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# Formulation Development of Atorvastatin Calcium Tablets by Gel Liquisolid Compact Technique for improving Solid State Stability and Dissolution Profile

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## Abstract

**Background:** BCS class II and IV drugs, which have low solubility, provide a number of challenges for formulation scientists working on oral delivery of drugs.

**Aims:** The aim and purpose of the present work was to design a gel liquisolid tablets for Atorvastatin calcium a water insoluble drug to increase its dissolution rate there by its bioavailability.

**Materials and Methods:** The preformulation studies like solubility studies of API in different non-volatile solvents, optimization of gelling agent and adsorbent quantity were performed. Gel liquisolid compacts (GLS1-GLS10) and directly compressible tablets (DCT 1 and DCT 2) of Atorvastatin calcium were prepared and evaluated for flow properties, post compression parameters and *in vitro* dissolution studies. Structural analysis of GLS was done using differential scanning calorimetry (DSC) and X- ray powder diffraction (XRD) techniques. Finally, the ideal batches (GLS1 and DCT 1) were subjected for *in vivo* bioavailability studies.

**Results:** The solubility was found to be highest in propylene glycol (150.05 ± 0.4278 mg/mL). *In vitro* dissolution studies of the prepared GLS had shown maximum dissolution within one hour when compared to that of prepared DCT tablets. DSC and XRD studies revealed that the drug in the GLS had been solubilized. From the obtained pharmacokinetic data such as AUC, $t_{max}$ and $C_{max}$ through *in vivo* bioavailability studies it was established that GLS have shown better bioavailability compared to that of prepared DCT tablets.

**Conclusion:** This study confirms that Atorvastatin calcium prepared by GLS have better dissolution and bioavailability compare to conventional DCT dosage form and therefore GLS could be a promising drug delivery for Atorvastatin calcium.

**Keywords:** Atorvastatin calcium; Gel liquisolid compact; Neusilin® US2; Dissolution rate; Bioavailability

## Introduction

BCS class II and IV drugs, which have low solubility, provide a number of challenges for formulation scientists working on oral delivery of drugs [1]. The major hindrance in developing a pharmaceutical dosage form of water insoluble drug is its poor dissolution rate [2]. The oral absorption of drugs is most often controlled by dissolution in the gastrointestinal tract. The dissolution characteristics of poorly water soluble dugs can be enhanced by different methods [3] via pH adjustment, solubilization, co-solvents, self-emulsification, micro emulsion [4], drug complexation, polymeric modification, particle size reduction, the pro-drug approach, use of a solid solutions and surfactant as a solubilizing agent [5,6]. Among all these methods the use of liquisolid system is considered to be the most promising method to enhance dissolution [7,8]. Gel based liquisolid compact approach is an extreme case of viscosity enhancement that restricts the molecular motion of drug molecules, in which the movement of the dispersion phase is restricted by interlacing three dimensional network of particles or solvated macromolecules of dispersed medium. A good bioavailability was also related to the fact that the drug did not precipitate out, but staying in a solubilized form when the gel interacted with the aqueous gastric fluids. Some of the other applications of gel liquisolid technique are solubility and dissolution improvement, flowability and compressibility, designing of sustained release tablets, solid state stability enhancement and bioavailability enhancement. Hence, the current project work deals with the improving of the dissolution rate and solid state stability by restricting the movement of Atorvastatin calcium (ATC) using gel liquisolid compact systems. ATC belongs to class of anti-hyperlipidemic drugs. It acts by inhibiting HMG Co A reductase enzymes like other statins. It is most widely used anti-hyperlipidemic drug among the all statin derivatives and it was also known by bestselling statin. ATC belongs to BCS II drugs, like all BCS class II drugs, solubility and dissolution is the rate limiting step for oral bioavailability. This undesired characteristic makes ATC to stay long time in gastro intestinal mucosa, which leads to gastro intestinal damage. It was also reported that due to this poor dissolution rate ATC has bioavailability of only 12% from a tablets dosage form (40 mg) [4]. Hence, the aim of the present work is to design GLS tablets for ATC to enhance its solubility, there by its bioavailability. In this work, a poorly water soluble drug ATC was formulated into GLS using excipients like propylene glycol (non-volatile solvent), neusilin® US2 (carrier), microcrystalline cellulose PH 102 (diluent), aerosil (coating material), crospovidine (super disintegrant), HPC (LF) (gelling agent), HPMC K4M (gelling agent) and talc (glidant). Preformulation studies, powder flow properties, post compression parameters and *in vitro* dissolution studies were performed. *In vivo* bioavailability studied was conducted on male albino wistar rats.

