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Liquisolid Tablets Formulation of Atorvastatin Calcium Using Polyethylene Glycol 400 as Solvent and Some Carrier Materials

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ABSTRACT

The dissolution of atorvastatin calcium need to be improved since included BCS Class II drugs with low solubility and high permeability, meaning that the dissolution affects the bioavailability of drugs. This research aimed to develop a formulation of a liquisolid tablet using PEG 400 as a solvent and some carrier materials in various compositions to increase the dissolution of atorvastatin calcium. Different formulations of liquisolid tablets were conducted using different quantities of carrier and coating material for adsorbing liquid solvent to produce a free-flowing and compressible powder. Avicel PH 101, Avicel PH 102, Neusilin US2 were employed as the carrier and Aerosil 200 as the coating material. A disintegrant and lubricant were then added to the formed liquisolid system and compressed into tablets by the direct compressing method. The liquisolid tablets were characterized for their tableting properties and possible drug-excipient interaction by XRD and FTIR analysis. The tableting characteristics of atorvastatin calcium liquisolid tablets were within the acceptable limits criteria. The dissolution of AA4 and NA1 liquisolid tablets was higher compared to marketed tablets. Based on the XRD and FTIR analysis, no interactions between drug and excipient.

Keywords: Atorvastatin calcium, Dissolution, Liquisolid tablets, Polyethylene Glycol 400

INTRODUCTION

Atorvastatin calcium is an oral antihyperlipidemic statin group that belongs to Class II of the Biopharmaceutical Classification System (BCS). The solubility is pH-dependent i.e at pH 1.2 is 0.02mg/mL while increases to 1.23mg/mL at pH 6.8 (Kearney *et al*., 1993). The dose/solubility ratio for atorvastatin calcium is more than 250mL for the 10mg dose at pH 1.2 and dissolves in 250mL at pH 6.8 (Popy *et al*., 2012). The low oral bioavailability of atorvastatin calcium (12-14%) is caused by low aqueous solubility in the gastric and high first-pass metabolism in the liver (Sonje *et al*., 2010). The dissolution profiles of atorvastatin calcium tablets which are currently marketed with generic and branded generic names vary per product and affect their bioavailability profiles (Oishi *et al*., 2011; Popy *et al*., 2012). Several techniques have been developed to increase the dissolution of atorvastatin calcium, including crystal modification (Gozali *et al*., 2014; Wicaksono *et al*., 2017[a]), co-grinding (Prabhu and Patravale, 2015), solid dispersion (Gozali *et al*., 2015; Rodde *et al*., 2014; Panghal *et al*., 2014; Khan and Dehghan, 2011), lipid-based formulations such as micro and nanoemulsions (Chouksey *et al*., 2011; Snela *et al*., 2019; Kadu *et al*., 2011), and liquisolid technique (Gubbi and Jarag, 2010; Baskaran *et al*., 2016). Among all these methods the most promising method for enhancing dissolution for poorly soluble drugs is the formulation of liquisolid system. This technique is technically applicable at relatively low costs because it does not require a large amount of energy (e.g. for heating) and the absence of a volatile organic solvent. As a result, this technique can be implemented on an industrial scale (Lu *et al*., 2017; Yadav and Yadav, 2009)

Liquisolid technique is a technique of manufacturing tablets by dissolving their active ingredients in non-volatile solvents in order to be developed into suspension or liquid form and subsequently converted into a powder that is free-flowing, non-adherent, and readily compressible, with the addition of carriers and coatings (Spireas, 2002).

Table I. Composition of liquisolid tablets with 10mg of atorvastatin calcium.

