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Original Article

Comparative Studies for Enhancement of the Dissolution Profile of Pitavastatin

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Abstract:
The main objective of the present study is to enhance the solubility, dissolution rate, bioavailability of water insoluble drug pitavastatin by liquisolid technology and solid dispersions. The liquisolid compacts were prepared by different ratios of polyethylene glycol 400 as a non volatile liquid vehicle, micro crystalline cellulose used as carrier material and colloidal silicon dioxide as coating material. Solid dispersions were prepared by different ratios (1:2, 1:4, 1:6, 1:8) of poly ethylene glycol 6000 as carrier. All these formulations were characterized for different physical parameters to comply with pharmacopoeial limits. *Invitro* dissolution profiles of liquisolid formulation, solid dispersions were studied and compared with that of pure pitavastatin tablet formulation in 0.1N HCL. It was found that liquisolid formulation tablets formulated with microcrystalline cellulose showed percentage drug release 63±2.42 at 5min and they showed significant higher drug release rates than pure drug 13±1.44 due to increase in wetting properties and surface of drug available for dissolution. FTIR spectral studies showed that there is no interaction between the drug and excipients.

Key words:
Liquisolid technologies, solid dispersions, pitavastatin, PEG6000.

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1. INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. As a result, patient compliance and drug treatment is typically more effective with orally administrated medications as compared with other routes of administration. But the poor absorption of water insoluble drugs is the major problem for pharmaceutical formulators to prepare in the form of tablets.

According to IUPAC, solubility may be defined as "The analytical composition of a saturated solution, expressed in terms of the proportion of a designated solute in a designated solvent, is the solubility of that solute. The solubility may be expressed as a concentration, molality, mole fraction, mole ratio, etc. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. The solubility phenomenon is one of the least understood of all the physicochemical properties particularly with reference to pharmaceutical solutions. Solubility behavior of the drug is one of the key determinants for its oral bioavailability. Solubility problem is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products, since nearly half of the active substances being either insoluble or poorly soluble in water.[1]

2. MATERIALS AND METHOD [2-4]

Preparation of standard curve

Standard calibration curve of pitavastatin in 0.1 N HCl were prepared. First dissolve 100mg of pure drug in 100ml 0.1 N HCl buffer this is primary stock solution. From the above primary stock solution pipette out 10ml of solution and again make up to 100ml this is secondary stock solution. From this secondary stock solution different concentrations of pitavastatin (3, 6, 9, 12, 15,18µg/mL) in 0.1 N HCl buffer were prepared & absorbance of these solutions measured at 245 nm by spectrophotometrically (Shimazdu-1700, UV Visible spectrophotometer, Shimadzu Corp, Kyoto, Japan) using 0.1 N HCl as reference solution. [5]

λmax determination

pitavastatin λmax was determined by using 0.1N HCl medium. First dissolve 100mg of pure drug in 100ml 0.1 N HCl this is primary stock solution. From this 10µg/mL solution was prepared by using 0.1 N HCl. 10µg/mL solution absorbance was measured at 200-400 nm range by spectrophotometrically (Shimazdu-1700, UV Visible spectrophotometer, Shimadzu Corp, Kyoto, Japan) using 0.1 N HCl as reference solution.

Drug excipients compatibility

Fourier transform infrared (FTIR) spectroscopy studies

FTIR spectra of pure pitavastatin were obtained using a FTIR spectrophotometer according to the potassium bromide disk method. Analyses were performed at room temperature. The disks were scanned over a wave number range of 4000-400 cm^{-1}.

Solubility studies

For the selection of the best non volatile solvent solubility studies are used, in this procedure pure drug was dissolved in two different non volatile solvents i.e., PEG, PG and in 0.1N HCL 6.8 P^H buffer and distilled water. Excess amount of pure drug was added to the above solvents. From this obtained saturation solutions were shaken on rotator shaker for 48hrs at 25^oc under constant vibration. After 48 hrs period the saturated solution was filtered through a filter paper and analysed by UVspectrophotometer.

Calculation of loading factor (L_f) for liquisolid compacts

Loading factors were calculated for different carriers, using various solvents. By using Lf=w/q (w: amt of liquid medication and Q: amt of carrier material), drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. The results showed that the viscosity of solvent is higher, lower amount of carrier and coating materials are needed to produce flowable powder.

