

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ABSTRACT:
To obtain an enhanced in-vitro dissolution rate of simvastatin by using Liquisolid technique and Liquisolid tablets were optimized by DoE approach 3^2 full factorial design using Design Expert Software.Theliquisolid tablets were formulated by using propylene glycol (PG), as liquid vehicle, Avicel PH-102 as a carrier material, Aerosil as a coating material, and aspartame as sweetener and Kyron 314 as a superdisintegrant. The new mathematical model 3^2 full factorial design was utilized to formulate various liquisolid powder systems and to calculate amount of carrier material and coating material. All prepared liquisolid batches were subjected to weight variation, drug content uniformity, hardness, friability test, and disintegration test and dissolution tests. Liquisolid systems were also tested for DSC, FT-IR. From result of check point analysis of design data, , SMLCFDT10 shows higher Drug release (89.257 %) at less wetting time (124.682 sec.) and disintegrating time (31.843 sec). Simvasatin liquisolid compacts enhance aqueous solubility and dissolution rate in compare to other solubility enhancement technique. Hence, this research work may be useful to formulate fast disintegrating Tablets using Liquisolid Technique which may give rapid onset of action by rapid absorption, maximize efficacy, reduce dose and dose frequency & hence increase patient Compliance.
Key Words: Liquisolid technology, solubility enhancement, fast disintegrating tablet, dissolution rate, DoE.

1. INTRODUCTION

Liquisolid technology, as described by Spireas may be used to transform a liquid into a free flowing, easily compressible and apparently dry powder by simple physical mixing with selected excipients named the carrier and coating material. The liquid portion can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles[4]. This liquid is incorporated into the porous carrier material. Organic solvent systems which are inert and preferably water-miscible with high boiling point, such as propylene glycol, liquid polyethylene glycols, or glycerine are best suitable as liquid vehicles. Upon saturation of the carrier with liquid, a liquid layer is formed on the particle surface which is readily adsorbed by the fine coating particles. Hence, a dry, free flowing, and compressible powder is obtained[5].

Theory of Liquisolid technology

A powder can retain only certain amount of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials), a mathematical approach for the formulation of liquisolid systems has been developed by Spireas[6]. This approach is based on

the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination[7].

The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow, by measurement of the angle of repose or by measurement of angle of slide.

The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression. The compactability may be determined by pactisity measurement which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces[8].

The terms "acceptable flow and compression properties" imply the desired and thus preselected flow and compaction properties which must be met by the final liquisolid formulation.

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed "liquid load factor Lf" [w/w] and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

$$Lf = W / Q$$

R represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation:

$$R = Q/q$$

The liquid load factor that ensures acceptable flowability (ΦLf) can be determined by:

$$\Phi Lf = \Phi + \varphi(1/R)$$

where Φ and φ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid systems with acceptable compactability (ΨLf) can be determined by:

$$^{\Psi}Lf = \Psi + \psi(1/R)$$

where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively. Therefore, the optimum liquid load factor (Lo) required to obtain acceptably flowing and compressible liquisolid systems is equal to either ΦLf or ΨLf, whichever represents the lower value.

As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Qo) and coating (qo) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

$$Qo = W / Lo$$

$$qo = Qo / R$$

The validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow and compaction properties[9].

Concept of Liquisolid Technology

When the drug dissolved in the liquid vehicle, it is incorporated into a carrier material which has a porous surface and closely matted fibres in its interior as cellulose, both absorption and adsorption take place. Liquid at initially absorbed into within atom is gotten by its inward surface. After submersion, adsorption of liquid onto inward and external surface of porous carrier atom happens. By then, covering material gives appealing stream property to Liquisolid structure in view of its high adsorptive properties and far reaching surface zone[10].

The wettability of compacts in crumbling media is one of proposed part to clarify enhanced deterioration rate from Liquisolid compacts. Non-temperamental dissolvable present in Liquisolid structure empower wetting of solution particles

by decreasing interfacial weight between tablet surface and crumbling medium. Subsequently, Liquisolid tablets may be depended upon to announce overhauled release profiles of water insoluble medicine due to liberal addition in wettability and effective surface locale for breaking down[11].

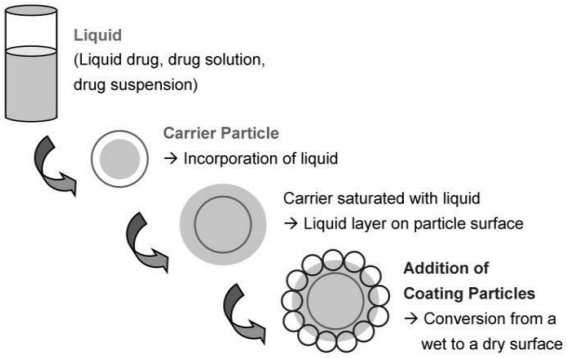


Fig. 1: Concept of Liquisolid Technology
Mechanisms of enhanced drug release from liquisolid systems

The three recommended mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles[12].

Increased drug surface area

When the drug within the liquisolid system is absolutely dissolved in the liquid vehicle it is positioned in the powder substrate in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets[13].

Therefore,

$$FM = Sd / Cd$$

Where, FM =1 if Sd ≥ Cd

Increased aqueous solubility of the drug

In addition to the first mechanism of drug release enhancement it is expected that Cs, the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a co solvent[14].

Improved wetting properties

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved[15].

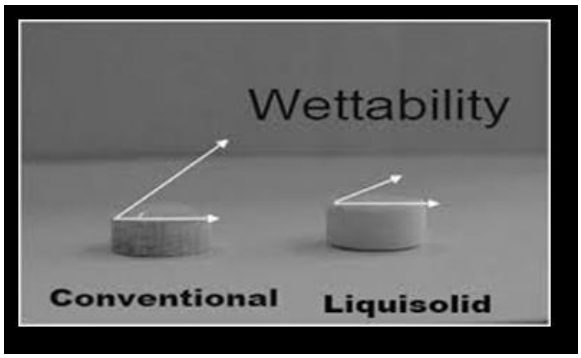


Fig. 2: Comparison of wettability between conventional tablet and Liquisolid compacts

Components of liquisolid compact[16]

Drug:

The drug used in liquisolid systems must be water insoluble, low dose drug. It must be in BCS class II.It should have water insolubility or fairly dissolvable in water.

Non-volatile solvent:

It must be inert water miscible, not highly viscous and should have high boiling point.

Eg: PEG 200 and 400, Glycerin, N, N dimethyl acetamide, Span 80 and19, Tween 80and19 Propylene glycol and Fixed oils etc.

Carrier materials:

These are highly porous materials and have a wide surface area and the recommended to absorb the drugs on to them.

Eg: Cellulose (microcrystalline and amorphous), starch, sorbitol, Lactose, MCC (Avicel PH102), DCP, Eudragit RSandRL.

Coating materials:

There are fine materials having a particle size range from 10 nm to 5000 mm in diameter. These must be highly adsorptive to cover the carrier particles and show dry look.

Eg: Silica of various grades like cab-o-sil M5, Aerosil200 and Syloid 244fp etc.

Disintegrants:

These are used to break the compacts to smaller particles.

Eg: Crosscarmellose sodium, Crosspovidone, Explotab and Pre gelatinized starch etc.

Lubricants:

These are intended to reduce the friction.

Eg: Stearic acid, Stearic acid salts and Talc etc.

Glidants:

Intended to promote the flow between particles by reducing the friction.Eg: Silica derivatives, Talc and Corn starch etc.

Classification of liquisolid systems

Based on the type of liquid medication:

This class further classified into four types that are:

- Powdered drug solutions
- Powdered drug suspensions
- Powdered liquid drugs
- Powdered Drug emulsion

The underlying three are made by changing over solid Water insoluble pharmaceutical into plan, suspension and emulsion using non-unusual dissolvable. Fourth one is in state of liquid itself[12].

Based on the formulation technique:

Liquisolid system may be further classified into two types, which are:

- Liquisolid compacts
- Liquisolid Microsystems[15]

Method of Preparation

The liquisolid tablet preparation method involves, first a mathematically calculated amount of pure drug weighed and dissolved in the suitable amount of solvent in a molecularly dispersed state. For attaining good flow properties trial and error methods were used i.e. changing the carrier: coating material ratio. This liquid medication is poured on the suitable amount of carrier material. The liquid medication is absorbed into the carrier material internally and externally and then a suitable disintegrant was added to this material. Finally, coating material was added for dry looking, adherent to the carrier material for achieving good compression properties[17]. Liquid medication is incorporated into carrier material which has a porous surface and closely matted fibers in its interior as cellulose. Both absorption and adsorption take place, i.e. the liquid absorbed into the interior of the particles is captured by its internal structure and after saturation of this process, adsorption of the liquid onto the internal and external surface of the porous carrier particles occurs. Excipients possessing fine and highly adsorptive particles such as various types of amorphous silicon dioxide (silica) are most suitable for this step[18]. Before compression or encapsulation, various ingredients such as lubricants disintegrants or Polymers, and binders may be mixed with the finished liquisolid systems to produce liquisolid compacts in the dosage form of tablets or capsules[19].

Characterization of Liquisolid Compacts

- Hardness
- Thickness and diameter
- Weight variation
- Friability
- Wetting time
- *In-vitro*Dispersion time
- Water absorption time
- *In-vitro*Disintegration time
- % Drug content uniformity
- *In-vitro*Dissolution study
- Stability study[19]

Formulations of Liquisolid Compacts:[15]

Table 1: Formulations of Liquisolid systems with enhanced drug release

Polymer/ Variations	Drug / Molecule
Lactose + Cremophor® EL	Griseofulvin
Cremophor® EL, Synperonic® PE/L61, PEG400 + Avicel® PH102	Naproxen
Tween 80 + Microcrystalline Cellulose	Piroxicam
Avicel® PH102	Famotidine
Neusilin®	Griseofulvin
Avicel®PH 200	Prednisolone
Avicel PH 102, Aerosil 200	Carbamazepine
Silica–Eudragit RL or RS	Theophylline
Eudragit RL or RS as the carrier and silica as the coating material	Propranolol hydrochloride
Capryol™ 90,Solutol® HS-15 and Kollicoat® SR 30 D as non-volatile liquid vehicles	Spironolactone
Propylene glycol as solvent, Avicel PH102 as carrier, and Aerosil 200 as the coating material	Valsartan

Advantages

- Number of water-insoluble solid drugs can be formulated into liquisolid systems.
- Can be applied to formulate liquid medications such as oily liquid drugs.
- Better availability of an orally administered water insoluble drug.
- Lower production cost than that of soft gelatin capsules[5]
- Production of liquisolid systems is similar to that of conventional tablets.
- Can be used for formulation of liquid oily drugs
- Exhibits enhanced in-vitro and in-vivo drug release as compared to commercial counterparts, including soft gelatin capsule preparations.
- Can be used in controlled drug delivery[6].
- Drug release can be modified using suitable formulation ingredients
- Drug can be molecularly dispersed in the formulation.
- Capability of industrial production is also possible[7].
- Enhanced bioavailability can be obtained as compared to conventional tablets.