Code	Carrier- coating	% Cd (w/w)	Lf	W	R	Q	q	SSG	Tablet weight (g)
AA1	Avicel PH 101-Aerosil	10	0.123	100	20	800	40	94	1.043
AA2		20	0.123	50	20	400	20	47	0.522
AA3		30	0.123	33.3	20	280	14	33	0.363
AA4	Avicel PH 102-Aerosil	10	0.123	100	20	800	40	94	1.043
AA5		20	0.123	50	20	400	20	47	0.522
AA6		30	0.123	33.3	20	280	14	33	0.363
NA1	Neusilin-Aerosil	10	0.334	100	20	300	15	21	0.438
NA2		15	0.334	66.7	20	200	10	14	0.294
NA3		20	0.334	50	20	150	7.5	11	0.221

%Cd: amount of active substance in non-volatile solvent (expressed in percentage); Lf: liquid load factor (W/Q); W: weight of active substance and non-volatile solvent; R: excipient ratio (Q/q); Q: carrier; q: coating

Some of the non-volatile solvents are propylene glycol, polyethylene glycol (PEG) 200 and 400, glycerin, and polysorbate 80. PEG 400 was selected to prepare liquid medication because the solubility of atorvastatin calcium in PEG 400 was 7.32% w/w (Gubbi and Jarag, 2010). In this work, the excipients like microcrystalline cellulose (PH 101 and 102) and Neusilin® are used as carrier materials, Aerosil® as a coating material, and sodium starch glycolate as superdisintegrant. The use of Neusilin® with a large surface specific area and high porosity cause high adsorption capacity that is proven to be effective in maintaining drugs in the liquid state, thus increasing the dissolution (Vranikova and Gajdziok, 2013; Vraníková *et al*., 2015). The purpose of this research was to enhance the dissolution of atorvastatin calcium tablets using the liquisolid technique.

MATERIAL AND METHODS

Atorvastatin calcium trihydrate was obtained as a gift sample from Etercon Pharma, Polyethylene glycol 400, Avicel PH 101, Avicel PH 102, Wacker HDK, Sodium starch glycolate and Mg stearate (Bratachem), Neusilin US2 (Megasetia), NaOH, and KH_2PO_4 (Merck). Branded generic tablets 10mg (AT®), from a local pharmacy.

Preparation for liquisolid tablets

The mathematical model developed by Spireas (2002) was used to calculate the amount of material used for each liquisolid tablet formula

which contains 10mg of atorvastatin calcium, (Table I). Atorvastatin calcium was dispersed in PEG 400 with continuous mixing using pestle and mortar to obtain liquid medication. The binary mixture of carrier and coating material at a ratio 20:1 was added to the admixture of drug and solvent, blended at an approximate mixing rate to obtain homogeneously distribute the drug. The admixture is evenly spread as a uniform layer to allow drug dispersion to be adsorbed in the interior of powder particles. Dried with a binary mixture of a carrier and a coating made at a ratio of 20: 1. A precompression analysis was carried out by testing the flowability to obtain the parameters of the repose angle and flow time. Besides, bulk and tapped density were also tested to determine the compressibility index. Subsequently, Sodium Starch Glycolate and Mg Stearate 1%, functioning as a disintegrant, glidant, and a lubricant respectively, were added to the liquisolid powder that satisfied the criteria of good flowability before it was compressed into tablets.

Evaluation of liquisolid tablets

Weight variation

For each formulation, 20 tablets were selected randomly and weighed individually on an analytical balance. The average weight and standard deviation for each tablet formulation were calculated. Not more than two of the individual tablet weight deviate from the average weight by more than the percentage given in the USP Pharmacopeia, and none deviates by more than twice that percentage.

Drug content uniformity

In each formulation, 10 randomly selected tablets were evaluated for their drug content. The individual tablet was powdered, transferred into a

beaker containing 100 mL phosphate buffer pH 6.8. The solution was stirred for 1h, filtered, and the drug content was estimated spectrophotometrically (Shimadzu UV-1800 240V) using maximum wavelength at 24.6nm. The atorvastatin calcium concentration was determined based on the calibration curve previously built-in range 6-16µg/mL. The percentage of single-tablet drug content was determined and evaluated to the theoretical drug content (10mg).

Hardness and friability

Five tablets were taken randomly from the whole liquisolid systems and tested for their hardness with a hardness tester as to calculate the average values. On the other hand, friability testing was conducted using a friability tester according to USP regulations, and the testing was repeated 3 times. The percentage of weight loss was expressed as the friability value.

Disintegration time

The disintegration time of the liquisolid tablets was tested according to the testing procedure for uncoated tablets as outlined in USP regulations, and the test was performed 3 times. Based on the tests conducted, the disintegration time of those tablets was no longer than 15min.