## Materials and Methods

### Materials

The following chemicals were procured: Atorvastatin calcium (ATC) (Dr. Reddy's Labs, India), propylene glycol (PG) (Dow Chemical Company, U.S.A.), neusilin® US2 (fine ultra light granule of magnesium alumino metasilicate) (Gangwal Chem Pvt Ltd, Mumbai), hydroxypropyl cellulose (HPC) LF (Coloron Asia Pvt Ltd, Mumbai), hydroxypropyl methylcellulose (HPMC) K4M (Arihant Trading Company, Mumbai), micro crystalline cellulose (MCC) PH 101and PH 102 (Ran Q Remedies Pvt Ltd., Nasik), ethyl cellulose 10cps (Coloron Asia Pvt Ltd, Mumbai), crospovidone (FMC biopolymer, Ireland), magnesium stearate (JRS Pharma, Germany), talc (Talc India, India), acetonitrile (Sigma Aldrich, USA).

### Chromatographic conditions

The chromatographic system consisted of a Shimadzu HPLC (Kyoto, Japan) with a PDA detector. Chromatographic separation was performed on a reversed-phase Hibar $C_8$ column (150 mm × 4.6 mm) by using a mobile phase containing 20 mM phosphate buffer: acetonitrile (35:65) at a pH of 6.5. The mobile phase was delivered at a flow rate of 1 mL/min and detection was carried out at 238 nm.

### Preformulation studies

**Saturation Solubility studies of API:** The saturation solubility of ATC was determined using four different non-volatile solvents i.e., PG, polyethylene glycol (PEG) 400, tween 80 and PEG 200 by adding an excess amount of drug to 5 mL of selected non-volatile solvents in glass vials. The vials were kept at 25 ± 0.5°C in an isothermal shaker for 72 h to reach equilibrium. Subsequently, the supernatant was collected and filtered through a 0.22 µm membrane filter and concentration of ATC in non-volatile solvents after successive dilutions was determined using HPLC at 238 nm against blank (blank sample having the same dilutions as that of drug but without drug).

### Compatibility study

**Differential scanning calorimetry (DSC):** Thermograms of samples were recorded using DSC Q-200 (TA Instruments, USA). Samples were placed in T-Zero aluminum pans and the lids were locked using T- Zero press. Thermal behavior of the samples was investigated at a scanning rate of 10°C/min, covering a temperature range of 50-200°C using nitrogen gas at 50 mL/min flow rate. The instrument was calibrated with indium standard [9].

**Optimization of gelling agent:** HPC (LF) and HPMC (K4M) were proposed as gelling agents. Different amounts of 5, 8, 12, 16 mg of HPC (LF) was added to 0.06 mL (76 mg) of non-volatile solvent (PG) containing drug by continuous stirring until a clear viscous gel was obtained. Similarly, different amounts of HPMC (K4M) i.e., 5, 10, 16, 18 mg was added to 0.06 mL (76 mg) of non-volatile solvent (PG) containing drug by continuous stirring until a clear viscous gel was obtained.

**Optimization of adsorbent quantity:** Different amount of adsorbent 20, 40, 60, 80, 100, 120 mg of neusilin® US2 was added to 0.06 mL (76 mg) of non-volatile solvent i.e. PG containing drug, by continuous mixing until a free flowing blend was obtained.

### Formulation of GLS

Ten batches of GLS compacts as GLS1 to GLS10 were prepared using cadmach16 station tablet compression machine. ATC was dispersed in PG and then solubilized by gently warming followed by sonication of the resulting solution. This solution was converted in to gel by HPC (LF) & HPMC (K4M), which is having interconnected pore morphology that helps in high and quick solvent absorption. To this, calculated amount of adsorbent, neusilin® US2 was added in different concentrations (80 mg, 100 mg and 120 mg) to form a freely flowing powder. To the above powder blend, aerosil and crospovidone were added. Subsequently, MCC PH 102 was added and to this powder blend 0.5% PVP in IPA was added drop wise until wet mass was formed. Finally, the wet mass was passed through sieve.no.16 to obtain granules. The granules were dried at room temperature for 30 min. The dried granules were passed through sieve no.22 and evaluated for flow properties and then compressed using 12 mm die (Figure 1). The composition of GLS and DCT are given in table 1.

