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Research Article

FORMULATION AND *IN VITRO*/IN VIVO EVALUATION OF DRIED NANOSUSPENSIONS OF PITAVASTATIN

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A B S T R A C T

The present study is aimed to formulate and evaluate Pitavastatin oral nanosuspension to improve the bioavailability of the drug with varying concentrations of surfactants and co surfactants. Nanosuspension containing the drug was prepared by precipitation method using combinations of polymers (such as tween 80, tween 20, soluplus, PEG 400 and methanol) in to 10 formulations F1to F10. The developed formulations were characterized for particle size and total drug content, SEM, Zeta Potential and FTIR. The *in vitro* drug release studies and *in vitro* drug release kinetics were performed for optimized formulations. FTIR studies revealed that drug is compatible with the excipients. The particle size of optimized formulation was found to be 98nm and the zeta potential was found to be 20mV and concluded that the system had sufficient stability. The *in vitro* drug release was found within their acceptable ranges. The rate of dissolution of best batch was enhanced to 99.98% in 15mins. Stability studies proved that nanosuspensions were more stable with no significant changes in particle size distribution. Thus the formulated oral nanosuspension of Pitavastatin offers a superior conventional dosage forms for drug release.

INTRODUCTION

Drug delivery system is the device that enables the introduction of the therapeutic substance in the body and improves it s efficacy and safety by controlling the rate, time, place release of the body [1]. It is typically concerned with the quantity and duration of the drug presence [2]. Improved method of the drug delivery system would be advantageous and more convenient to maintain a dosing frequency. The problem associated with poorly soluble drugs is too low bioavailability. [3] Oral drug delivery system has been known for decades as the most widely utilized route of administration among all route of administration that have been employed for the systemic delivery of drug via and various pharmaceutical products of different dosage forms compared to conventional dosage forms oral liquid drug delivery system offers unique advantage to patient compliance. Conventional drug delivery is convenient and non invasive unit dosage form with higher compliance. The challenges for oral liquid dosage forms are they have better dose adaptability, rapid absorption from the stomach and intestine compare d to conventional dosage forms and stability of drugs in li quid form [4].

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It provides benefits to BCS Class II, III, IV candidates, which exhibit poor aqueous, or lipid solubility and also drugs having a log P value greater than 2 [5]. In the process of overcoming issues involving solubility and pharmacokinetic benefits of the drugs, nano suspensions have revealed potential advantage to tackle the problem. A nanosuspension is a submicron colloid al dispersion of drug particles. The dispersion medium can be water, aqueous solutions or non-aqueous media. Nanosuspension is also called as (nanocrystals) [6] are nano scopic crystals of the compound wit h the particle size below 1μm. Nanotechnology can be used to improve the solubility as well as the bio avail ability of poorly soluble drugs. Reduction of the particles to nanometer range leads to the enhanced dissolution rate and increased surface area. Surfactants and polymeric stabilizers are used for the stabilization of the system. A nano sized particle increases dissolution velocity and saturation solubility because of pressure effect [7]. Drugs encapsulated with nanosuspensions exist in pharmaceutically accepted crystalline or amorphous state. Nanosuspensions can be given by any route [8]. Oral administration of the nano suspension provides rapid onset and improved bioavailability, possibility of large-scale production for the introduction of delivery system to the market [9].

The present study is aimed to formulate and evaluate Pitavastatin oral nanosuspension to improve the bioavailability

of the drug with varying concentrations of surfactants and co surfactants.

MATERIALS AND METHODS

Materials

Pitavastatin drug was procured by Spectrum labs, Hyderabad as a gift sample. PEG 4000, soluplus and Mithanol was procured form Nihar chemicals Ltd. Tween 20, Tween 80 and water was procured from SD labs and all other excipients used were of analytical grade.

Methods

Pre-formulation studies: The overall objective of the pre-formulation is to generate information useful to the formulator in developing stable and bio available dosage forms which can be mass produced.

Organoleptic properties: The colour, odour and taste of the drug were recorded using descriptive terminology and found to be white to off-white crystalline powder, tasteless and odourless.