Limitations

- Low drug loading capacities
- Requirement of high solubility of drug in non-volatile liquid vehicles
- If more amounts of carrier is added it increase the flow properties of powder, it may increases the tablet weight too, hence it is difficult to swallow[8]
- It does not require chemical modification of drugs.
- Acceptable compression may not be achieved because the liquid drug may be squeezed out during compression resulting in unsatisfactory tablet weight[9]

Applications

- Rapid release rates are gained in Liquisolid These can be capably used for water insoluble solid drugs or liquid lipophilic solutions[10].
- Sustained entry of solutions which are water dissolvable pharmaceuticals, for instance, propranolol hydrochloride has been gotten by usage of this methodology.
- Solubility and deterioration change[11]
- Designing of controlled release tablets
- Application in probiotics[12]

COMPARISON OF LIQUISOLID SYSTEM WITH CONVENTIONAL DDS[38-39]

Table 2: Comparison between Conventional Drug Delivery System and Oral Fast Disintegrating Tablets using Liqisolid compacts

Conventional Drug Delivery System	Oral Fast Disintegrating Tablets using Liqisolid compact
Poor aqueous solubility	Enhanced aqueous solubility
Low dissolution rate	Enhanced dissolution rate
Slower absorption	Better absorption
Poor drug release profile	Enhanced drug release profile
Poor bioavailability	Enhanced bioavailability
Poor therapeutic effect	Better therapeutic effect

Introduction to Hyper-cholesterolaemia (elevated cholesterol) and Its Treatment

It is a medical condition characterized by an elevation of any or all lipid profile and/or lipoproteins in the blood. This medical condition or problem divided into two subtypes which are: primary hyperlipidemia and secondary hyperlipidemia[40].

Primary hyperlipidemia which is usually taken place as a result of genetic problems i.e., mutation within receptor protein, while secondary hyperlipidemia will arises as a result of other underlining diseases like diabetes[41].

Alteration and/ or abnormality in the metabolism of lipid and lipoproteins is very common condition that taken place within general population, and it consider as one of the main risk factor in the incidence of cardiovascular disease due to their influence on atherosclerosis[42].

SIGNS AND SYMPTOMS OF HYPERLIPIDEMIA

Hyperlipidemia usually has no noticeable symptoms and tends to be discovered during routine examination or evaluation for atherosclerotic cardiovascular disease .

- Xanthoma
- Xanthelasma of eyelid
- Chest Pain
- Abdominal Pain
- Enlarged Spleen
- Liver Enlarged
- High cholesterol or triglyceride levels
- Heart attacks
- Higher rate of obesity and glucose intolerance
- Pimple like lesions across body
- Atheromatous plaques in the arteries
- Arcus senilis
- Xanthomata[43]

Table 3: Treatment of hypercholesterolaemia (elevated cholesterol)

CLASS	DRUG
HMG co-enzyme reductase Inhibitor	Rosuvastatin
Fibric Acid	Fenofibric Acid, Gemfibrozil
Nicotinic Acid	Niacor
Fibrates	Lofibra
Bile acid sequestrants	Cholestyramine, colestipol, Colesevelam
Miscellaneous antihyperlipidemic agents	Icosapent, Mipomersen
Proprotein convertase subtilisin/kexin type 9 (PCSK9)	Alirocumab, Evolocumab

2. MATERIALS AND METHODS

Materials

Simvastatin was a gift sample from IPCA laboratories, Maharastra, India. Propylene glycol was gifted by (Suvidhinathlaboratories, Vadodara, India) and Avicel PH 102, Aerosil& Kyron T 314 were obtained from (Balaji pharmaceutical, Surat,

India). Aspartame was gifted by (Chemdyes Corporation, Vadodara, India). All other ingredients and reagents were of analytical grade.

Method of preparation of Liquisolid Compacts

Liquisolid compacts were readied as takes after. Searched for measures of ahead of time weighed of strong pharmaceutical and fluid vehicle PG were blended. Game-plan was then sonicated for 15 min until homogeneous remedy arrangement was gotten. Next, figured weight (W) of happening fluid meds were merged into learn measures of transporter material (Avicel PH102) (Q) and blended completely. Happening wet blend was then mixed with decided measure of covering material (Aerosil) (q) utilizing standard blending procedure to plot direct admixture.

Characterization of Simvastatin Liquisolid Fast Disintegrating tablets:

Thickness and Hardness test:

Thickness of tablets was determined using Werner caliper; examining showed was noted. Hardness will be attempted by using Monsanto analyzer.

Friability test:

Friability of tablets was resolved utilizing Roche friabilator. % friability was then ascertained utilizing recipe:

$$\% \text{ friability} = \frac{\text{inital weight} - \text{final weight}}{\text{inital weight}} \times 100$$

Weight variation test:

Test was performed by measuring 20 tablets solely on electronic adjustment, finding out ordinary weight, and standing out individual tablet weights from typical.

***In-vitro* dispersion time:**

In-vitro taking after with specific end goal to scatter time was measured methodology. Tablet will then unequivocally organized in focal point of petri dish containing 6 ml of water and time required for tablet to totally isolate into fine particles will be noted. Three tablets from every course of action will subjectively picked and In-vitro diffusing reality will surface over long haul measured.

***In-vitro* disintegration test:**

Test was finished on 6 tablet using tablet crumbling analyzer. Water at 37 ± 2 °C will be used as disintegrating medium and time brought for complete separating of tablet will noted with no discernable mass staying in mechanical gathering will be measured.

Wetting time:

A Piece of tissue paper was collapsed and put twice and put in little petri dish containing adequate water. Tablet will be continued paper and time for complete wetting of tablet will measured.

Water absorption ratio (R):

Largeness of tablet going before position in petri dish was noted (Wb). Wetted tablet will be emptied and measured (Wa). Water absorption extent, R, was then chosen by correlation.

$$R=100 \times (Wa-Wb)/Wb$$

Where, Wb and Wa are tablet weights before and after water absorption, respectively

***In-vitro* release studies:**

Drug release rate of points of interest was measured by using USP apparatus type II. Dissolution studies was done using 900 ml of Phosphate buffer solution pH 6.8 at 37±0.5 °C at 50 RPM. 5 ml tests was draw back at various time breaks and set by 5 ml fresh phosphate buffer pH 6.8 to keep up sink condition. Courses of action was expeditiously isolated through channel paper, debilitated and centralization of solution was determined spectrophotometric.

Comparison of optimized Liquisolid Fast Disintegrating Tablets and marketed Conventional tablet of Simvastatin

Examination was completed by utilizing different parameters, for example, wetting time, water assimilation proportion, *In-vitro* crumbling time, *In-vitro* drug discharge.

Stability studies:

Prescription or estimations structure quality may impact under impact of by fluctuating temperature, dampness and light with time which can be found by security testing. It should be possible at 25°C ± 2°C/60% RH ± 5% RH and 40°C ± 2°C/75% RH ± 5% RH for picked itemizing for three months. Tests were pulled back on 0th, 15th, 30th day and were dismembered for physical appearance and drug content.

Table 4: ICH Specification for Stability Study

Study type with duration	Storage condition
Long Period (12 Months)	25°C ± 2°C/ 60% RH ± 5% RH and 30°C ± 2°C/ 65% RH ± 5% RH
Intermediate Period (12 Months)	30°C ± 2°C/ 65% RH ± 5% RH
Accelerated Period (12 Months)	40°C ± 2°C/ 75% RH ± 5% RH

3. RESULTS

Organoleptic Characteristics of Simvastatin:

Table 5: Organoleptic Characteristics

Parameter	Observation
Colour	White powder
Odour	Odourless
Appearance	White powder

The colour of Simvastatin was visualized white with odorless having white powder appearance as shown in Table.

Determination of Melting Point of Simvastatin

Table 6: Melting point of Simvastatin

Drug Name	Standard Value	Observed Value (Mean ± S.D.) (n = 3)
Simvastatin	135°C-138°C	136-138 °C

Melting point was carried out by capillary rise method. Drug sample has melting point of 136 - 138°C which was in range and indicate purity of sample as Simvastatin.

Identification and Determination of λ_{max} of Simvastatin

Identification of λ_{max} of Simvastatin in phosphate buffer pH 6.8 (simulated salivary fluid)

A stock course of action of 1 mg/ml of Simvastatin was prepared by dissolving 100 mg of drug in little measure of Methanol and sonicated for couple of minutes and debilitated with 100 ml of phosphate bolster (pH 6.8). Stock course of action was serially debilitated to get game plan in extent of 20µg/ml and λ max of game plan was found by checking from 200 - 400 nm.

Table 7: λ_{max} of Simvastatin in pH 6.8 phosphate buffer solution

Drug Name	Actual λ_{max}	Observed λ_{max}
Simvastatin	238 nm	239 nm

Identification of λ_{max} of simvastatin in 0.1 N HCl

A stock course of action of 1 mg/ml of Simvastatin was prepared by dissolving 100 mg of drug in little measure of Methanol and sonicated for couple of minutes and debilitated with 100 ml of 0.1 N HCl. Stock course of action was serially debilitated to get game plan in extent of 20µg/ml and λ max of game plan was found by checking from 200 - 400 nm.