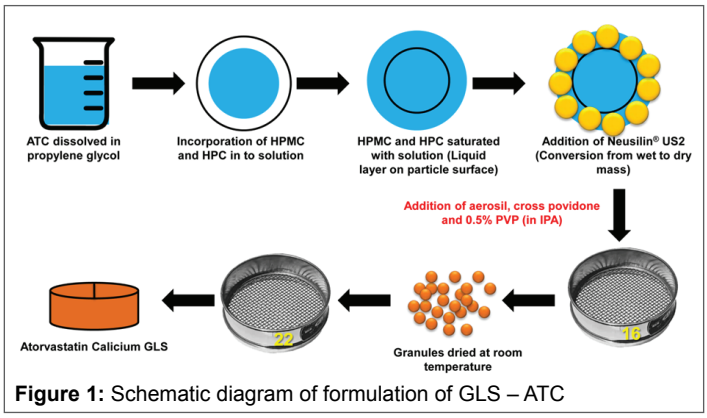


**Figure 1:** Schematic diagram of formulation of GLS – ATC

| Ingredients | Formula (mg) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | GLS 1 | GLS 2 | GLS 3 | GLS 4 | GLS 5 | GLS 6 | GLS 7 | GLS 8 | GLS 9 | GLS 10 | DCT 1 | DCT 2 |
| Atorvastatin calcium | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Propylene Glycol | (0.06 ml) 66 mg | (0.06 ml) 66 mg | (0.06 ml) 66 mg | (0.06 ml) 66 mg | (0.06 ml) 66 mg | (0.06 ml) 66 mg | (0.06 ml) 66 mg | (0.06 ml) 66 mg | (0.06 ml) 66 mg | (0.06 ml) 66 mg | - | - |
| Neusilin US2 | 80 | 100 | 120 | - | - | 80 | 100 | 120 | - | - | - | - |
| Aerosil | 6.5 | 10 | 13 | 24 | 26.6 | 6.5 | 10 | 13 | 24 | 26.6 | 13 | 13 |
| MCC PH 102 | 212 | 188 | 165 | 582 | 732 | 210 | 186 | 163 | 580 | 730 | 171 | 171 |
| Crospovidone | 8 | 8 | 8 | 21 | 26 | 8 | 8 | 8 | 21 | 26 | 6 | 6 |
| HPC (LF) | 16 | 16 | 16 | 16 | 16 | - | - | - | - | - | 16 | - |
| HPMC K4M | - | - | - | - | - | 18 | 18 | 18 | 18 | 18 | - | 18 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Total weight | 400 | 400 | 400 | 720 | 880 | 400 | 400 | 400 | 720 | 880 | 300 | 300 |

**Table 1:** Composition of Liquisolid compacts (GLS 1-GLS 10) and directly compressible batch (DCT 1 & DCT 2)

**Formulation of directly compressible tablets:** Two batches of DCT (DCT 1, DCT 2) were prepared using cadmach16 station tablet compression machine. The known quantity of drug and the calculated amount of adsorbent, gelling agent and other excipients without non-volatile solvent i.e., PG were triturated to form a free flowing powder. To this powder blend, 0.5% of PVP in IPA was added drop wise until wet mass was formed. Consequently, the wet mass was passed through sieve no 16 to obtain granules and prepared granules were dried at room temperature for 30 min. Finally, the dried granules were passed through sieve number 22 and evaluated for flow properties and then compressed using 10 mm die [10].

## Flow properties/Precompression studies of the prepared liquisolid powders

The flow properties of prepared powders were determined by angle of repose, bulk density, compressibility, hausner's ratio. The angle of repose was measured using Fixed funnel free standing cone method and remaining bulk density, compressibility [11], hausner's ratio were measured using bulk density apparatus [12].

## X-ray powder diffractometer (XRD)

The physical forms of drug in ideal batches were characterized using X-ray powder diffraction. The tablets were crushed to a fine powder with the help of mortar and pestle [13,14]. The fine powder was packed into sample holder and the sample was scanned using the instrument parameters: Instrument used: Powder X-ray diffractometer, Model: PANalytical, X'Pert PRO, Goniometer: Theta/Theta vertical, Measuring circle: 480 mm, Radiation: Cu K α (wavelength=1.5418 Å), Detector: X'Celerator, Voltage current: 45 kV, 40 mA, Scan range: 3o-44o 2θ, Step size: 0.020 2θ, Time per step: 200 sec, Scan mode: Continuous, Divergent slit: Automatic 10 mm, Anti scattering slit: Automatic 10 mm, Specimen length: 10 mm, Synchronous rotation: On.

## Post compression parameters of the prepared GLS and DCT

All the prepared GLS and DCT were evaluated for the parameters like average weight, friability, hardness, disintegration, drug content and *in vitro* drug release adopting the following procedures.

**Drug content:** The drug content in tablets was determined by using HPLC analysis. Five tablets were powdered and a quantity equivalent to 100 mg of ATC was transferred into a beaker containing phosphate buffer pH 6.8. The solution was stirred for 1h, filtered and the drug content was estimated using peak area at 238 nm.

**Weight variation:** 20 tablets were selected randomly and weighed individually. The average weight was calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage given in the USP pharmacopeia and none deviates by more than twice that percentage [15].

**Hardness:** Monsanto hardness tester was used to determine the hardness of tablets. It consisted of a tube containing a compressible spring in between two plungers. 20 tablets were randomly selected and each tablet was placed in contact with lower plunger and zero reading was noted. The plunger was then forced against the spring by turning the thread bolt until the tablet was fractured. The force required to fracture the tablet was recorded [16].

**Friability testing:** Friability of the tablets was determined by using Roche friabilator. Ten tablets from each batch were placed in the friabilator and rotated at 25 rpm for a period of 4 min. The friability was determined using the following formula [16].

$$\text{Friability}(\%) = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \text{X}100$$

**Disintegration test:** The disintegration test was carried out using disintegration test apparatus as specified in the Indian Pharmacopoeia [17].