Melting Point: The temperature at which the first particle of the substance completely melts is regarded as melting point of the substance. The temperature at which the first particle starts to melt and last particle completely melts is regarded as the range of melting point. Melting point of the drug was determined by capillary tube method and found to be 156-160^{o}C.

Drug-Excipient Interactions Studies*:* There is always possibility of drug excipient interaction in any formulation due to their intimate contact. The technique employed in this study is IR spectroscopy. IR spectroscopy is one of the most powerful analytical techniques, which offers possibility of chemical identification. The IR spectra of Pitavastatin, Tween 80, PEG-400, Tween 20, PG, Soluplus Methanol and formulations (F_1 to F_{12}) were obtained by KBr pellet method.(Perkin-Elmer series 1615 FTIR Spectrometer). [10, 11]

Determination of absorption maximum (λmax)

The wavelength at which maximum absorption of radiation takes place is called as λmax. This λmax is characteristic or unique for every substance and useful in identifying the substance. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Most drugs absorb radiation in ultraviolet region (190-390nm), as they are aromatic or contain double bonds.

Accurately weighed 100mg of Pitavastatin was dissolved in 0.1N Hcl buffer taken in a clean 100ml volumetric flask. The volume was made up to 100ml with the same which will give stock solution-I with concentration 1000µg/ml. From the stock solution-I, 5ml was pipette out in 50ml volumetric flask. The volume was made up to 50ml using 0.1N Hcl buffer to obtain stock solution-II with a concentration 100µg/ml. From stock solution-II, 1ml was pipette out in 10ml volumetric flask. The volume was made up to 10ml using 0.1N Hcl buffer to get a concentration of 10µg/ml. This solution was then scanned at 200-400nm in UV-Visible double beam spectrophotometer to attain the absorption maximum (λ-max).

Preparation of Calibration Curve of Pitavastatin Procedure for Standard Curve in methanol

10 mg of' Pitavastatin was dissolved in 10 ml of methanol by slight shaking (1000µg/ml). 1 ml of this solution was taken and made up to 10 ml with methanol, which gives 40µg/ml concentration (stock solution). From the stock solution, concentrations of 4, 8, 12, 16 and 10µg/m1 in methanol were prepared. The absorbances of diluted solutions were measured at 250nm and a standard plot was drawn using the data obtained.

Procedure for standard curve in 0.1NHCL

10 mg of Pitavastatin was dissolved in 10 ml of pH 0.1N Hcl by slight shaking (1000μg/ml). 1 ml of this solution was taken and made up to 20 ml with 0.1NHcl, which gives 40 μg/ ml concentration (stock solution). From the stock solution, concentrations of 4, 8, 12, 16 and 10µg/ml in 0.1NHcl were prepared. The absorbance of diluted solutions was measured at 250 nm and a standard plot was drawn using the data obtained.

Method of Preparation of Nanosuspension

Preparation: Nano suspension precipitation method has been employed to prepare oral Nanosuspension of Pitavastatin using sodium lauryl sulphate, PVP K-30, Polaxomer (188) Methanol, as polymers.

Procedure: All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula (Table-1). The required amount of polymer (carrier) and stabilizer were accurately weighted and added to required measure of H2O in a beaker. The drug is dissolved in solvent (methanol) and added to the above mixture in a drop wise manner using a syringe while on slow stirring. Magnetic stirring for 1 hour then sonication for 1 hour then check for absorbance and calculated amount of drug released.

Table 1 Composition of Nano suspension of Pitavastatin

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Pitavastatin (mg)	2	2	2	2	2	2	2	2	2	2
Tween 20 (ml)	2	2	2	2	2	2	-	-	-	-
Tween 80 (ml)	-	-	-	-	-	-	2	2	2	2
Soluplus (mg)	1	2	0.5	1	1.5	2	1	2	1	1.5
PEG 400 (ml)	2	1	0.5	1	1.5	2	2	1	1	1.5
Propylene glycol (ml)	1	1	1	1	1	1	1	1	1	1
Aspertame (mg)	70	70	70	70	70	70	70	70	70	70
Methanol (ml)	2	2	2	2	2	2	2	2	2	2
Purified water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation parameters of Nanosuspension Pitavastatin

The nanosuspension was evaluated for various parameters:

Drug content uniformity

10ml of each formulation was taken and dissolved in 10ml isotonic solution and kept overnight. 10 mg (similar as in formulation) of drug was taken and dilution was made to 10µg/ml. The dilutions were filtered and analyzed using UV for their content uniformity. The absorbance of the formulations were read using one cm cell in a UV-Vis spectrophotometer. The instrument was set at 282 nm. The drug content in each formulation was calculated based on the absorbance values of known standard solutions. [12]

Entrapment efficacy

Entrapment efficacy was calculated by following formula:
%Entrapment efficiency= Drug content *100/Drug added in each formulation

In vitro drug release study: This is carried out in USP XXIII dissolution test apparatus-II (Electrolab TDT-06N), employing paddle stirrer at 50 rpm and 200 ml of pH 0.1N HCl buffer as dissolution medium. The release study is performed at 37 ±0.5^{O}C. The disk is placed at the bottom of the dissolution vessel. Samples of 5 ml are withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.22 µm membrane filter disc (Millipore Corporation) and analyzed for Pitavastatin after appropriate dilution by measuring the absorbance at 282 nm.

Zeta potential

The zeta Potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electro-neutral region of the solution. [13, 14]

Stability studies

Short- term stability studies were performed at a temperature of 40 ± 2^{O} C / 75 ± 5% RH over a period of three months (90 days) on the promising Nanosuspension of Pitavastatin (formulations F_1 to F_{10}). Sufficient number of Nanosuspension (10) were packed in amber colored rubber Stoppard vials and kept in stability chamber maintained at 40± 2^{O} C / 75± 5% RH. Samples were taken at one month interval for drug content estimation. At the end of three month period, dissolution test was also performed to determine the drug release profiles. [15, 16]

Spray drying of Nanosuspension

Spray drying was carried out to get the dry nano size powder. An optimised batch of aqueous nanosuspension was transferred into nano size powder by a lab spray dryer LU-222 lab ultima. Spray dried powder was directly collected after the process. In this process, the spray dryer was set to the conditions given in following table.

In vivo studies of Pitavastatin

Animal preparation

Twelve New Zealand white rabbits of either sex rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25^{0}C, RH 45% and 12h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee.

In vivo study design

The rabbits were fasted overnight before administration of the formulations the rabbits were randomly divided into two groups each group contains six animals. The group A rabbits were received optimized formulation contain Pitavastatin nanosuspensions in a dose of 2mg/kg then group b receives pure Pitavastatin 2mg/kg. Animals are treated with equivalent to animal body weight

Blood samples for pharmacokinetic analysis were obtained at different time intervals 0, 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00 & 24.00h after dosing. Blood samples were collected in heparinised tubes and were centrifuged for 10min at 3,000 rpm at room temperature.

Determination of Pitavastatin in Rabbit plasma by HPLC method

Determination of Pitavastatin by high performance liquid chromatography using a RP-C18 chromatographic column, Phenomenex Kinetex (150 mm × 4.6 mm with i.d of 0.5 mm.) and 0.1 % orthophosphoric acid: acetonitrile: triethylamine (19.8: 80: 0.2, v/v/v), pH 3 ± 0.05, at a flow rate of 1.4 mL/min. and the wavelength detection was 250nm. ezetimibe (EZE) used as internal standard. The retention times were about 6.98 and 2.36 min for PIT and EZE, respectively [17].

Pharmacokinetic data analysis

Various pharmacokinetic parameters like area under the curve [AUC], elimination half life ($t_{½}$). Volume of distribution (V_d), total clearance (Cl_T) and mean residence time for each subject using a non compartmental pharmacokinetic programme. The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean ±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Determination of absorption maximum (λmax)

Determination of Pitavastatin λ-max was done in 0.1N Hcl buffer medium for accurate quantitative assessment of drug dissolution rate.

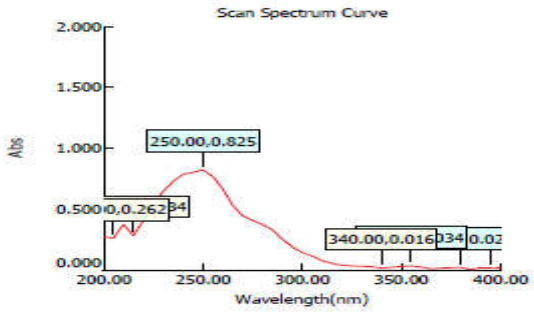

Figure 1 UV Spectrum of Pitavastatin

The λ-max was found to be 250 nm, i.e., at its absorption maxima.