Table 1: Composition of pitavastatin liquisolid compacts

Formulation	Concentration of pitavastatin in PEG400 solvent (%)	Excipients ratio R=carrier/ coating R=(Q/q)	Liquid load factor L_f= W/Q	Avicel Q= W/L_f	Colloidal silicon dioxide q =Q/R	Per/unit tablet weight (mg)
F1	4	37.5	0.106	75.0	2	118.5
F2	4	33.5	0.238	67.0	2	106.7
F3	4	29.5	0.406	59.0	2	94.91
F4	4	25.5	0.627	51.0	2	83.13

Preparation of liquisolid compacts

According to solubility studies of Pitavastatin, desired quantities of drug was dissolved in PEG 400 and then stirred constantly, until a homogenous drug solution was obtained. A binary mixture of carrier and coating materials were selected. [6, 7]

Mixing: The mixing procedure was conducted in three stages. During the first stage, the obtained homogenous drug solution and micro crystalline cellulose was blended at an approximate mixing rate of one rotation/sec for approximately one minute in order to evenly distribute the liquid medication into the powder.

In the second mixing stage, calculated quantities of colloidal silica was added to the system and blended for 2 min.

This admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5 min to allow the drug solution to be absorbed in interior of the powder particles.

In the third stage, the powder was scraped off the mortar surfaces by means of a spatula and then obtained powder was compressed in to liquisolid compacts. [8, 9]

- Similar formulations were prepared by using varying the ratios of PEG 400.

Table 2: Formulation of pitavastatin liquisolid compacts

Ingredient	F 1	F2	F3	F4
Pitavastatin	4	4	4	4
PEG 400	8	16	24	32
MCC	75	67	59	51
Sodium Starch glycolate	5	5	5	5
Colloidal silicon dioxide	2	2	2	2
$Caco_3$	4	4	4	4
Talc	2	2	2	2
Total tablet wt (mg)	100	100	100	100

Preparation of solid dispersions

In hot melt method, the carrier such as PEG 6000 was melted in the china dish at about 60^0 C.

The drug was incorporated into the melted carrier with stirring to ensure homogeneity.

The mixture was heated until a clear homogeneous melt was obtained followed by flash cooling on an ice bath.

It was then scrapped dried and was passed through sieve no. 60.

To the obtained powder MCC, crosspovidone, calcium carbonate, magnesium stearate and talc were added and undergone for compression.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure of the flow ability of powder/granules. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Angle of repose was calculated from the average radius using the following formula.

$\theta = Tan^{-1} (h/r)$

Where,

θ = Angle of repose

h = Height of the pile

r = Average radius of the powder cone

Table 3: Pharmacopoeial specifications for Angle of repose

Angle of repose	Type of flow
<25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

Higher the angle of repose the rougher and more irregular is the surface of the particles.

Bulk and Tapped Density

An accurately weighed quantity of the granules (w) that was previously passed through # 40 was carefully poured into the graduated cylinder and the volume (vo) was measured.[68] The graduated measuring cylinder was tapped for 100 times and after that, the volume (vf) was measured and continued the operation till the two consecutive readings were equal. Bulk density and tapped density determines the floating capacity of the formulation. The bulk density and tapped density were calculated using the formulas below

Bulk density = w/v_o

Tapped density=w/v_f

Where w - Weight of powder

v_o - Initial volume.

v_f - Final volume.

Dissolution Studies

Drug release from pitavastatin tablets was determined by using United States Pharmacopoeia (USP) type I (Basket) dissolution apparatus.

Dissolution medium : 0.1N HCl

Volume : 900 ml

Temperature : $37^0C \pm 0.5^0C$

Speed : 100 rpm.

5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 15, 20, 25 and 30 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV-spectrophotometer. The concentration was calculated using standard calibration curve.

Stability Studies

According to WHO and ICH guidelines the stability of the tablets was studied at 40°C± 2°C with RH 75%± 5%. The tablets were weighed and wrapped in aluminum foil and placed in petriplates. These containers were stored for a period of three months. All the tablets were observed for any physical changes, such as color, appearance, flexibility and texture. The drug content and *in vitro* drug release was estimated at an interval of each month. [10, 11]

1. RESULTS AND DISCUSSON

Results of degradation studies

Pitavastatin λmax was determined by using 0.1N HCl medium. First dissolve 100mg of pure drug in 100ml 0.1 N HCl this is primary stock solution. From this 10µg/mL solution was prepared by using 0.1 N HCl. 10µg/mL solution absorbance was measured at 200-400 nm range by spectrophotometrically (Shimazdu-1700, UV Visible spectrophotometer, Shimadzu Corp,

pitavastatin λ max was found to be 245nm

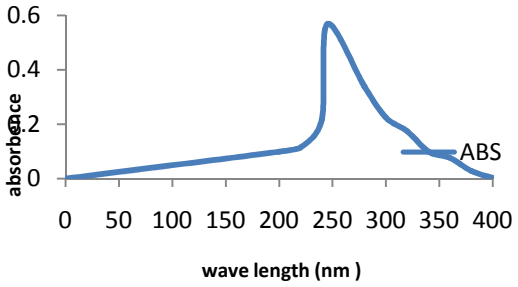

Fig 1: Spectrum of pitavastatin

Drug Excipients compatibility studies

Fourier transform infrared (FTIR) spectroscopy studies:

The pure drug, the optimized pitavastatin formulations and their placebo formulations were subjected to FTIR studies.