## *In vitro* dissolution studies

The *in vitro* dissolution studies of prepared GLS 1 to GLS 10 formulations were carried out using USP type 2 (paddle method) dissolution apparatus. The dissolution process was carried out using 900 mL of phosphate buffer at pH 6.8 with a rotation speed of 75 rpm and temperature of 37 ± 0.5°C. Prior to dissolution, the phosphate buffer was deaerated by sonication. The formulation GLS 1 to GLS 10 were placed in to the dissolution media and then an aliquot of 5 mL of sample was withdrawn at 0, 5, 10, 15, 30, 45, and 60 min time intervals, respectively. After each sampling, an equal quantity of buffer was replaced to maintain the sink conditions. The peak areas of filtered samples was measured using high pressure liquid chromatography (Figure 2) and percentage cumulative drug release at various time intervals was calculated [18,19].

## *In vivo* oral bioavailability studies in rats [20]

Male Albino Wistar rats of 200-250 gm were used for the oral bio-availability studies. Animal ethical clearance was approved by Institutional Animal Ethical Committee, J.S.S. College of Pharmacy, Ooty (Proposal no. JSSCP/IAEC/M.PHARM/Ph.ceutics/01/2011-2012) and all the animals were treated as per study protocol. The study was carried out by giving free access to water.

## Groupings

Twelve animals were grouped into two groups in such a way that each group contains six animals. Group one animals received test formulation (GLS); group two animals received standard formulation (drug suspension). All the formulations were administered using oral needle at a dose of 0.8 mg that is equivalent to human dose of 10 mg. [conversion factor=0.07 (10*0.08=0.8 mg)]. Blood samples were withdrawn at intervals of (0.25, 0.5, 0.75, 2, 4, 6, 8, 12, 24 h) in eppendorf tubes containing 0.3 mL anticoagulant (sodium citrate) and were centrifuged immediately. After centrifugation, the plasma obtained was collected in the eppendorf tube and stored at -20°C until further analysis.

## Method of analysis

Chromatographic data acquisition and analysis was performed by employing LC Solutions Software™. Simvastatin was used as internal standard (IS), as it belongs to same class of ATC and offered acceptable resolution with ATC peak The retention time of ATC was 4.1 min and IS was 6.2 min. Calibration curves were linear in the working range of 10-180 ng/mL in rat plasma. Quality control samples were prepared at three concentration levels of 30, 110 and 180 ng/mL covering entire linearity

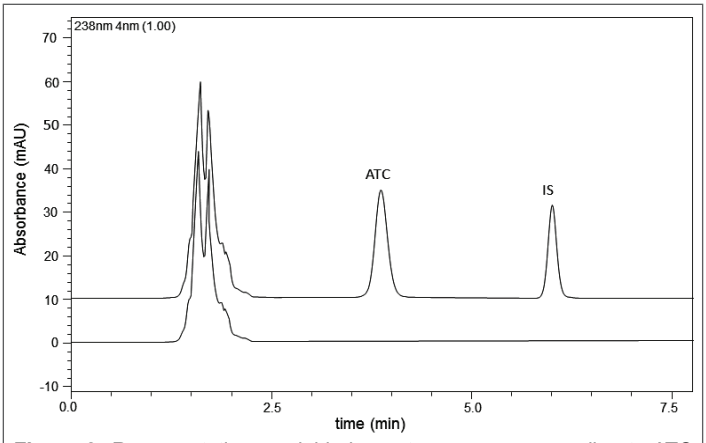


**Figure 2:** Representative overlaid chromatograms corresponding to ATC spiked in rat plasma with IS (simvastatin) and processed blank rat plasma

range for validation purposes. Intra and inter-day accuracy and precision values were within RSD of ≤ 7%. The extraction of ATC from plasma was performed using a simple protein precipitation technique using acetonitrile [21]. Extraction efficiency of ATC in case of spiked plasma samples was 97.9 ± 4.3%. Estimation of ATC in plasma samples by HPLC was carried out and obtained chromatograms are shown in figure 2.

### Statistical analysis

Statistical data were analyzed using GraphPad Prism® 6 program (Graph pad Inc., USA). Results are expressed as mean ± SD for the number of observations indicated. Mean values were compared using one-way analysis of variance (ANOVA) followed by Tukey post hoc test to compare means between the different treatment groups. Differences were considered significant at $p<0.05$ unless otherwise stated. The amount of drug in the plasma (*in vivo*) was estimated through HPLC.