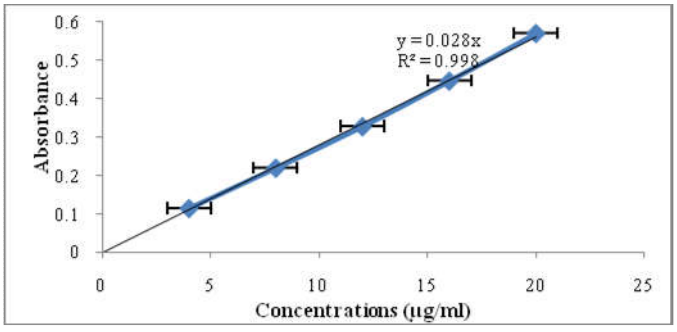

Figure 2 Standard calibration curve of Pitavastatin in methanol

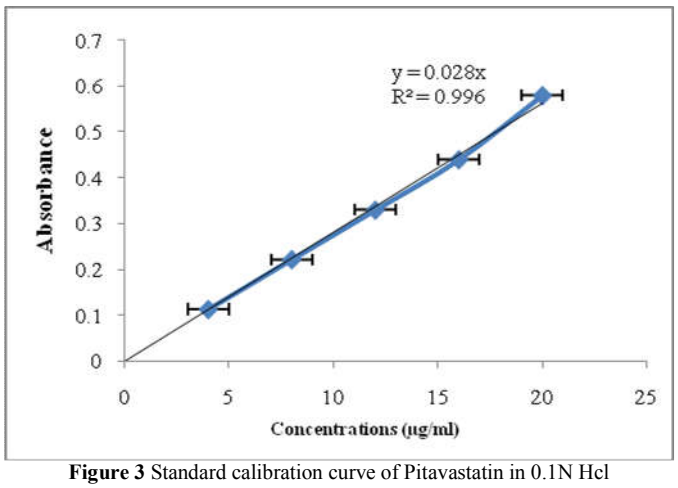

Figure 3 Standard calibration curve of Pitavastatin in 0.1N Hcl

DISCUSSION

The linearity was found to be in the range of 5-25μg/ml in methanol, 0.1N Hcl. The regression value was closer to 1 indicating the method obeyed Beer-lambert's law.

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

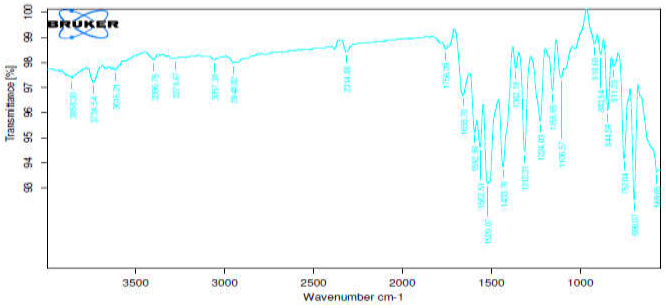

Figure 4 IR spectrum of Pitavastatin

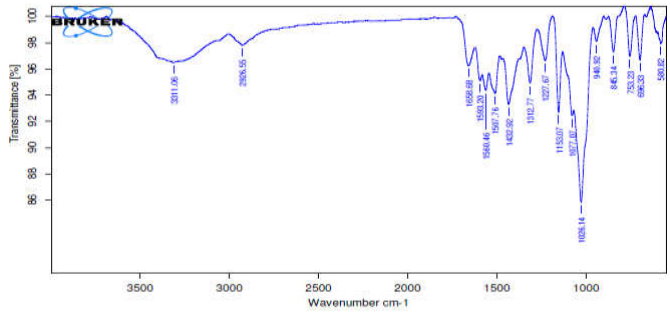

Figure 5 IR Spectrum of Pitavastatin Optimized Formulation

Table 2 Formulated Nanosuspension of Drug content

Formulation code	Mean % drug content* ± S.D (CV)
F1	94.72±0.76 (0.80)
F2	96.87±0.86 (0.88)
F3	95.57±1.02 (1.06)
F4	99.94±1.46 (1.56)
F5	95.75±0.89 (0.93)
F6	94.69±1.10(1.16)
F7	99.45±0.97 (1.01)
F8	96.56±0.67 (0.69)
F9	96.26±1.28 (1.33)
F10	99.87±0.84 (0.88)

The drug content of the formulated Nanosuspension was found in the range of 93.86 to 99.87 respectively.