Table 8: λ_{max} of simvastatin in 0.1 N HCl

Drug Name	Actual λ_{max}	Observed λ_{max}
Simvastatin	238nm	237.50nm

Solubility study of Simvastatin

Table 9: Solubility of Simvastatin

S.N.	Solvent	Solubility (mg/mL) (Mean ± S.D.) (n = 3)	Interpretation
1	Water	0.0012± 0.08	Very Slightly soluble
2	Acetate Buffer pH 4.5	0.0134± 0.022	Very Slightly soluble
3	Phosphate Buffer pH6.8	0.0582± 0.6	Very Slightly soluble
4	PEG 400	15.09± 0.31	Slightly Soluble
5	0.1 N HCl	0.004± 0.25	Very Slightly soluble
6	Propylene Glycol	65.5± 0.012	Freely Soluble
7	Methanol	60.08± 0.079	Freely Soluble

Preparation of Calibration Curve for Simvastatin

Preparation of Calibration Curve for Simvastatin in Phosphate Buffer 6.8

Table 10: Calibration curve of Simvastatinin Phosphate Buffer 6.8

S. No.	Concentration (mcg/mL)	Absorbance(nm) (Mean ± S.D.) (n = 3)
1	0	0
2	10	0.242±0.020
3	20	0.43±0.032
4	30	0.553±0.019
5	40	0.73±0.055
6	50	0.927±0.045

Preparation of Calibration Curve for Simvastatin in 0.1 N HCl

Table 11: Calibration Curve for Simvastatin in 0.1 N HCl

S. No	Concentration (mcg/mL)	Absorbance(nm) (Mean ± S.D.) (n = 3)
1	0	0
2	10	0.303±0.028
3	20	0.447±0.034
4	30	0.621±0.021
5	40	0.799±0.052
6	50	0.992±0.058

Table 12: Summary Report of calibration curve for Simvastatin

S. No.	Parameter	Phosphate Buffer pH 6.8	0.1 N HCl
1	Wavelength (λ_{max})	238.5	238.5
2	Beer's limit (µg/mL)	0-50	0-50
3	Corrélation coefficient (R^2)	0.988	0.980
4	Slope	0.018	0.020

Identification of Drug- Simvastatin by FT-IR Spectroscopy:

Potassium bromide IR disc was prepared using 1 mg of Simvastatin on Hydraulic Pellet press and scanned in region of 4000-400 cm^{-1}. Obtained IR Spectrum was compared with reference spectrum of Simvastatin**.-**

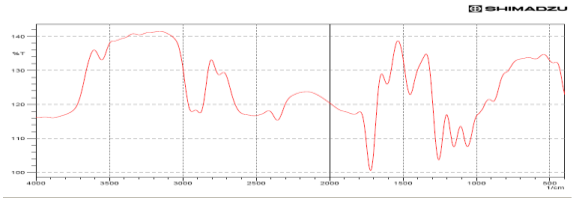


Fig. 3: FTIR spectrum of Pure Drug Simvastatin

Table 13: Characteristic peaks of simvastatin

Type of Vibration	Standard wave number (cm^{-1})	Observed wave number (cm^{-1})
O-H stretching	3546	3546.5
C-H stretching	2924	2929.7
C=O stretching	1697	1695.05
-C-O-C- stretching	1268	1265.93
N-H stretching	1568	1567

Identification of Drug- Simvastatin by DSC:

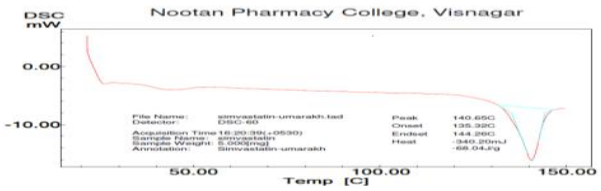


Fig. 4: DSC thermogram of Pure Drug Simvastatin

DSC curves of commercial Simvastatin Figure 5.7 shows broad endotherm ranging from 30 to 120°C indicating loss of water and sharp endotherm at 135.32 °C might be due to melting point of Simvastatin. Obtained FT-IR spectrum and DSC graph compiles with standard data which further confirms identity and purity of Drug.

Particle Size Analysis of Pure Drug Simvastatin

Particle size of Drug simvastatin was studied by using Zeta Sizer or Malvern Instrument.

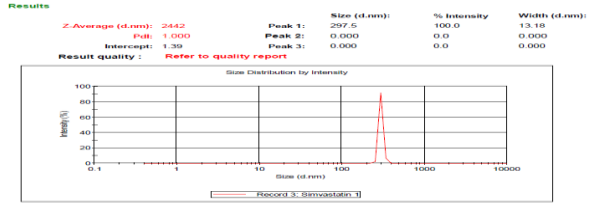


Fig. 5: Particle Size Analysis of Pure Drug Simvastatin

Saturation Solubility of Pure Drug:

Table 14: Saturation Solubility of Pure Drug (Simvastatin)

Pure Drug	Amount per ml (mg/ml)
Simvastatin	0.014±0.01

Calculation of liquid load factor (L_f)

It was determined by dissolving or dispersing drug in different concentration in a non-volatile solvent. Using Eq. (1) and (2), drug loading factor is determined and used to calculate amount of carrier and coating material.

$$\Phi Lf = \Phi + \varphi \left(\frac{1}{R}\right) \quad \text{---- (1)}$$

And

$$\psi Lf = \psi + \psi \left(\frac{1}{R}\right) \quad \text{--- (2)}$$

Table 15: Liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles

Powder excipient or system	Φ – value		Ψ- numbers	
	PG	PEG 400	PG	PEG 400
Avicel pH102	0.16	0.005	0.224	0.242
Avicel pH200	0.26	0.02	0.209	0.232
Cab-O-Sil M5 (Silica)* with Avicel PH 102	3.31	3.26	0.560	0.653
Cab-O-Sil M5 (Silica)* with Avicel PH 200	2.57	2.44	0.712	0.717

***Included as coating material in carrier/coating powder systems.**

$Lf = \Phi ca + \Phi co\ (1/R)$

$Lf = \Psi ca + \Psi co\ (1/R)$

$Lf = 0.16 + 3.31\ (1/20)$

$Lf = 0.224 + 0.560\ (1/20)$

$= 0.3255 = 0.252$

So, Lo=Lf

$Q = W/Lf$

= 0.0519/0.252

Q = 0.2059 gm per tablet

R = Q/q

Selection of Formulation and Process Variables by Preliminary Trial Batches of Liquisolid compact

Liquisolid compact was formulate using various Carrier: Coating Ratio, volume of non-volatile solvent containing Drug, type of non-volatile solvent and evaluated for disintegration time and % cumulative drug release for preliminary selection to develop DoE Approach.

Table 16: Proposed design for Preliminary Trial Batches

Formulation Variables	
Carrier : coating Ratio	5:1 -35:1
Volume of Non-volatile solvent containing Drug	0.02-0.1 ml
Type of non-volatile solvent	PG

Formulation of simvastatin Liquisolid compacts by using Factorial Design (DoE) Approach

A design space can signify formulation and process understanding viz. attributes which are related to drug substance, materials, equipment, IP and finished product quality.[3] For this purpose, risk assessment had done based on understanding process and formulation related parameters on Liquisolid compacts quality. Preliminary studies and later Design of Experimentation (DoE) will be carried out for high risk parameters. Based on effect of critical quality attributes of target product profile, we proposed design space for obtaining robust formulation. Characterization of Liquisolid compacts was done for various parameters.

Preliminary Trial Batches for Selection of Formulation Variables of Liquisolid compact

Table 17: Preliminary trial batches for selection of formulation variables

Batch	Carrier : coating Ratio	Volume of non volatile solvent (ml)	Simvastatin (mg)
Selection of volume of non-volatile solvent			
SIMLC1	20	0.02	5
SIMLC2	20	0.04	5
SIMCL3	20	0.06	5
SIMCL4	20	0.08	5
SIMLC5	20	1.0	5
Selection of carrier :coating ratio			
SIMLC6	5	0.04	5
SIMLC7	10	0.04	5
SIMLC8	15	0.04	5
SIMLC9	20	0.04	5
SIMLC10	25	0.04	5
SIMLC11	30	0.04	5
SIMLC12	35	0.04	5

Characterization of Batch SIMLC1-SIMLC5 for Selection of Volume of Non-Volatile Solvent

Table 18: Characterization of Batch SIMLC1-SIMLC5 for Selection of Volume of Non-Volatile Solvent

Batch	Volume of non-volatile solvent (ml)	Angle of slide (mean ± S.D.) (n =3)	Wetting time (sec.) (mean ± S.D.) (n = 3)	Disintegration time (sec.) (mean ± S.D.) (n = 3)
SIMLC1	0.02	29.1± 1.2	215± 1.16	35.32± 2.63
SIMLC2	0.04	33.1± 1.01	164± 1.1	31.32± 1.83
SIMLC3	0.06	36.1± 1.25	117± 1.3	25.12± 1.66
SIMLC4	0.08	44.2± 1.1	95± 1.6	23.53± 1.53
SIMLC5	0.1	56.6± 1.2	89± 1.5	21.63± 1.65

Fig. 6: Wetting time study batch SIMLC1-SIMLC5

Fig. 7: Determination of Angle of Slide

Characterization of Batch SIMLC6- SIMLC12 for Selection of Carrier: Coating Ratio (R-Value)

Table 19: Characterization of Batch SIMLC6-SIMLC12 for Selection of Carrier: Coating Ratio (R-Value)

Batch	Carrier : coating ratio	Angle of slide (mean± S.D.) (n =3)	Wetting time (sec.) (mean ± S.D.) (n = 3)	DT (sec.) (mean ± S.D.) (n = 3)
SIMLC6	5	27.1± 1.3	206± 1.6	37.14± 2.3
SIMLC7	10	29.4± 1.5	159± 1.4	36.52± 1.5
SIMLC8	**15**	**31.3± 1.6**	**112± 1.6**	**27.12± 1.4**
SIMLC9	**20**	**33.5± 1.8**	**94± 1.1**	**22.43± 1.2**
SIMLC10	**25**	**35.1± 1.9**	**73± 1.2**	**21.32± 1.3**
SIMLC11	30	39.6± 1.5	62± 1.5	21.14± 1.4
SIMLC12	35	41.3± 1.8	58± 1.7	20.54± 1.9

Fig. 8: Wetting time study batch SIMLC6- SIMLC12

Fig. 9: Determination of Angle of Slide

Risk Assessment of Critical Quality Attributes from Preliminary trial Batches to Develop DoE

Approach:

Critical quality attributes are categorized in high, medium and low risk parameters based on knowledge space to check influence of formulation and process parameters. Usually high risk parameters are considered important for Design of Experiments as they are having more effect than others and need to be in accepted multivariate ranges. Critical parameters and critical quality attributes (CQAs) for selection of optimum formulation are shown in table 5.22