## Results

### Preformulation studies

ATC was selected as a model drug for these studies, because it's a very poorly water soluble drug and suitable candidate for testing the potential of GLS. The perfect linearity between the concentration and peak area was observed in the concentration range of 10 µg/mL to 50 µg/mL. The "Slope (K)" and "Intercept (β)" values were found to be 0.0443 and 0.0097. The solubility is found to be maximum in PG (150.05 ± 0.4278 mg/mL), where as in case of other non-volatile solvents it is found to be PEG 400 (6.323 ± 0.136 mg/mL), tween 80 (6.352 ± 0.068 mg/mL), PEG 200 (52.562 ± 0.1055 mg/mL). Therefore, PG was selected as better solvent to prepare liquid medication. In the optimization of gelling agent, various quantities of gelling agents HPC (LF) and HPMC (K4M) were added to 0.06 mL (76 mg) of liquid drug to form a clear viscous gel which shown in table 2. In this optimization, it was conformed that amount of HPC (LF) 16 mg and HPMC (K4M) 18 mg are required to form clear viscous gel with 0.06 mL (76 mg) of liquid drug. Additionally, from table 3, it was concluded that a minimum amount of 80 mg neusilin® US2 is required to obtain a free flowing powder with 16 mg of HPC (LF) and 18 mg of HPMC (K4M).

### Precompression studies of prepared liquisolid powders

The results for angle of repose, bulk density, compressibility, hausner's ratio are shown in the table 4. The obtained results suggest that all parameters were within the limits, and these powders can be effectively converted in to liquisolid dosage forms.

### Formulation of GLS compacts and DCT

A series of tablet batches were prepared i.e., GLS 1 to GLS 10 to known the effect of different excipients with different concentrations on dissolution rate, which is shown in the table 4 and then subjected to post compression evaluations. The series from GLS 1 to GLS 5 contains constant amount of HPC (LF) and ATC with variable amounts of remaining excipients and series from GLS 6 to GLS 10 contains constant amount HPMC (K4M) and ATC with variable amounts of remaining excipients. Whereas, the series from DCT 1 and DCT 2 contains constant amount of ATC as such without converting in to GLS compact, where DCT 1 having 16 mg of HPC (LF) but not in DCT 2 and 18 mg of HPMC (K4M) in DCT 2 but not in DCT 1.

### Evaluation of prepared GLS and DCT

The GLS compacts and DCT were evaluated for average weight, friability, hardness, disintegration, and drug content and obtained results are presented in table 5. The data indicate that all the parameters were within the limits.

### Structural analysis of ATC-GLS

**Differential scanning calorimetry (DSC):** The DSC overlay of pure drug and the formulation GLS-1 are shown in figure 3. The thermogram of pure drug ATC showed an endothermic peak at $T_{melting}$=155°C. As the drug was melting at this temperature, which indicates that drug is in crystalline form. While in the formulation characteristic peaks of ATC had disappeared which indicates the drug has got solubilized in the vehicle and also it indicates that there were no interactions between drug and excipients. This is further confirmed by XRD studies.

**X-ray powder diffractometer (XRD):** The powder X-ray patterns of pure drug and formulation are shown in figure 4. The diffraction pattern of drug in liquid solid compacts showed the disappearance of sharp distinctive peaks, which indicates that drug was solubilized in the prepared formulations. In case of pure drug, the diffraction pattern showed numerous distinctive peaks, which indicates that drug is in highly crystalline nature. From the above structural analysis studies of ATC-GLS compacts it can be assumed that ATC was completely solubilized in the prepared formulations. These results prove that GLS compacts can be a promising technology for improving the solubility of poorly water-soluble drugs like ATC.

***In vitro* release studies:** The dissolution profiles of all formulations are shown in figure 5. From *in vitro* dissolution release profiles, it can be seen that GLS compacts of ATC has maximum dissolution, when compared to that of DCT formulations containing ATC in powder form. It is observed that GLS compacts of ATC using neusilin® US2 in combination with microcrystalline cellulose (GLS1, GLS2, GLS3, GLS6, GLS7, GLS8) showed maximum release and dissolution of the ATC within 1 h from the formulations when compared with formulations where microcrystalline is

| # | Gelling agent required For 0.06 ml (76 mg) of liquid drug | | Result |
|---|---|---|---|
| | Name of the gelling agent | Amount of gelling agent (mg) | |
| 1. | HPC(LF) | 5 | No clear viscous gel |
| 2. | | 8 | No clear viscous gel |
| 3. | | 12 | No clear viscous gel |
| 4. | | 16 | Clear viscous gel |
| 1. | HPMC K4M | 5 | No clear viscous gel |
| 2. | | 10 | No clear viscous gel |
| 3. | | 16 | No clear viscous gel |
| 4. | | 18 | Clear viscous gel |

**Table 2:** Optimization of gelling agent

| # | Adsorbent required For 0.06ml (76mg) of liquid drug | | | Result |
|---|---|---|---|---|
| | Name of the gelling agent | Name of adsorbent | Amount of adsorbent (mg) | |
| 1. | HPC(LF) | Neusilin US2® | 20 | No free flowing powder |
| 2. | | | 40 | No free flowing powder |
| 3. | | | 60 | No free flowing powder |
| 4. | | | 80 | Free flowing powder |
| 5. | | | 100 | Free flowing powder |
| 6. | | | 120 | Free flowing powder |
| 1. | HPMC K4M | Neusilin US2® | 20 | No free flowing powder |
| 2. | | | 40 | No free flowing powder |
| 3. | | | 60 | No free flowing powder |
| 4. | | | 80 | Free flowing powder |
| 5. | | | 100 | Free flowing powder |
| 6. | | | 120 | Free flowing powder |