The IR absorption spectra of the pure drug was taken in the range of 4000-400 cm-1 using KBr disc method .The major peaks were reported for evaluation of purity. The results were showed that there is no interaction between the drug and excipients.

Solubility studies:

The solubility of pitavastatin were done in different non volatile solvents i.e., PEG400, PG, 0.1 N HCl, 6.8 pH Phosphate Buffer and distilled water was indicated in table 8.2.

- The highest solubility was found in PEG400 compared to other non volatile solvents and buffers.

Table 3: solubility studies of pitavastatin in various solvents

Sl.No	Solvent	Solubility(mg/ml)
1	Propylene glycol	0.5188±0.03
2	Poly ethylene glycol -400	72.50±2.34
3	Poly ethylene glycol -600	5.56±0.9
4	0.1 N Hcl	2.52±0.02
5	6.8 P^H Buffer	1.06±0.03
6	7.4 p^H Buffer	0.008±0.02
7	Distilled water	0.0005±0.01

Table 4 : Pre compression studies of solid dispersions powder blend

Formulation	Angle of repose	Bulk density (gm/cc^3)	Tapped density (gm/cc^3)	Carr's index (%)	Hausner's ratio
F5	27.30±1.22	0.315±0.01	0.656±0.01	17.8±0.32	1.26±0.04
F6	30.25±1.36	0.446±0.01	0.633±0.01	14.2±0.52	1.26±0.03
F7	29.87±0.82	0.386±0.01	0.682 ±0.01	17.6±0.40	1.30±0.04
F8	30.72±1.52	0.456±0.01	0.456 ±0.01	15.5±0.46	1.18±0.03

All values were expressed as mean ± S.D; Number of trials (n) = 3

The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped), Hausner's ratio, compressibility index and their values were shown in Table 8.3 and 8.4.The apparent bulk density and tapped bulk density values ranged from 0.315±0.01 to 0.456±0.01gm/cm^2 and 0.461±0.01 to 0.682±0.01 gm/cm^2 respectively. The results of angle of repose and Hausner's ratio and compressibility index (%) ranged from 27.72±1.22 to 30.72±1.52 and 1.18±0.03 to 1.30±0.04 and 14.2±0.52 to 17.8±0.362 respectively.

pitavastatin pure drug angle of repose ratio, (%)apparent bulk density , tapped bulk density compressibility index and Hausner's values were shown in Table 8.5 and their values are 29.87±1.32, 0.315±0.01, 0.621±0.01, 14.6±0.40, 1.18±0.04 respectively. The results of angle of repose (< 40) and compressibility index (< 22) indicates fair to passable flow properties of the powder mixture.

Post compression evaluation parameters:

Table 5: Post Compression evaluation studies of pitavastatin solid dispersions tablets

Formulation Code	*Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	**Friability (%)	Content uniformity (%)	Disintegration time(sec)

F1	98±1.21	2.8±0.35	2.29±0.12	0.47	99.2±1.76	121±0.28
F2	99±1.5	3.2±0.32	2.24±0.09	0.62	95.9±0.61	136±1.24
F3	96±2.8	3.1±0.42	2.30±0.61	0.64	98.2±0.70	162±1.88
F4	100±1.6	3.5±0.61	2.30±0.09	0.48	97.2±0.28	125±1.05

Formulation (F9) is prepared by pure drug with excipients. Dissolution studies were carried out and the results were shown in table

Thus, it was observed that liquisolid compacts of PEG 400 in 1:6 drug to carrier ratio had maximum solubility of pitavastatin with enhanced dissolution rate compared to solid dispersions and pure drug. The formulation rate of PEG 400 in the ratio of 1:6 had increased the solubility almost 6 fold compared to that of pure drug.

The mechanisms involved are solubilization and improved wetting of the drug in PEG 400 rich microenvironment formed at the surface of drug after the dissolution of the polymer. Further increase in polymer content was accompanied by a decrease in drug dissolution. This can be attributed to a viscosity delaying effect on drug dissolution caused by higher polymer

Stability studies:

The stability of the tablets was studied at 40°C± 2°C with RH 75%± 5%. The tablets were weighed and wrapped in aluminum foil and placed in Petri plates. These containers were stored for a period of three months. All the tablets were observed for any physical changes, such as color, appearance, flexibility, or texture. The drug content and *in vitro* drug release was estimated at an interval of each month.

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