Entrapment efficacy

The entrapment efficacy of the formulated Nanosuspension was found to be in the range of 55.4%-99.87% respectively.

Transmittance measurement

UV-Visible spectrum of pure Nanosuspension was recorded in range of 200-400 nm.

Zeta Potential

F10 the measurement itself is a particle electrophoresis, the particle velocity is determined via the doppler shift of the laser light scattered by the moving particles. The field strength applied was 20 V/cm. The electrophoretic mobility was converted to the zeta potential in mV using the Helmholtz-Smoluchowski equation. At standard measuring conditions (room temperature of 25 °C, water) this equation can be simplified to the multiplication of the measured electrophoretic mobility (µm/cm per V/cm) by a factor of 12.8, yielding the ZP in mV. The graph showed in figure 7

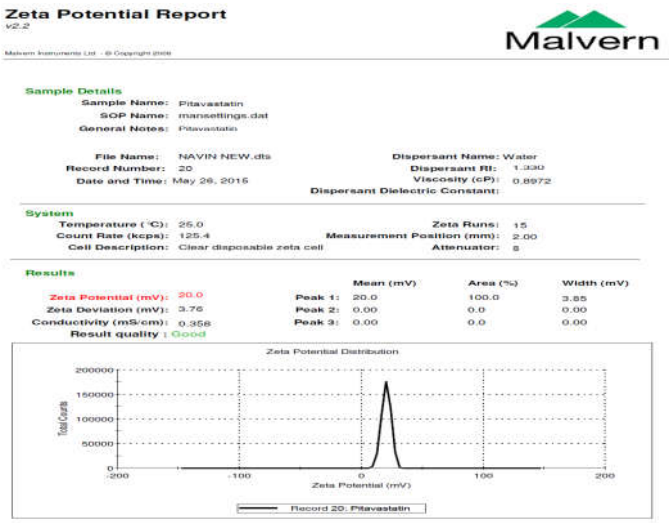

Figure 6 Particle size graph for optimized formulation F10

The optimized batch (F10) had a average particle size of 325.3nm with 0.218 poly- dispersivity index which indicate the particles are in uniform distribution. The particle size distribution pattern of the optimized nanosuspension formulation is given in figure 8.