**Table 3:** Optimization of adsorbent quantity

| Formulation | Angle of repose (θ)* (Mean ± SD) | Tapped Density* (Mean ± SD) | Bulk Density* (Mean ± SD) | Carrs' Index* (Mean ± SD) | Hausner's Ratio* (Mean ± SD) |
|---|---|---|---|---|---|
| **GLS 1** | 27.13 ± 0.70 | 0.57 ± 0.36 | 0.7 ± 0.47 | 16.59 ± 1.5 | 1.51 ± 0.31 |
| **GLS 2** | 28.34 ± 0.38 | 0.5 ± 0.33 | 0.8 ± 0.51 | 16.85 ± 0.95 | 1.48 ± 0.35 |
| **GLS 3** | 236.03 ± 0.70 | 0.46 ± 0.28 | 0.5 ± 0.41 | 13.15 ± 0.76 | 1.04 ± 0.13 |
| **GLS 4** | 36.31 ± 0.59 | 0.73 ± 0.40 | 0.55 ± 0.39 | 25.04 ± 0.99 | 1.22 ± 0.27 |
| **GLS 5** | 33.04 ± 0.06 | 0.49 ± 0.21 | 0.80 ± 0.62 | 18.62 ± 0.54 | 1.12 ± 0.22 |
| **GLS 6** | 27.42 ± 0.14 | 0.57 ± 0.37 | 0.79 ± 0.54 | 16.72 ± 0.72 | 1.26 ± 0.35 |
| **GLS 7** | 27.57 ± 0.29 | 0.73 ± 0.47 | 0.68 ± 0.38 | 18.61 ± 0.82 | 1.44 ± 0.30 |
| **GLS 8** | 23.26 ± 0.43 | 0.66 ± 0.39 | 0.58 ± 0.37 | 14.74 ± 1.48 | 1.31 ± 0.21 |
| **GLS 9** | 32.5 ± 0.26 | 0.74 ± 0.65 | 0.86 ± 0.65 | 24.19 ± 0.521 | 1.38 ± 0.47 |
| **GLS 10** | 33.48 ± 0.44 | 0.86 ± 0.59 | 0.67 ± 0.56 | 19.07 ± 0.66 | 1.1 ± 0.19 |
| **DCT 1** | 26.58 ± 0.20 | 1.01 ± 0.74 | 0.66 ± 0.5 | 15.11 ± 0.83 | 1.14 ± 0.46 |
| **DCT 2** | 27.50 ± 0.36 | 0.91 ± 0.90 | 0.59 ± 0.35 | 16.55 ± 0.84 | 1.8 ± 0.65 |

**Table 4:** Flow properties
*Measurements were made in triplicate

| Formulation | Weight variation (in mg) *(Mean ± SD) | Hardness (Kg lbs/cm²) *(Mean ± SD) | % Friability *(Mean ± SD) | Disintegration Time (min) *(Mean ± SD) | % Drug Content *(Mean ± SD) |
|---|---|---|---|---|---|
| **GLS 1** | 398 ± 0.53 | 5.63 ± 1.15 | 0.74 ± 0.21 | 0.47 ± 0.18 | 97.26 ± 0.91 |
| **GLS 2** | 399 ± 0.02 | 4.59 ± 0.92 | 0.67 ± 0.19 | 0.92 ± 0.58 | 98.33 ± 0.30 |
| **GLS 3** | 398.5 ± 0.2 | 4.16 ± 0.74 | 0.57 ± 0.23 | 0.61 ± 0.33 | 97.57 ± 0.48 |
| **GLS 4** | 718 ± 0.50 | 5.1 ± 0.82 | 0.42 ± 0.32 | 2.77 ± 0.47 | 98.57 ± 0.45 |
| **GLS 5** | 879 ± 0.42 | 5.63 ± 0.57 | 0.5 ± 0.33 | 2.35 ± 0.47 | 97.52 ± 0.56 |
| **GLS 6** | 398 ± 0.70 | 4.52 ± 0.49 | 0.55 ± 0.11 | 0.53 ± 0.40 | 97.51 ± 1.00 |
| **GLS 7** | 399 ± 0.20 | 4.54 ± 0.49 | 0.63 ± 0.14 | 0.47 ± 0.27 | 98.03 ± 1.01 |
| **GLS 8** | 398.5 ± 0.60 | 4.48 ± 0.45 | 0.71 ± 0.26 | 0.95 ± 0.38 | 97.3 ± 0.51 |
| **GLS 9** | 718 ± 0.70 | 4.95 ± 0.21 | 0.94 ± 0.37 | 2.97 ± 0.47 | 95.676 ± 0.88 |
| **GLS 10** | 819 ± 0.20 | 5.47 ± 0.38 | 1.51 ± 0.64 | 2.21 ± 0.38 | 96.67 ± 0.45 |
| **DCT 1** | 299 ± 0.20 | 5.21 ± 0.55 | 0.99 ± 0.45 | 4.94 ± 0.52 | 97.51 ± 0.21 |
| **DCT 2** | 298 ± 0.50 | 4.62 ± 0.34 | 0.6 ± 0.42 | 4.53 ± 0.45 | 97.12 ± 0.69 |