In vitro dissolution

The dissolution test was conducted using a type II dissolution test apparatus (Electrolab TDT-08L). The dissolution study was carried out in 900mL of phosphate buffer at pH 6.8 with a rotation speed of 75rpm and maintained at 37±0.5℃ according to USP. The aliquot of 5mL samples was withdrawn at 5, 15, 30, 45, and 60min time intervals, respectively. Afterward, each sample was replaced with a fresh buffer medium in an equal quantity to maintain the sink conditions. The withdrawn sample was analyzed spectrophotometrically at 240.6nm. Six tablets from each liquisolid formulation were selected randomly for dissolution testing. The results were presented as mean values and standard deviations.

X-ray powder diffraction

The physical form of atorvastatin calcium in the liquisolid tablet was characterized using X-ray powder diffraction. The tablet was crushed to a fine powder and packed into a sample holder. The sample scanned using the instrument Shimadzu XRD-7000 with Cu as a target. The sample was analyzed in a 2θ angle range of 10-70° with scanning step time 0.5s. The operating voltage and current settings were 400kV and 300mA respectively. The X-ray diffractogram of major excipient and pure atorvastatin calcium powder was also obtained in the same way.

Fourier Transform Infra-red spectrum analysis

The spectrum of liquisolid tablet, major excipient, and pure atorvastatin calcium powder were recorded using a Perkin Elmer FTIR instrument with software version 10.4 by the KBr method. A baseline correction was made using dried potassium bromide. The spectrum were scanned in the wavelength region of 4000cm^{-1} to 400cm^{-1}.

RESULT AND DISCUSSION

Evaluation of prepared liquisolid powders

The flow properties of the liquisolid powder are shown by different flow parameters. The results for flow rate, angle of repose, compressibility index (Table II). The obtained results suggest that all parameters were within the limits, and considered acceptable flowability. The liquisolid system of atorvastatin calcium was made using non-volatile solvent PEG 400 since it is soluble in that solvent. The carriers used materials like microcrystalline cellulose (Avicel PH 101 and PH 102) and magnesium aluminum metasilicate (Neusilin US2), which can adsorb solvent PEG 400, but still, have good flowability. About the coating, colloidal silicon dioxide (Aerosil) functioned as the material, as it is voluminous, thus appearing to be effective in adsorbing the solvent being used. These liquisolid powder can be effectively converted into liquisolid dosage form.

Characteristic of liquisolid tablets

The liquisolid tablets of atorvastatin calcium were characterized for average weight, drug content uniformity, hardness, friability, disintegration time, and obtained results (Table III). The tablet weight is found uniform due to a uniform size powder blend. A precise dose of drugs from one tablet to another is a basic quality for all pharmaceutical dosage forms. All of the liquisolid tablets contained atorvastatin calcium, with a range of 97-104%. As suggested by the compendia, 10mg atorvastatin tablets should meet the uniformity of the active substance in the range 94.5-105% according to USP.

Table II. Flow properties of atorvastatin calcium liquisolid system

Code	Flow rate (g/s)	Angle of repose (°)	Carr's compressibility index
AA1	49.85±1.04	24.42±1.00	13.92±1.57
AA2	42.56±1.54	21.35±1.00	18.37±0.58
AA3	26.57±0.22	17.68±1.00	17.67±0.58
AA4	28.53±0.79	22.36±1.09	14.17±0.38
AA5	35.36±1.52	19.51±0.21	16.53±0.62
AA6	26.43±0.46	17.40±0.71	18.07±0.19
NA1	16.95±0.80	5.56±0.54	15.33±1.15
NA2	15.38±0.80	7.72±0.21	15.00±1.00
NA3	15.87±0.66	9.83±1.51	14.33±1.53