Table 20: Risk assessment to identify variables affecting drug product quality

Drug product CQAs	Carrier : coating ratio	Volume of non – volatile solvent
Solubility	Low	High
Wetting time	Medium	High
Disintegration time	High	Medium
Drug release (% CDR)	Medium	High

Statistical analysis using Design Expert Software (Version 9.0.2.0) using Two Way ANOVA Method

Formulation and Development of Liquisolid compact of Simvastatin by using 3^2 Factorial Design Approach

3^2 Factorial Design Approach:

Table 21: 3^2Factorial Batches

Independent variables of formulations			
Independent variables	**LOW (-1)**	**Medium (0)**	**High (+1)**
Carrier : coating ratio (mg)(X1)	15:1	20:1	25:1
Volume of non –volatile solvent (ml) (X2)	0.04	0.06	0.08
Dependent variables			
Y1- wetting time			
Y2- disintegration time			
Y3- drug release in 30 min (% CDR)			

Table 22: Compositions of Factorial Batches in Coded Form

SIMLCT 3^2 = batches		
Batch	**Variable level in coded form**	
	Carrier : coating ratio – mg (X1)	**Vol. of non-volatile solvent –ml (X2)**
SIMLCT1	-1	-1
SIMLCT2	-1	0
SIMLCT3	-1	+1
SIMLCT4	0	-1
SIMLCT5	0	0
SIMLCT6	0	+1
SIMLCT7	+1	-1
SIMLCT8	+1	0
SIMLCT9	+1	+1

Table 23: Compositions of Factorial Batches in Decoded Form

SIMLCT 3^2 = Batches		
Batch	**Variable level in De-coded form**	
	Carrier : coating ratio – mg (X1)	**Volume of non- volatile solvent –ml (X2)**
SIMLCT1	15 : 1	0.04
SIMLCT2	15 : 1	0.06
SIMLCT3	15 : 1	0.08
SIMLCT4	20 : 1	0.04
SIMLCT5	20 :1	0.06
SIMLCT6	20 : 1	0.08
SIMLCT7	25 :1	0.04
SIMLCT8	25 :1	0.06
SIMLCT9	25 :1	0.08

Table 24: Calculated Values of Formulation of simvastatin Liquisolid Compacts

R	Φ	φ	Lf (Φ)	Φ	φ	Lf (Ψ)	Drug wt.	Density PG	Vol.(PG)	W	Q	Q	Total
15	0.16	3.31	0.380	0.224	0.560	0.261	0.005	1.038	0.04	0.0415	0.159	0.0106	0.211
15	0.16	3.31	0.380	0.224	0.560	0.261	0.005	1.038	0.06	0.0622	0.238	0.0159	0.316
15	0.16	3.31	0.380	0.224	0.560	0.261	0.005	1.038	0.08	0.0830	0.318	0.0212	0.422
20	0.16	3.31	0.325	0.224	0.560	0.252	0.005	1.038	0.04	0.0415	0.164	0.0082	0.214
20	0.16	3.31	0.325	0.224	0.560	0.252	0.005	1.038	0.06	0.0622	0.246	0.0123	0.320
20	0.16	3.31	0.325	0.224	0.560	0.252	0.005	1.038	0.08	0.0830	0.329	0.0164	0.428
25	0.16	3.31	0.292	0.224	0.560	0.246	0.005	1.038	0.04	0.0415	0.168	0.0067	0.216
25	0.16	3.31	0.292	0.224	0.560	0.246	0.005	1.038	0.06	0.0622	0.251	0.010	0.324
25	0.16	3.31	0.292	0.224	0.560	0.246	0.005	1.038	0.08	0.0830	0.336	0.0143	0.432

Table 25: Characterization of Batches SIMLCT1- SIMLCT9

Batch No.	**Wetting Time (Sec.)**	**Disintegration Time (Sec.)**	**CDR in 30 Min (%)**	Solubility Study (mg/ml) (Mean±S.D) n=3	Saturated Solubility (mg/ml) (Mean±S.D) n=3
SIMLCT1	189.23±0.35	32±1.66	83.4±1.46	2.21±1.31	3.26±1.22
SIMLCT2	116.12±0.31	36±1.35	77.4±1.31	1.80±0.32	2.85±1.33
SIMLCT3	108.01±0.51	24±1.46	95.6±1.46	2.50±1.22	3.65±1.20
SIMLCT4	159.51±0.36	28±1.51	90.3±1.53	3.05±1.37	4.35±1.25
SIMLCT5	94.23±0.66	30±1.69	86.3±1.32	3.15±1.28	4.45±1.30
SIMLCT6	62.82±0.52	33±1.47	81.7±1.53	3.18±1.24	4.55±1.21
SIMLCT7	138.12±0.39	21±1.59	98.5±1.44	4.18±1.27	4.85±1.35
SIMLCT8	71.79±0.51	25±1.43	94.3±1.66	4.25±1.21	5.15±1.26
SIMLCT9	68.19±0.37	29±1.32	88.7±1.31	4.29±1.34	5.25±1.33

Table 267: % Cumulative Drug Release Study of Batches SIMLCT1- SIMLCT9

Time (Min)	% Cumulative Drug Release of Batches SIMLCT1- SIMLCT9								
	1	2	3	4	5	6	7	8	9
0	0	0	0	0	0	0	0	0	0
5	15.23± 1.21	20.23± 1.47	24.63± 1.79	19.41± 1.14	29.63± 1.21	18.69± 1.24	18.86± 1.14	32.45± 1.24	32.89± 1.17
10	35.15± 1.54	32.82± 1.58	35.52± 1.58	32.52± 1.25	40.75± 1.34	35.58± 1.17	32.63± 1.37	46.23± 1.47	46.42± 1.37
15	48.14± 1.32	47.36± 1.59	47.36± 1.67	45.95± 1.57	52.46± 1.47	55.47± 1.38	44.86± 1.97	59.85± 1.87	59.86± 1.87
20	65.53± 1.35	59.86± 1.12	67.59± 1.23	58.63± 1.37	65.18± 1.23	61.83± 1.97	69.56± 1.54	70.12± 1.14	70.56± 1.67
25	71.13± 1.48	65.15± 1.34	82.69± 1.57	79.56± 1.28	72.25± 1.24	72.56± 1.12	85.56± 1.87	82.56± 1.37	81.96± 1.71
30	83.4± 1.46	77.4± 1.31	95.6± 1.46	90.3± 1.53	86.3± 1.32	81.7± 1.53	98.5± 1.44	94.3± 1.66	88.7± 1.31

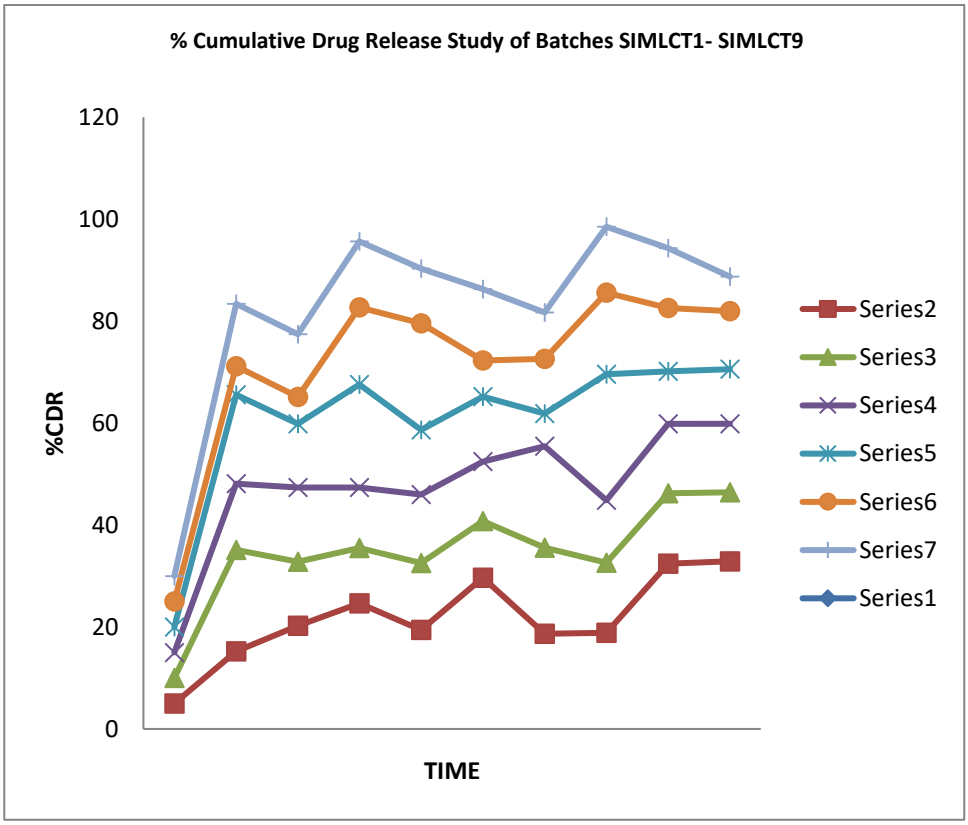


Fig. 10: % Cumulative Drug Release Study of Batches SIMLCT1- SIMLCT9

Statistical Analysis:

Design expert software version 9.0.2.0 was used for Statistical analysis and produced first order polynomial equations. From preliminary results, 3^2 full factorial design was utilized in which two factors were evaluated, separately at three levels and possible nine combinations were formulated. Three level factorial studies were carried out

using two different variables. In first factorial design, amount of carrier:coating ratio (X1) and volume of non-volatile solvent (X2) were taken as independent variables while wetting time (Y1), disintegration time (Y2) and % CDR (Y3) were selected as dependent variables for both factorial designs.