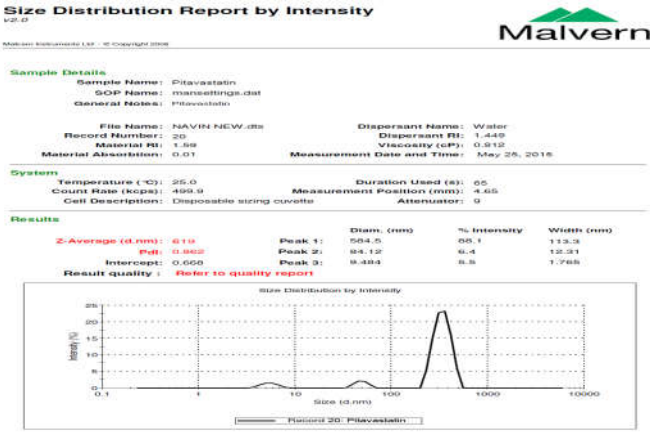

Figure 7 Size distribution pattern of the optimized nanosuspension F10

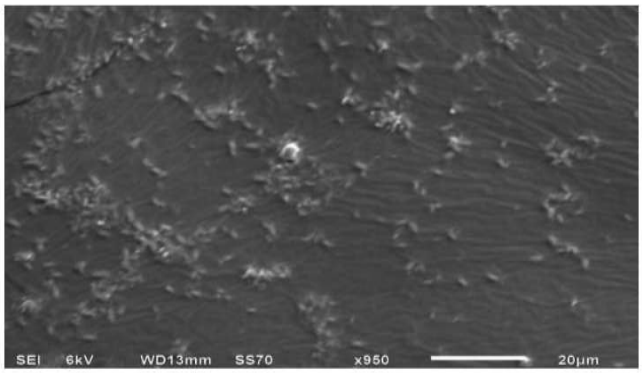

Figure 8 SEM Photograph Nanosuspensions F10
Dissolution Studies of Pitavastatin

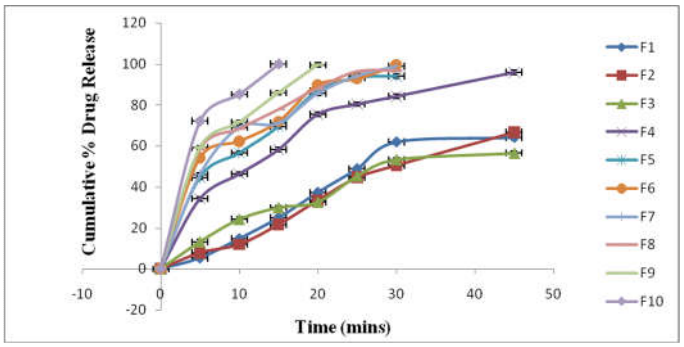

Figure 9 Dissolution parameters for the formulations F1-F10

The *in vitro* drug release studies were compared for F1 to F10 formulations. Soluplus used as carrier, Tween 20 used as stabilizing agent(F1toF6), and Tween 80 (F7toF10), used as in these formulations.

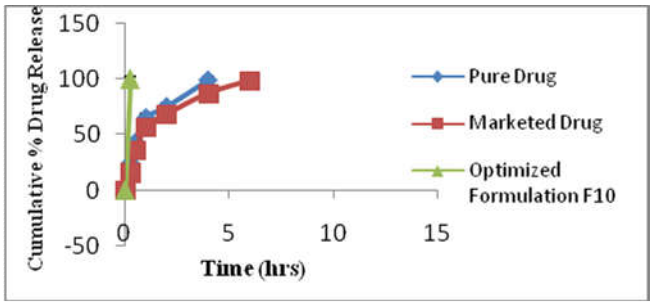

Figure 10 *in virto* dissolution comparison for Pure Drug, Marketed Drug and Optimized Formulation

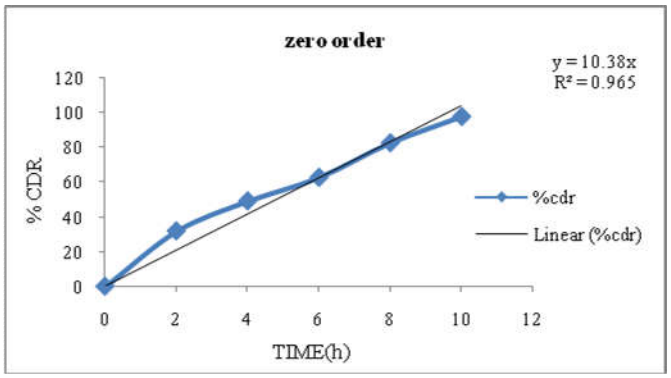

Figure 11 Cumulative percent drug released vs time plots (zero order) of formulation F10

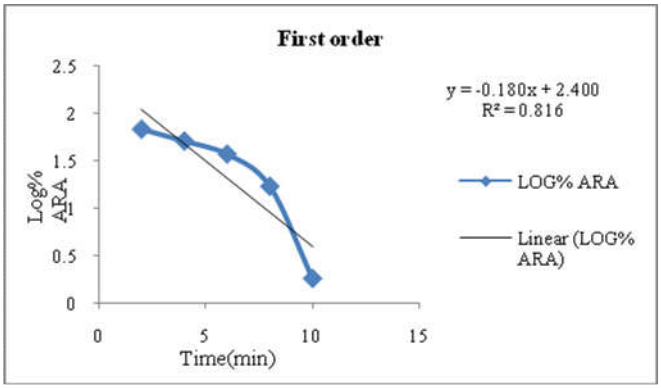

Figure 12 Log cumulative percent drug released vs time plots (first order) of formulation F10