**Table 5:** Evaluation of different parameters of DCT containing HPC (LF) & HPMC K4M

| Pharmacokinetic Parameters | ATC-GLS | DCT |
|---|---|---|
| **$C_{max}$ (ng/ml)** | 148.42 | 88.56 |
| **$t_{max}$ (h)** | 1 | 2 |
| **Ke (h)** | 0.18 | 0.24 |
| **$t_{½}$ (h)** | 3.82 | 2.84 |
| **$AUC_{0-t}$ (h.ng/ml)** | 476.68 | 396.05 |
| **$AUC_{0-\alpha}$ (h.ng/ml)** | 1295.19 | 759.23 |

**Table 6:** Pharmacokinetic parameters for ATC in the plasma after oral Administration

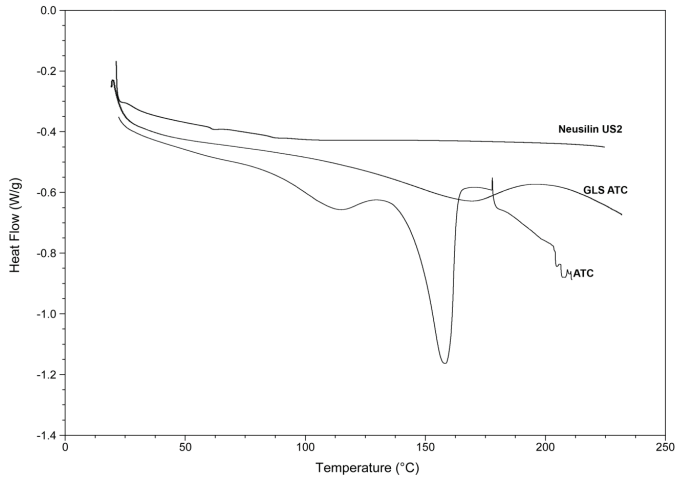


**Figure 3:** Overlaid DSC thermogram of ATC, Neuslin, Neuslin and ATC

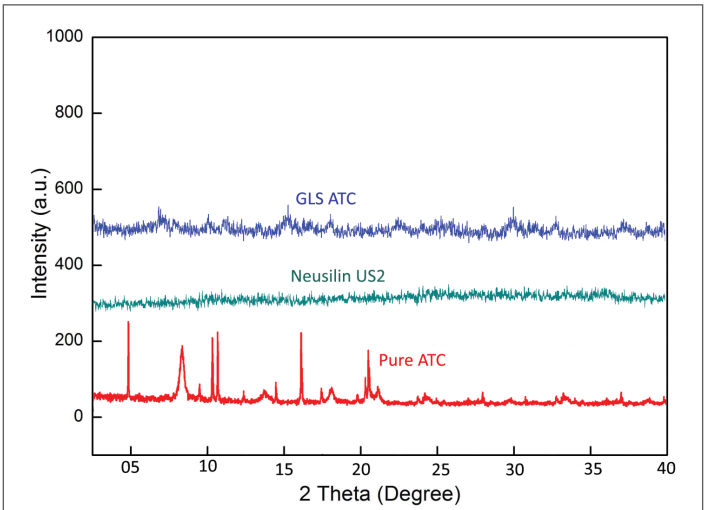


**Figure 4:** XRD spectrum of **(a)** pure drug, **(b)** Neuslin, **(c)** GLS

used alone (GLS4, GLS5, GLS9, GLS10). It can also be further perceived that GLS compacts of ATC containing HPC (LF) & HPMC (K4M) showed 90.3% & 88.3% release after 1 hour. There is also much significant difference in release behavior between GLS and DCT formulations. The DCT formulations have 53.9% & 50.4% release. It is clear from the *in vitro* release data that GLS formulations containing minimum amount of neusilin® US2 has maximum release and dissolution than that of remaining formulations including DCT formulation. The reason behind this is might be due to the more dissolution in case of GLS compacts compare to that of DCT since ATC is in solubilized state in GLS compacts.