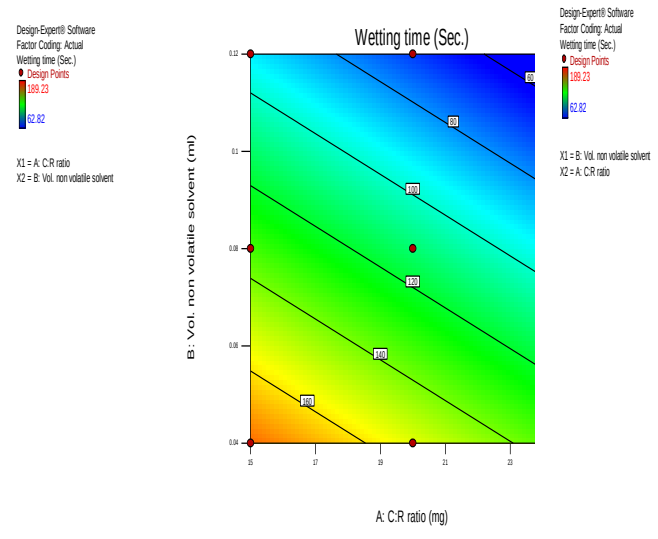
Effect on wetting time (Y1) - Surface Response Study:

Negative value for coefficient of X1- Carrier: coating ratio in equation indicates decrease in wetting time. Negative value of coefficient of X2- volume of non-volatile solvent indicates decrease in response of Y1 i.e. wetting time. It indicates linearity of surface response and contour plot as shown in figure 5.27 and 5.28. Reduced linear model was significant. Therefore, it was applied for all two independent variables and detailed ANOVA, Response Surface Counter Plot and 3 D plot are as follows:

Wetting time=+111.62--21.98*X_1-41.97*X_2

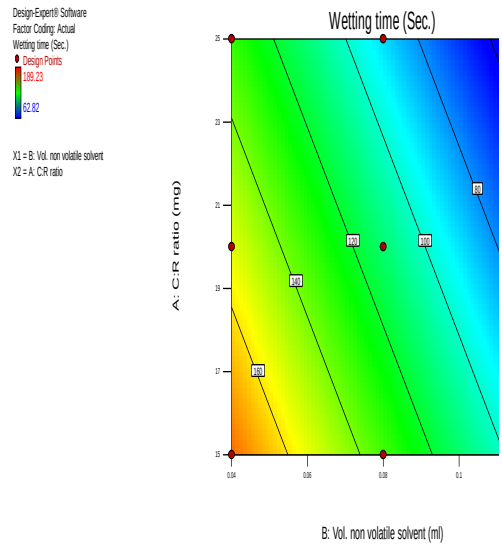
Table 28: ANOVA Table for Response Y1 (Wetting time)

ANOVA for Response Surface Linear model					
Analysis of variance table [Partial sum of squares - Type III]					
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob> F**
Model	13468.41	2	6734.20	22.56	0.0016*
A-C:R ratio	2897.84	1	2897.84	9.71	0.0207
B-Vol. non volatile solvent	10570.56	1	10570.56	35.41	0.0010
Residual	1790.97	6	298.50		
Cor Total	15259.38	8			



Carrier:Coating Ratio (mg)

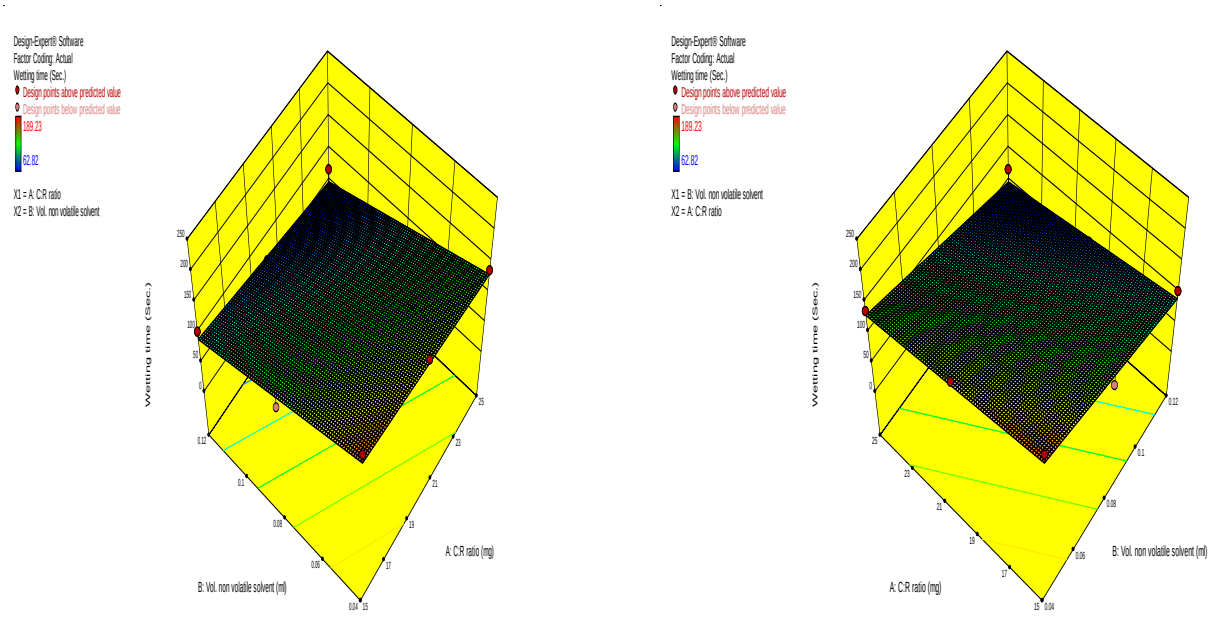
(a)



B: Vol.of Non-Volatile Solvent (ml)

(b)

Fig. 11: Response Surface Plot



(a) (b)

Fig. 12: 3D Surface Plot

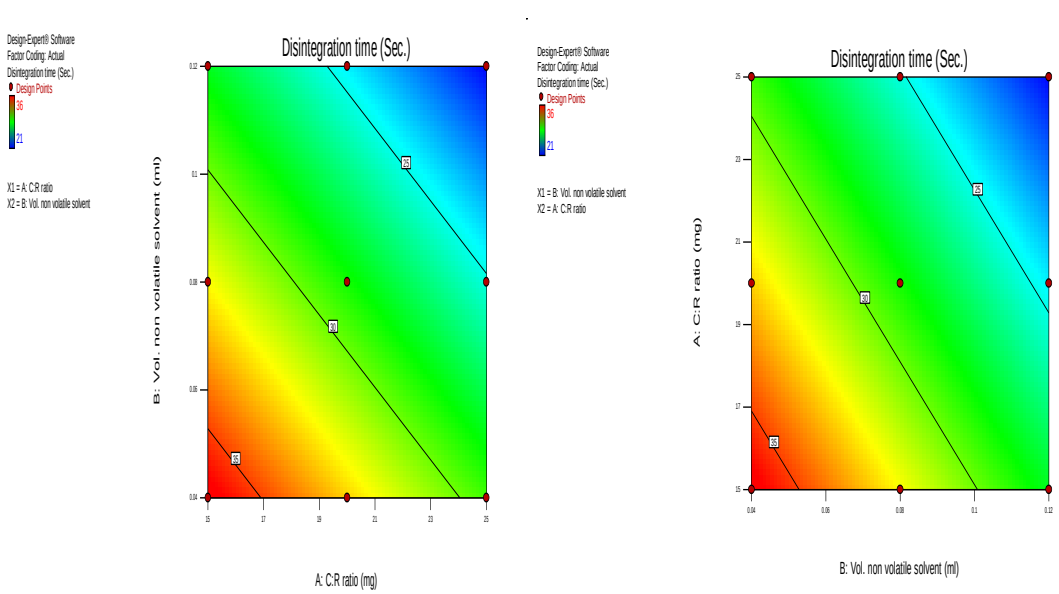
Effect on Disintegration time (Y2) - Surface Response Study:

Negative value for coefficient of X1- Carrier: coating Ratio in equation indicates decrease in disintegration time. Negative value of coefficient of X2-volume of non-volatile solvent also indicates decrease in response of Y2 i.e. disintegration time. It indicates linearity of surface response and contour plot as shown in figure 5.29 and 5.30.

Disintegration time=+51.00000-0.70000*X_1-104.16667*X_2

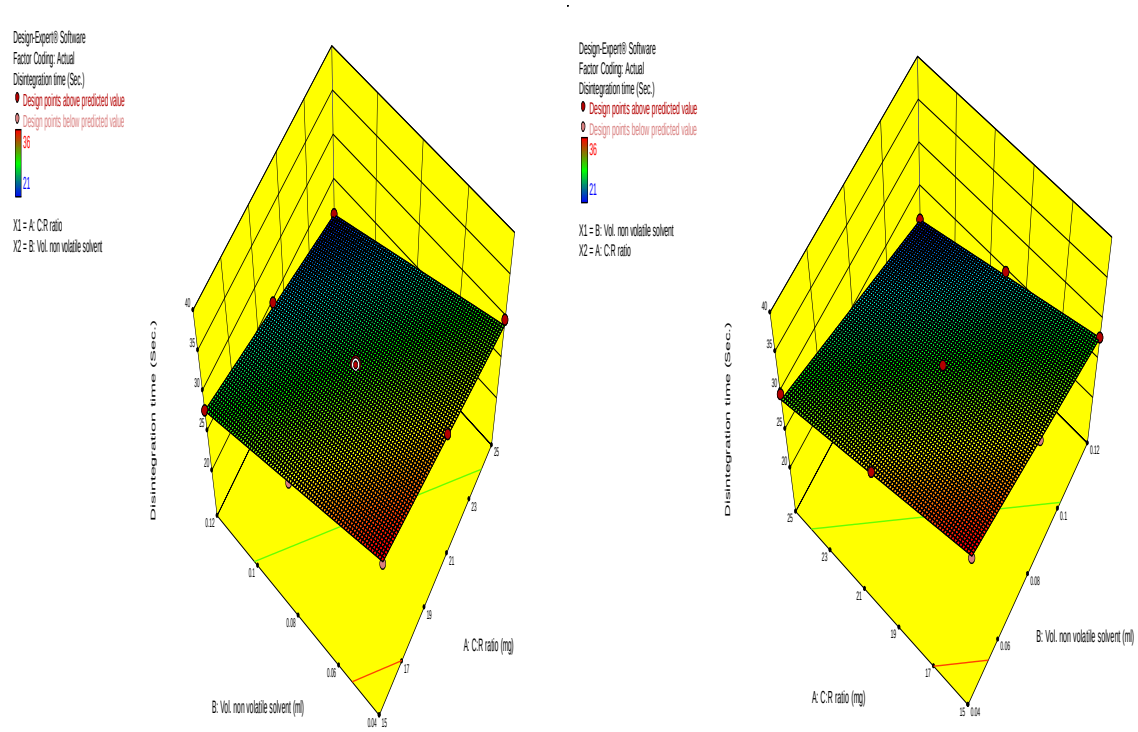
Table 29: ANOVA Table for Response Y2 (Disintegration time)