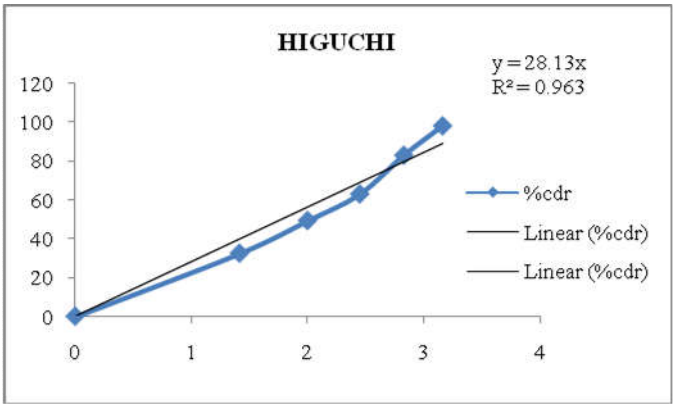

Figure 13 Cumulative percent drug released vs square root of time (Higuchi plots) of formulation F10

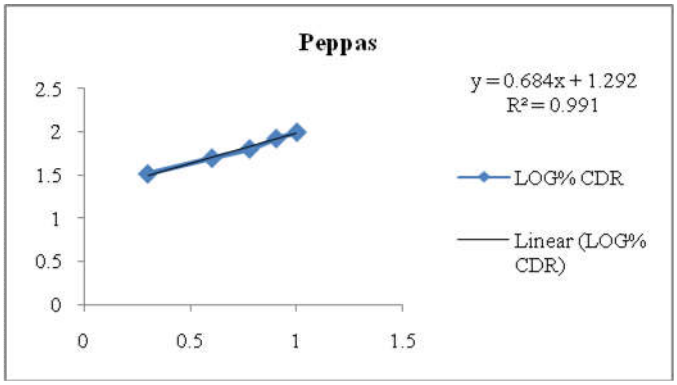

Figure 14 Log cumulative percent drug released vs Log time (Peppas plots) of formulation F10

Table 3 Kinetic data of the optimized formulation F10

Order of kinetics	Zero order	First	Higuchi	Peppas
REGRESSION	0.965	0.816	0.963	0.991

DISCUSSION

The drug release from the Nanosuspension were explained by the using mathematical model equations such as zero order, first order, Higuchi`s and Korsmeyer-Peppas equation methods. Based on the regression values it was concluded that the optimized formulation F10, followed zero order, and pepas release it was also found that the drug was released by diffusion as the regression in Peppas plot was 0.991.

Table 4 *In vitro* drug release data of the stability formulation (F10)

Sl. No.	Time (min)	Cumulative* % drug released* ± S.D at 40± 1° C			
		1 st day	30th day	60 th day	90 th day
1	0	0	0	0	0
2	5	72.1±0.64	71.7±0.56	71.0±0.68	70.4±0.68
3	10	85.2±0.88	85.1±0.38	85.0±1.01	84.6±0.48
4	15	99.9±0.89	99.0±0.69	98.6±0.49	98.1±0.57

Pharmacokinetic study

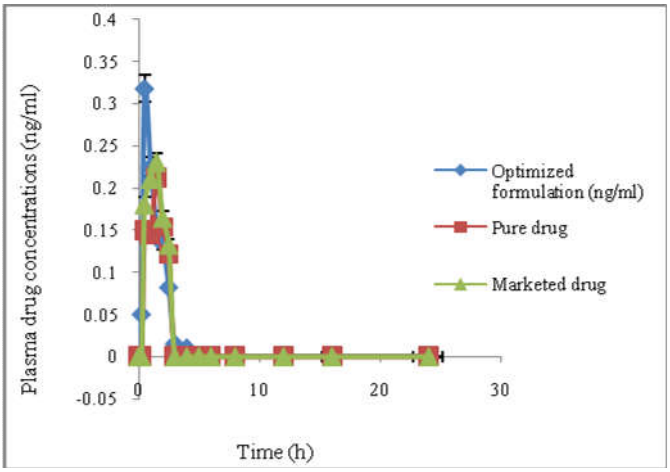

Figure 15 Plasma concentrations at different time intervals of Pitavastatin Optimized formulation, marketed and pure drug