Table III. Characteristics of atorvastatin calcium's liquisolid tablets

Code	Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Disintegration Time (minute)	Active ingredients (%)
AA1	1033.76±23.67	6.28±0.23	0.03±0.00	3.25±0.01	102.11
AA2	525.88±8.75	6.14±0.34	0.09±0.00	2.63±0.15	103.94
AA3	343.65±4.06	5.91±0.27	0.05±0.00	2.12±0.02	99.71
AA4	1066.67±9.66	6.93±0.35	0.02±0.00	1.78±0.39	99.28
AA5	531.44±3.51	5.01±0.16	0.03±0.01	2.04±0.05	101.86
AA6	352.74±2.17	6.71±0.14	0.06±0.04	3.09±1.02	104.00
NA1	439.70±1.72	5.25±0.55	0.61±0.04	6.39±0.03	97.68
NA2	292.25±1.59	5.07±0.44	0.51±0.11	4.08±0.07	103.51
NA3	221.20±2.02	4.92±0.53	0.38±0.24	2.23±0.02	102.97

All the prepared formulation had hardness in the range of 4-7kg/cm^2 and friability below 1%. No tablet was broken or deformed. Since all prepared formulation met the standard criteria of hardness and friability, they are expected to show acceptable toughness and withstand abrasion during handling, packaging, and shipment. All the prepared formulation had a disintegration time below 15min (1-6min). Faster disintegration time indicates rapid release rates.

The tablet's characteristic data indicate that all the parameters were within the limits. The fulfillment of the liquisolid tablet's parameters was adherent to the fact that the formation of the liquisolid system was processed according to the tablet manufacturing procedure by the direct compressing method and using materials with good compressibility and compatibility. As the carriers as well as the main components in the liquisolid tablets, Microcrystalline cellulose (Avicel PH) and Neusilin are best known to have good characteristics of tablet forming materials. Coupled with Aerosil as the coating material, these two materials produced liquisolid powder that can be used as a free-flowing and easily compressible. The use of sodium starch glycolate as a disintegrant made the liquisolid tablets disintegrate faster, while magnesium stearate used as glidant and lubricant led to the formation of tablets with relatively low friability.

***In vitro* dissolution studies**

The dissolution of the liquisolid tablets was carried out in a medium of phosphate buffer pH 6.8, following that as an active ingredient, atorvastatin calcium is more soluble in a medium with that pH than with lower pH. The dissolution profiles of the liquisolid tablets and the branded tablet of atorvastatin calcium (AT®) available in the market (Figure 1). The percentage drug release at the 30^{th} min was 83.66% for AA4 and 84.61% for NA1. Meanwhile, at 30 min the percentage drug release of AT® was 62.07%. In the liquisolid tablets, the drug surface available for dissolution since a suspension of the drug in a non-volatile solvent is used for the preparation of this system. The presence of PEG 400 as a non-volatile solvent, which dispersed the active substance into finer and more soluble particles. After disintegration in the dissolving medium, the liquisolid particles of the

drug suspended and dispersed molecularly. The surface area of the particle drug is much greater for dissolution.

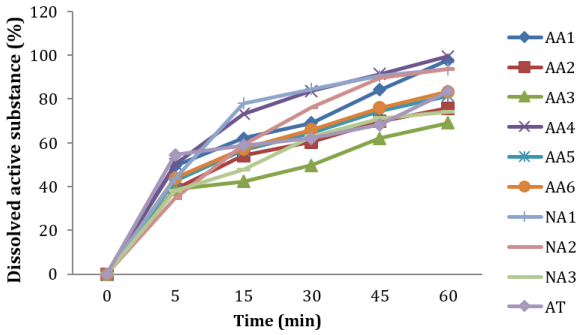

Figure 1. Dissolution profiles of atorvastatin calcium's liquisolid tablets and a branded tablet available on the market (AT®)

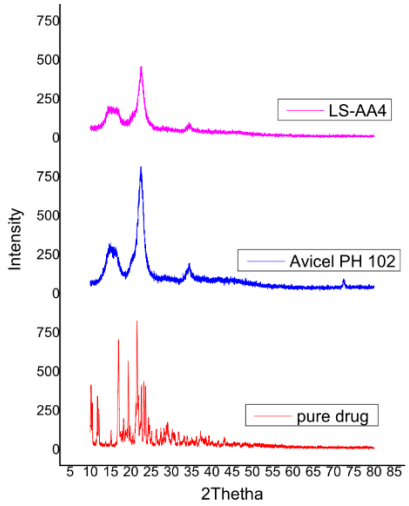

Figure 2. XRD diffractogram of the liquisolid tablet AA4, Avicel PH 102, and pure drug atorvastatin calcium powder.