ANOVA for Response Surface Linear model						
Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob> F**	
Model	177.67	2	88.83	228.43	< 0.0001	significant
A-C:R ratio	73.50	1	73.50	189.00	< 0.0001	
B-Vol. non volatile solvent	104.17	1	104.17	267.86	< 0.0001	
Residual	2.33	6	0.39			
Cor Total	180.00	8				



(a) (b)

Fig. 13: Response Surface Plot



(a) **(b)**

Fig. 14: 3D Surface Plot

Effect on % CDR (Y3) - Surface Response Study:

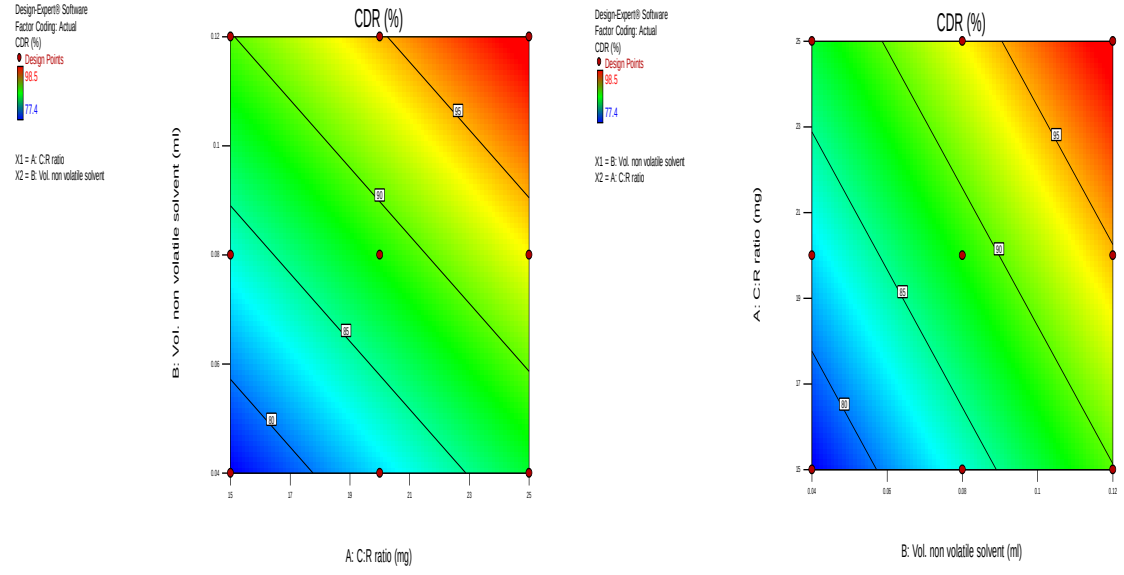
Positive value for coefficient of X1-Carrier: coating ratio in equation indicates increase in Drug release. Positive value of coefficient of X2- volume of non-volatile solvent indicates increase in response of Y3 i.e. drug

release. It indicates linearity of surface response and contour plot as shown in figure 5.31 and 5.32. Reduced model was applied for all two independent variables and detailed ANOVA, Response Surface Counter Plot and 3 D plot are as follows:

$$CDR=+56.36667+0.97667*X_1+157.08333*X_2$$

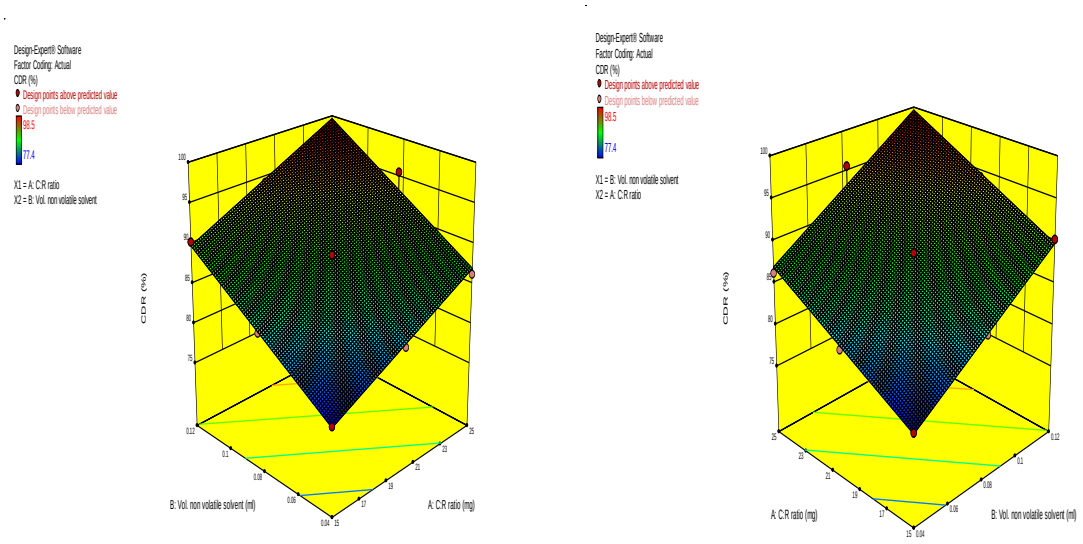
Table 30: ANOVA Table for Response Y3 (%CDR)

ANOVA for Response Surface Linear model						
Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of**		**Mean**	**F**	**p-value**	
	Squares	**df**	**Square**	**Value**	**Prob> F**	
Model	379.96	2	189.98	148.88	< 0.0001	significant
A-C:R ratio	143.08	1	143.08	112.12	< 0.0001	
B-Vol. non volatile solvent	236.88	1	236.88	185.63	< 0.0001	
Residual	7.66	6	1.28			
Cor Total	387.62	8				



(a) **(b)**

Fig. 15: Response Surface Plot



(a) (b)

Fig. 16: 3D Surface Plot

Establishing Design Space and Control Strategy :

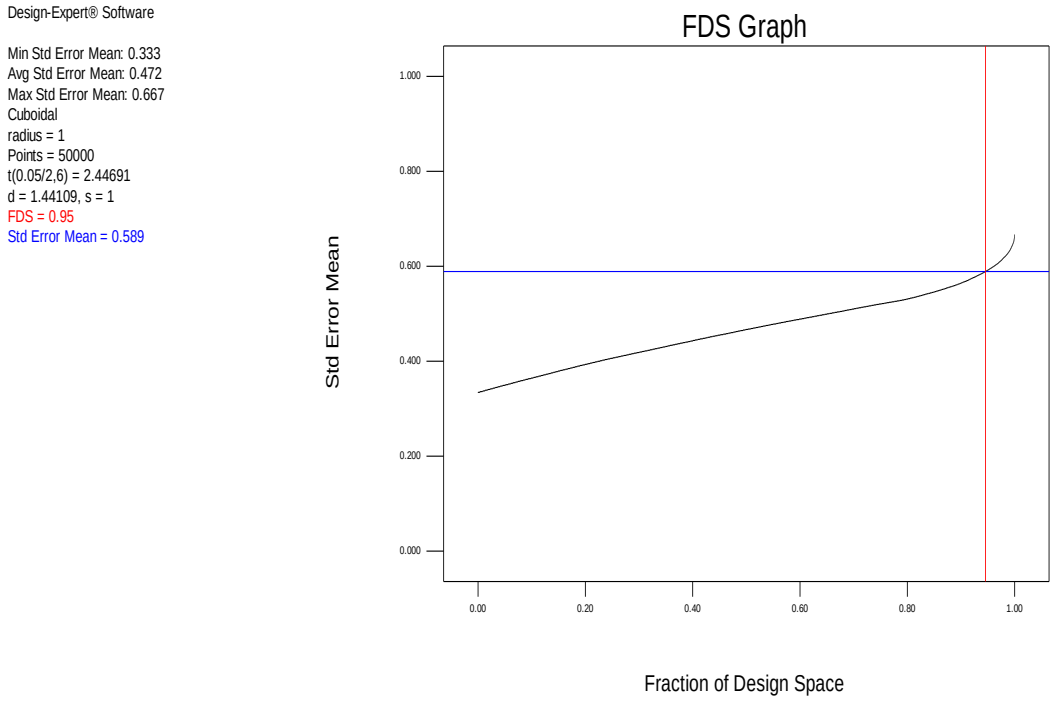
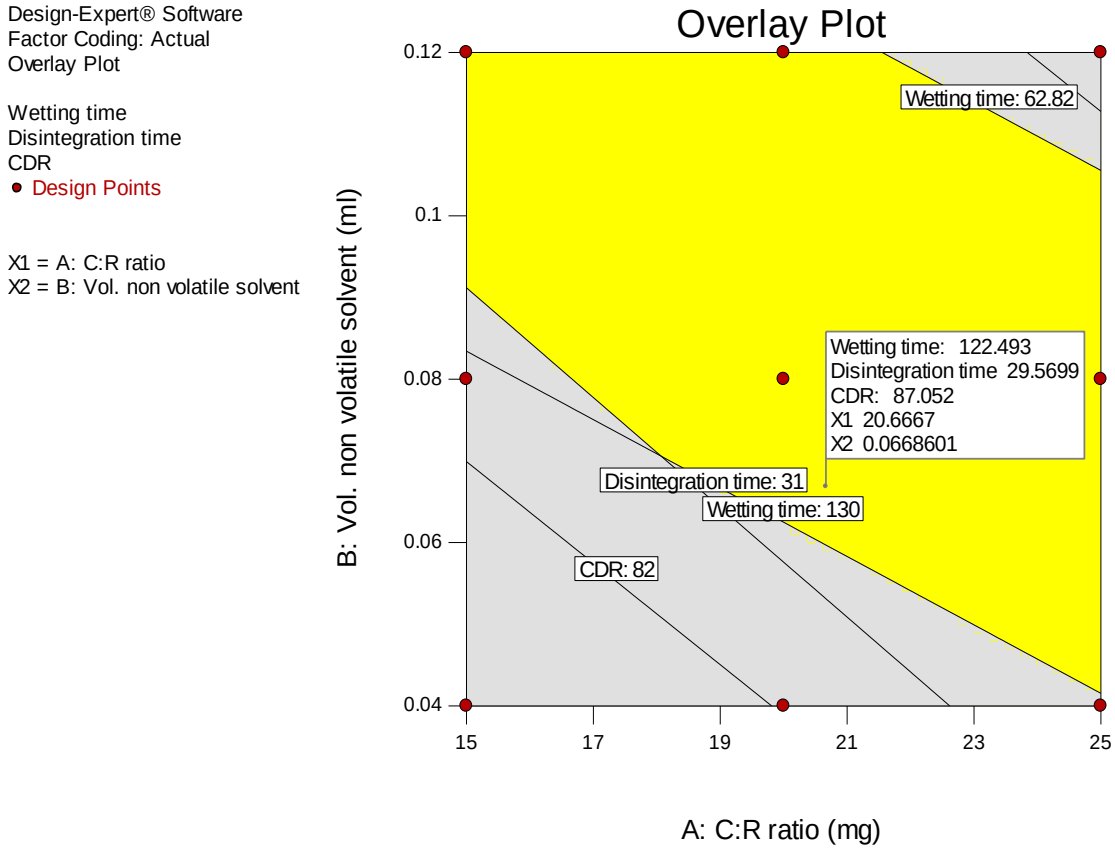


Fig. 17: FDS Graph

FDS curve indicates what % fraction of design space has given prediction error or lower. Good design will have flatter and lower curve than poor design as shown in figure 5.33. Flatter means overall prediction error will be constant. Lower means overall prediction .error will be smaller. FDS should be at least 0.84 or 80% for exploration, and 100% for robustness testing. Here, FDS is 0.95.