Table 5 Comparison of pharmacokinetic parameters of Pitavastatin optimized formulation, marketed and Pure drug (mean ± SD, n = 6)

Parameters	optimized formulation	Pure drug	Marketed drug
C_{max}(ng/ml)	0.318±0.1	0.213±0.1	0.245±0.1
AUC_{0-t}(ng hr/ml)	1.16±0.44	0.95±0.26	1.05±0.26
$AUC_{0-\infty}$(ng hr/ml)	1.94±0.14	1.04±0.12	1.34±0.12
T_{max}(h)	0.50±0.5	1.50±0.1	1.50±0.1
$t_{1/2}$(h)	1.253 ± 0.519	2.664 ± 0.01	2.664 ± 0.01
Kel (hr^{-1})	1.336 ± 0.11	1.196 ± 0.33	1.186 ± 0.33

DISCUSSION

The main goal of this work was to develop new Nanosuspension of Pitavastatin an Total 10 formulations of Nanosuspension of Pitavastatin using excipients are soluplus, Tween 80, Propylene glycol, methanol and quantity sufficient of distilled water were prepared and evaluated for biological, physical and mechanical parameters.

The average drug content of the Nanosuspension was found to be 98.16 % and the low values of standard deviation and coefficient of variation (< 2) indicate uniform distribution of the drug within the prepared Nano suspension.

In vitro release studies were carried out in USP XXIII tablet dissolution test apparatus-II employing paddle stirrer at 50 rpm and 200 ml of 0.1N Hcl as dissolution medium. The *in vitro* dissolution data of all the designed formulations are shown in table 6.and dissolution profiles depicted in figure 9. *In vitro* drug release data of all the Nanosuspension formulation(F10) of Pitavastatin was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetics and according to Higuchi's and Peppas equations to ascertain mechanism of drug release. The results of linear regression analysis including regression coefficients from the above data it is evident that all the formulations displayed zero-order, first order release kinetics (0.965, 0.816). Higuchi and Peppas data (0.963, 0.991) reveals that the drug is released by non-Fickian diffusion mechanism. Drug-excipient interactions were ruled out by IR spectroscopic studies on the samples stored for three months at 40 ± 2o C / 75 ± 5% RH.

From the stability studies data it can be seen that the drug release of the F10 formulations was not significantly affected at ± S.D at 40± 1º C RH after storage for three months.

The bioavailability of optimized formulation, marketed drug and Pure drug parameters for the both test and reference standard are summarized in Table 5. Mean time to reach peak drug concentration (T_{max}) was 0.50±0.5h, 1.50±0.1h and 1.50±0.1h for the optimized and commercial formulations, respectively while mean maximum drug concentration (C_{max}) was 0.318±0.1ng/ml, 0.245±0.1ng/ml and 0.213±0.1ng/ml, respectively. The statistical comparison of $AUC_{0-\infty}$ and AUC_{0-t} indicated significant difference between the two treatments, and there was a significant difference for the C_{max} and T_{max} was observed in this study. As the prepared nano suspensions were exhibited immediate release higher bioavailability when compared with pure drug and marketed drug.

CONCLUSIONS

Oral Nanosuspension of Pitavastatin can be prepared by precipitation method using Tween20, Tween80, PEG 400, soluplus, methanol and water. IR spectroscopic studies indicated that there are no drug-excepient interactions. All the designed formulations of Nanosuspension displayed first order release kinetics and drug release. Among all the formulations F10 containing Tween 20, Tween 80 , soluplus, PEG 400 and methanol, found to be promising, which showed formulation F10 is 99.98% of drug released within 15 mins. Among all formulations (F1-F10) of Nanosuspensions, the F10 was showed best drug released compared to remaining formulations. Short-term stability studies of the promising formulations indicated that there are no significant changes in dissolution parameter values after 3 months at 40 ± 2º C / 75 ±5% RH. From the *in vivo* study as the prepared nano suspensions were exhibited immediate release higher bioavailability when compared with pure drug and Marketed drug.

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