X-ray diffraction analysis

Polymorphic changes in the active pharmaceutical ingredient are important since they might affect the dissolution and in line bioavailability. The polymorphic changes of atorvastatin calcium in liquisolid tablet is important to study to know there were changes compared to the initial powder. The results of the XRD diffractogram (Figure 2). The diffraction pattern of atorvastatin calcium showed numerous distinctive peaks indicates that the drug is in a highly crystalline state. Avicel PH 102 as a major excipient in AA4 tablet has a sharp diffraction peak at 22.37 (2θ). Whereas the liquisolid powder showed diffraction peaks at 22,40 (2θ) proof that the excipient stays in its state. However, the diffraction pattern of atorvastatin calcium in the liquisolid tablet showed the disappearance of sharp distinctive peaks indicates that the drug was solubilized in liquisolid formulation or entirely converted into an amorphous form. No crystalline state in the liquisolid system is perhaps the result of solubilization in the non-volatile solvent as a vehicle that is possibly adsorbed on the carrier and coating material. The amophization or solubilization of atorvastatin calcium may result in increased dissolution.

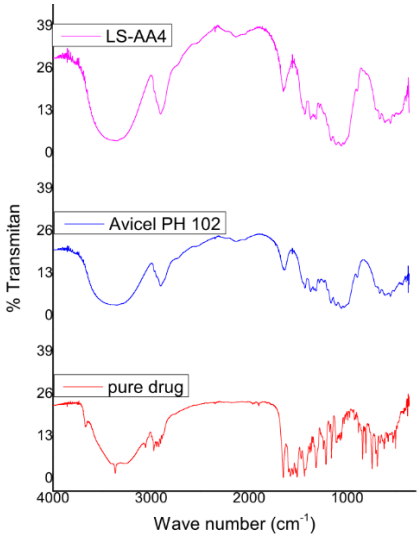

Figure 3. IR spectrum of the liquisolid tablet AA4, Avicel PH 102, and pure drug atorvastatin calcium powder.

IR spectra analysis

The IR spectral changes in formulation showed the chemical interaction between the drug and excipients. The spectral changes of atorvastatin calcium in liquisolid tablets are important to study to know there were changes compared to the initial powder. The characterization results by the FTIR spectroscopy (Figure 3). The characteristic peaks of N-H stretching and aromatic C=O stretching at 3365.08cm-1 and 1651.26cm-1 respectively. As seen in the IR spectrum, it is clear that the pure atorvastatin calcium powder used in the liquisolid tablet showed a typical functional group of atorvastatin calcium. The pattern of the liquisolid tablet AA4 showed the same characteristic peaks at 3350.3 and 1647.47 cm-1 respectively, undergoes no chemical reaction with any of the excipients used in the preparation liquisolid formulation.

There is a reduction in the intensity of the characteristic of absorption peaks of atorvastatin calcium in liquisolid tablets which might be attributed to the hydrogen bonding interaction of the amino and the carboxyl group of atorvastatin calcium with the hydroxyl group of PEG 400 as a vehicle. This resulted in drug dissolution enhancement as shown by dissolution data. The characterization results of the FTIR were in line with those of the XRD. It can be concluded that the enhancement in dissolution due to increasing wetting.

CONCLUSION

The results indicated that the liquisolid tablets of atorvastatin calcium can be prepared using some carrier material and non-volatile solvent like PEG 400. The liquisolid powder showed good flowability. The liquisolid tablets meet the criteria of hardness, friability, weight variation, and disintegration time. The dissolution testing showed increased drug release compared to the marketed product. XRD and IR spectrum suggest that there were no chemical interactions between the drug and excipients. The enhanced dissolution may be due to improved wetting and greater surface area of particles. The liquisolid formulation can then be developed as an alternative for the production of atorvastatin calcium tablets in the pharmaceutical industry.

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