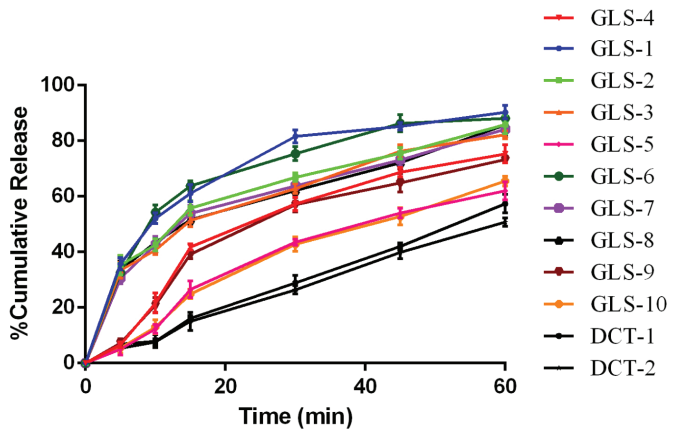


**Figure 5:** Drug release profiles of GLS and DCT Formulations

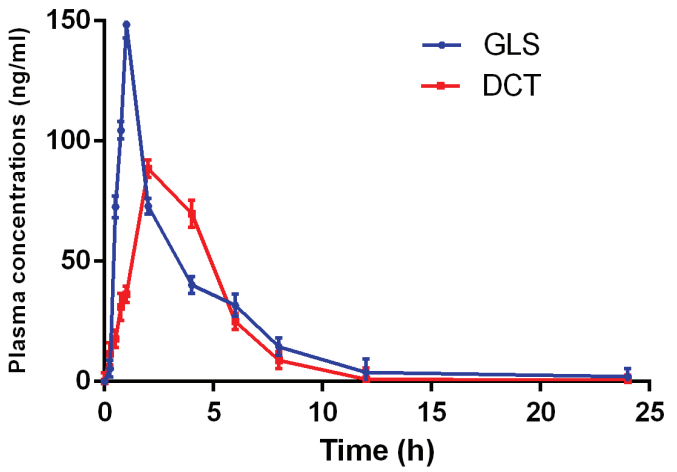


**Figure 6:** Plasma concentration versus time (min) profile for GLS and DCT

***In vivo* bioavailability studies:** The plasma concentration verses time profile of ATC-GLS and DCT compacts were shown in figure 6. GLS produced a higher concentration of ATC in plasma compared to DCT. GLS compacts demonstrate better bioavailability that can be confirmed from pharmacokinetic data shown in table 6. The pharmacokinetic parameter $AUC_{0-t}$, of GLS (476.68 ± 0.30 h.ng/mL) and DCT (396.05 ± 1.19 h.ng/mL), $AUC_{0-\infty}$ of GLS compact (1295.19 ± 0.78 h.ng/mL) and DCT compact (759.23 ± 0.89 h.ng/mL), $C_{max}$ of GLS compact (148.42 ± 1.54 ng/mL) and DCT compact (88.56 ± 0.26 ng/mL) showed significant differences between two formulations. GLS consistently exhibited significant ($p<0.5$) values of above mentioned bioavailability parameters. On the other hand, $K_e$, $t_{1/2}$ and $t_{max}$ of ATC-GL Sare (0.1813 ± 0.003 h, 3.822 ± 0.9 h and 1 ± 0.3 h) and DCT compacts are (0.2438 ± 0.030 h, 2.842 ± 0.3 h and 2 ± 0.2 h), which indicates no significant ($P<0.5$) difference between the formulations regarding $t_{1/2}$ and $t_{max}$. This also exhibited a significantly greater absorption than the DCT compacts. However, crossover and multiple dose studies should be carried out to check the formulation of drug to be used in clinical trials.

## Discussion

It has been shown that the selected carrier (HPC, HPMC) and coating material (Neusilin® US2) strongly affect the liquid adsorption capacity of GLS formulations. DSC and XRD studies were performed for one-month sample to confirm the amorphous nature of the GLS formulation. Replacement of carrier and coating materials by excipients with high specific surface area and good flow property allowed considerably higher liquid adsorption capacity. If Neusilin® US2 is used as carrier and coating material instead of Avicel and Aerosil, the liquid adsorption capacity was increased by a factor of 7. The enhanced drug dissolution rate from GLS was probably due to increase in wetting property and surface area of drug particles available for dissolution. Hence, GLS technique leads to enhancement of dissolution rate and subsequently improves bioavailability of ATC. Poorly water soluble drugs and high doses of drugs can be prepared as GLS by using neusilin® US2 as excipient to reduce the use of high amount of vehicles. Therefore, tablet weight was reduced in comparison with the commonly used carrier and coating materials. Furthermore, neusilin® US2 simplifies the preparation of GLS formulations as it acts both as carrier and coating material. Hence, the GLS approach can be useful for improving both solid state stability and dissolution profile of ATC.

## Conclusion

Gel Liquisolid Compacts of ATC has been successfully prepared and evaluated. This study confirms that ATC prepared by GLS have better dissolution and bioavailability compare to conventional DCT dosage form and therefore GLS could be a promising drug delivery for Atorvastatin calcium.

## Conflict of Interest

The authors declare that there are no conflicts of interest involved in this study.

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