Validation batches/ Check Point Analysis and its characterization (Predicted Batches Characterization)

From polynomial equations generated for response, intensive grid and integrated examine was performed over experimental field using Design Expert Software (9.0.2.0.).During independent variable characterization study, impact of parameters Carrier: coating ratio (mg) and vol. of non-volatile solvent (ml) were assessed. Criteria considered of response wetting time (Y1), disintegration time (Y2), %CDR (Y3). This study lead to knowledge space and ultimately design space from multidimensional combination of intensity, solvent volume leads to acceptable operating ranges for isolating mucilage with respect to target product profile. Design space shown in figure 5.34 also called as overlay plot which is shaded region with yellow colour indicates that region of successful operating ranges.



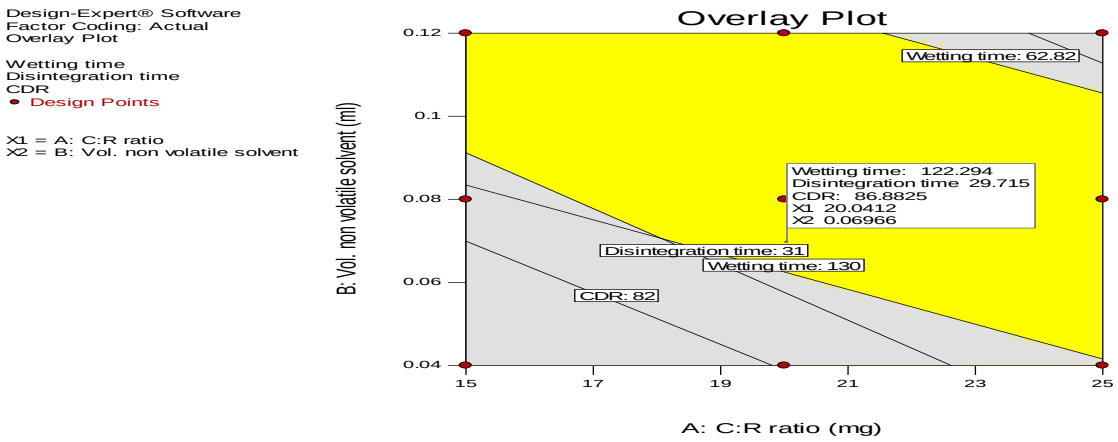


Fig. 18: Overlay Plot

Check point analysis of Validation Batches:

SIMLCT10 & SIMLCT11 formulations were made for check point analysis and predicted and experimental values were compared.

Table 31: Validation of Batches SIMLCT10 & SIMLCT11: Predicted Response

Batch No	Carrier:Coating Ratio (X1)	Volume of Non-Volatile solvent (X2)	Wetting Time (Sec.) (Y1)	Disintegration Time (Y2)	%CDR (Y3)
SIMLCT10	20.66	0.06	122.493	29.569	87.052
SIMLCT11	20.04	0.06	122.294	29.715	86.088

Table 32: Validation Batches SIMLCT10 & SIMLCT11: Actual Response

Batch No	Carrier:Coating Ratio (X1)	Volume of Non-Volatile solvent (X2)	Wetting Time (Sec.) (Y1)	Disintegration Time (Y2)	%CDR (Y3)
SIMLCT10	20.66	0.06	124.682	31.843	89.257
SIMLCT11	20.04	0.06	125.588	30.826	88.719

Selection of Optimized Batch

From result of check point analysis of design data, SIMLCT10 shows higher Drug release (89.257 %) at less wetting time (124.682 sec.) and disintegrating time (31.843 sec) in compare to SIMLCT11. Therefore, SIMLCT10 was selected as optimized batch for formulation of Simvastatin Liquisolid Fast Disintegrating tablets.As per result, we have concluded that Optimized Simvastatin Liquisolid tablet (SIMLCT10) formulation prepared from by using 0.06 ml of non-volatile solvent and 20.66 as R-value having good disintegration time and drug release profile. So Optimized Simvastatin Liquisolid Fast Disintegrating tablet (SIMLCT10) formulation will be greatly for making ideal oral preparation. From In – vitro drug dissolution study, we have

concluded that Optimized Simvastatin Liquisolid Fast Disintegrating tablet (SIMLCT10) increase release of drug which being helpful to increase solubility of Simvastatin which will surely be helpful in future. Optimized Batches are further taking for preparation of Simvastatin Liquisolid Fast Disintegrating Tablets by using appropriate amount of super-disintegrant which enhance disintegration and dissolution profile of Simvastatin Liquisolid Compacts.

Stability Study of SMLCT10 for 1 Month:

Table 33: Stability Study of SIMLCT10 for 1 Month

PARAMETER	Optimized batch (SIMLCT 10)			
	Room temperature			
	0 day	10 day	20 day	30 day
Wetting time(Sec)	124.682	124.583	124.546	124.753
Disintegrating time(sec)	31.843	31.743	31.279	31.586
% CDR	89.257	89.149	89.472	89.356

Formulation and characterization of simvastatin Fast Disintegrating Tablets

Table 34: Formulation of simvastatin fast disintegrating tablets

S.No.	Name of Ingredients	Weight of Ingredients/ 1 tab. (SIMLCT 10)		Weight of Ingredients/1 Tab. (SIMLCT 11)	
1	Simvastatin + PG	5 mg 0.06 ml	62.28 mg	5 mg 0.06 ml	62.28 mg
2	Avicel pH 102	248 mg		247.2 mg	
3	Aerosil	12 mg		12.33 mg	
4	Kyron T 314 (8 % of weight of liquisolid compact)	25.78 mg		25.74 mg	
5	Aspartame	2 mg		2 mg	
TOTAL		350		350	

Preliminary Trial Batches for Selection of Superdisintegrant and its Concentration

Table 35: Preliminary trial batches for selection of formulation variables

Batch	Type of superdisintegrant	Concentration of super disintegrant (8 %)	Simvastatin (mg)
SELECTION OF TYPE OF SUPER DISINTERANTS			
SMFDT 1	SSG	8	5
SMFDT 2	CCS	8	5
SMFDT 3	CP	8	5
SMFDT 4	Kyron T 314	8	5
SELECTION OF CONCENTRATION OF SUPER DISINTEGRANT			

SMFDT 5	**Kyron T 314**	**2**	**5**
SMFDT 6	**Kyron T 314**	**5**	**5**
SMFDT 7	**Kyron T 314**	**8**	**5**

SSG : sodium starch glycolate; CCS : cross caramalose sodium; CP : cross povidone

Characterization of Batch SMFDT1- SMFDT4 for Selection of Type of Super disintegrant

Table 36: Effect of Type of Super disintegrant

BATCH	Type of superdisintegrant	Wetting time (sec.) (Mean ± S.D.) (n = 3)	Disintegration time (Mean ± S.D.) (n = 3)
SMFDT 1	**SSG**	**89.24**	**8.26**
SMFDT 2	**CCS**	**78.59**	**7.56**
SMFDT 3	**CP**	**76.89**	**6.89**
SMFDT 4	**Kyron T 314**	**59.25**	**5.29**

From result, it can conclude that as all super disintegrant decreases disintegration time at different level. Here, Kyron T 314 shows maximum reduction in disintegration time and wetting time. Thus, Kyron T 314 was selected as super disintegrant for further study**.**

Characterization of Batch SMFDT5- SMFDT7 for Selection of Concentration of Superdisintegrant

Table 37: Effect of Concentration of Superdisintegrant

Batch	Concentration of superdisintegrant	Wetting time (sec) (Mean ± S.D.)	Disintegrant time (sec) (Mean ± S.D.)
SMFDT 5	**2**	**102.68**	**9.58**
SMFDT 6	**5**	**95.57**	**7.59**
SMFDT 7	**8**	**68.26**	**5.41**

From result, it can conclude that as concentration of super disintegrant increase wetting time and disintegration time decrease Therefore, 8 % of super disintegrant was selected for development of LiquisolidFast Disintegrating Tablets tablets to get rapid onset of action.

Pre-compression Evaluation of powder blend

Table 38: 27Pre-compression Evaluation of powder blend

Batch code	Pre –compression evaluation of powder blend				
	Bulk density (gm/cm^2) (n=3)	Tapped density (gm/cm^3) (n=3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
SMLCFDT1	0.50±0.010	0.60±0.005	5.34	1.13	25.43
SMLCFDT2	0.54±0.04	0.64±0.004	5.67	1.15	25.59

Bulk density and tapped density of blends was found to be in range of 0.50±0.010 to 0.54±0.04 gm/cm^3 and 0.60±0.005 to 0.64±0.004 gm/cm^3. Carr's index was found to be in range of 5.34 to 5.67 % showed good compressibility. Hausner's Ratio was found to be in range of 1.13 to 1.15 and angle of repose was found to be in range of 25º to 26º showing good flow property.

Characterization of simvastatin liquisolid fast disintegrating tablets

Post-compression evaluation parameter of tablets:

Table 39: Evaluation data of tablets

Formulation	Thickness (mm) (mean ± SD) (n =3)	% friability (mean ± SD) (n =3)	Weight variation (g) (mean ± SD) (n=20)	Drug content (%) (mean ± SD) (n=3)	Hardness (kg/cm^2) (mean ± SD) (n =3)
SMLCFDT1	4.15±0.15	0.150±0.3	0.155±0.5	97.89±0.12	3.26±0.1
SMLCFDT2	4.08±0.15	0.178±0.4	0.148±0.6	98.12±0.24	3.43±0.2

Table 40: Evaluation data of tablets

Formulation	Disintegration Time (sec) (mean ± SD) (n=3)	Wetting time (sec) (mean ± SD) (n=3)	Water absorption Ratio (sec) (mean ± SD) (n=3)	Dispersion Time(sec) (mean ± SD) (n=3)
SMLCFDT1	**5.24±1.26**	**51.22±1.26**	**1.05±1.57**	**14.24±1.79**
SMLCFDT2	**5.52±1.71**	**53.34±1.34**	**1.43±1.42**	**16.55±1.42**

***In-vitro* Release Study of simvastatin fast disintegrating tablet and Comparison with Conventional Marketed simvastatin Tablets:**

Table 41: *In-Vitro* Drug release study

Time (min)	% drug release		
	Marketed simvastatin tablet (mean ± S.D.)	SMLCFDT1 (mean ± SD) (n=3)	SMLCFDT2 (mean ± SD) (n=3)
0	0.00	0.00	0.00
2	7.25±1.26	42.16±1.05	40.92±1.09
4	14.58±203	57.95±1.68	53.68±1.27
6	20.59±1.58	73.37±1.71	73.74±1.37
8	29.59±1.72	86.07±1.89	83.46±1.71
10	35.74±1.69	97.59±1.07	95.68±1.57
15	42.36±1.03	-	-

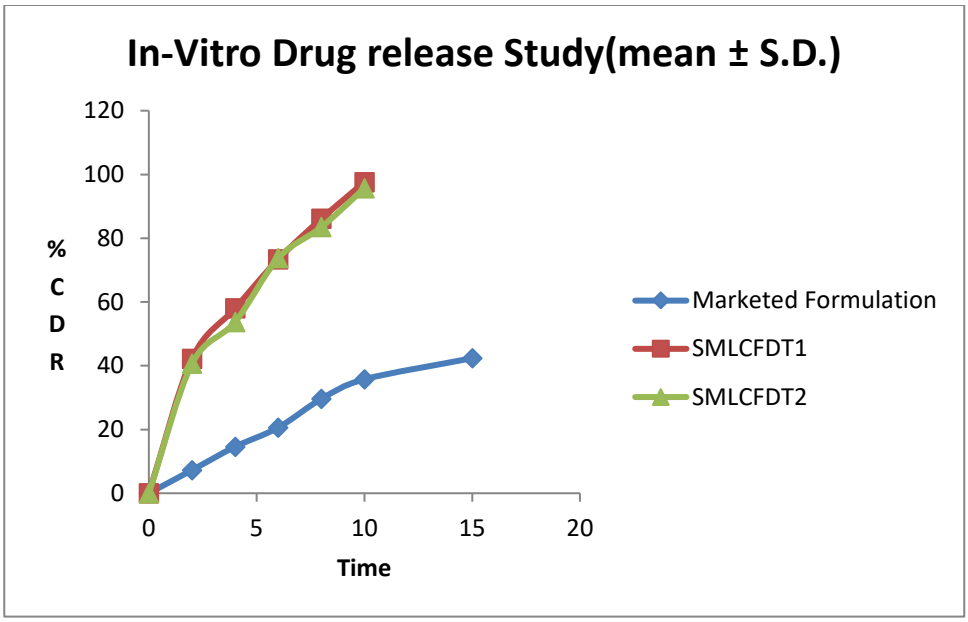


Fig. 19: *In-Vitro* Drug release study of Simvastatin Liquisolid Fast Disintegrating Tablet

Similarity-Dissimilarity Study of simvastatin liquisolid fast disintegrating tablet

According to USFDA, similarity factor should be in between 50-100. Here, f_2 is 38.57. From the result we can conclude that optimized batch was not having similarity with marketed preparation of Simvastatin.

Solubility Study of simvastatin liquisolid fast disintegrating tablet

Table 42: Solubility Study of Optimized batch SMLCFDT1 and SMLCFDT2

Pure drug Simvastatin(mg/ml)(mean± S.D.) (n = 3)	**SMLCFDT1 (mg/ml)(mean± S.D.) (n = 3)**	**SMLCFDT2 (mg/ml)(mean± S.D.) (n = 3)**
Solubility Study		
0.014±0.01	3.28±0.02	4.18±0.01
Saturation Solubility Study		
0.014±0.01	4.35±0.02	4.95±0.01

Taste evaluation of optimized batch SMLCFDT1

Table 43: Taste evaluation of optimized batch SMLCFDT1

Batch no.	Volunteer no.	Bitterness	Mouth feel
SMLCFDT1	**1**	**Absent**	**+++**
	2	**Absent**	**+++**
	3	**Absent**	**+++**
	4	**Absent**	**+++**
	5	**Absent**	**+++**
	6	**Absent**	**+++**

+++ pleasant taste

SEM study of optimized batch SMLCFDT1

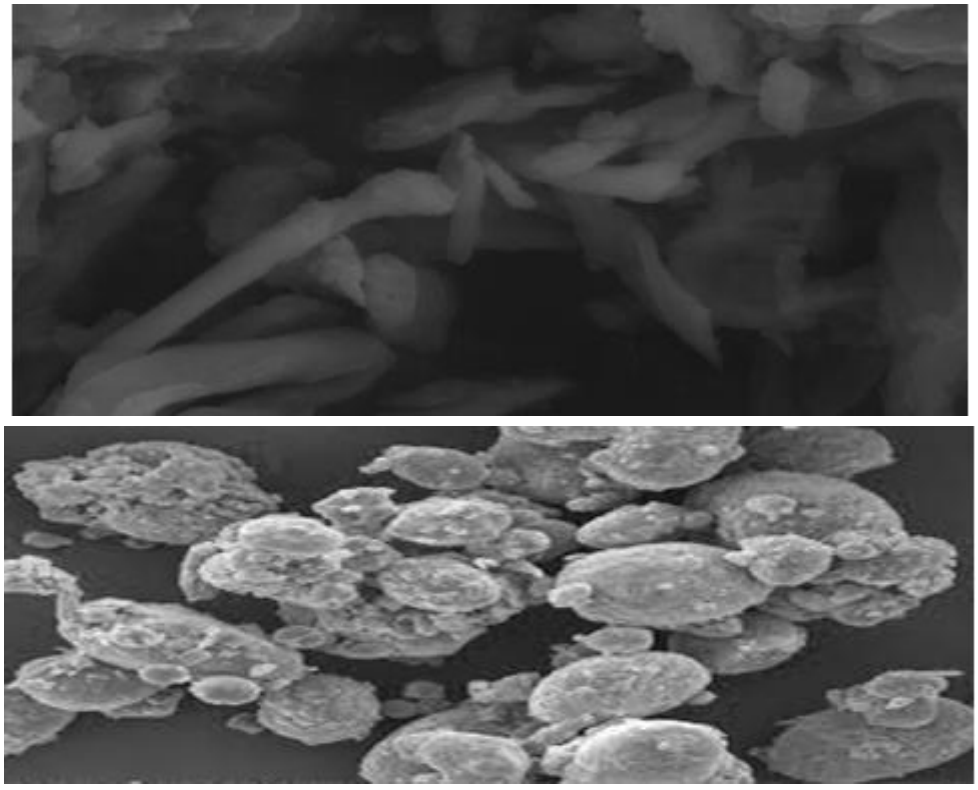


Fig. 20: **SEM study of optimized batch SMLCFDT1**

Stability Study

Table 44: Stability Study

Formulation	Parameter	After 0 day	After 15 day	After 30 day
SMLCFDT1	Physical appearance	No change	No change	No change
	Weight Variation (%± SD)	0.155±0.5	0.153±0.7	0.152±0.4
	Thickness (mm ± SD)	4.15±0.15	4.16±0.19	4.01±0.14
	Hardness (kg/cm^3 ± SD)	3.26±0.1	3.15±0.2	3.18±0.12
	Friability (%± SD)	0.150±0.3	0.153±0.1	0.148±0.16
	Drug content (% ± SD)	97.89±0.12	97.65±0.16	97.68±0.13
	Disintegration time (sec ± SD)	5.24±1.26	5.16±1.13	5.26±1.16

Results indicate that there was no evident of change in physical appearance and drug content of formulations after subjecting to stability studies. Optimized simvastatin liquisolid fast disintegrating tablet formulation was chosen for stability studies from each concentration based on their release characteristics and no significant changes when compared to initial formulations.

Therefore, we have concluded that Optimized simvastatin liquisolid fast disintegrating tablet formulation prepared from by using 0.06 ml of non-volatile solvent and 20.66 as R-value having good disintegration time and drug release profile.

So optimized simvastatin liquisolid fast disintegrating tablet formulation will be greatly for making ideal oral preparation. From In – vitro drug dissolution study, we have concluded that optimized simvastatin liquisolid fast disintegrating tablet increase release of drug which being helpful to increase solubility of simvastatin which will surely be helpful in future.

5. CONCLUSION

The Liquisolid system is the new technique for the formulation of water insoluble drugs to enhance their aqueous solubility, absorption as well as dissolution rate which leading to enhancement of bioavailability of drugs as compared to conventional tablets.

Simvastatin Liquisolid compacts may enhance aqueous solubility and dissolution rate by maximizing surface area, aqueous solubility and wettability.

Further, Simvastatin Fast Disintegrating Liquisolid Tablets may give rapid onset of action by rapid absorption through pre-gastric absorption of Simvastatin from mouth, pharynx and esophagus as saliva passed down and beneficial to reduce dose.

By combining Simvastatin Liquisolid technique and Fast Disintegrating DDS, may enhance solubility, dissolution rate by means of Liquisolid technique and can achieve rapid onset of action with lower dose of drug by using Fast Disintegrating DDS and hence may increase patient compliance.

Expected Outcomes:

Simvastatin Liquisolid compacts may enhance aqueous solubility and dissolution rate in compare to other solubility enhancement technique and Fast Disintegrating DDS also increases the solubility, faster the dissolution rate and rapid onset of action of drug which in turn reduces dose of the drug. Hence, this research work may be useful to formulate Fast Disintegrating Tablets using Liquisolid Technique which may give rapid onset of action by rapid absorption, maximize efficacy, reduce dose and dose frequency and hence increase patient Compliance.

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