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Solubility and dissolution enhancement of poorly aqueous soluble drug atorvastatin calcium using modified gum karaya as carrier: *In vitro-In vivo* evaluation

Shikha Aggarwal[1]*,G.D Gupta[1],Sandeep Chaudhary[1].

*Corresponding author:

Shikha Aggarwal

[1]ASBASJSM College of Pharmacy, BELA, Ropar, (Punjab).140111, INDIA.

Abstract

Solid dispersion is a unique and promising approach for improving the oral absorption and oral bioavailability of BCS class II drugs. Modified gum karaya a recently developed excipient was evaluated as a carrier for solubility and dissolution enhancement of poorly water soluble drug atorvastatin calcium. Physical mixtures along with solid dispersions of drug and polymer was prepared using three methods kneading, solvent evaporation and solvent wetting method in 5 different ratios (1:1,1:3,1:5,1:7,1:9). Among the three methods used atorvastatin calcium solid dispersions prepared by kneading method in 1:3 ratio showed most promising results in terms of percent yield, percent drug content, solubility of solid dispersions in phosphate buffer pH 6.8, XRD, DSC, SEM and In vitro release studies. These solid dispersions were selected to prepare tablets using Ac-di-sol as superdisintegrant (T1, T2, T3, T4 and T5). Tablets were characterized for hardness, friability, disintegration time, percent drug content, drug release studies and stability studies. Tablets T5 showed highest dissolution rate and best dissolution efficiency at (DE30) and (DE120) minutes. Release data of T5 tablet was subjected to various release kinetics models to know the type and order of drug release. Order was found to be Korsemeyer–Peppas>Hixson–Crowell cube root law >zero-order >first-order >Higuchi. The similarity factor was calculated for comparison of the dissolution profile before and after stability studies. The f2 value was found to be more than 50 (~ 90.9) thereby indicating a close similarity between both the dissolution profiles. In vivo studies was conducted on healthy albino rats and formulation given by oral route showed that at the end of 14 days solid dispersion 1:3 performed better than pure atorvastatin calcium in reducing total cholesterol and TG level and increasing HDL- cholesterol levels.

Keywords: Solid dispersion, solubility, dissolution, atorvastatin calcium, gum karaya, modified gum karaya, kneading, co-grinding, solvent evaporation, amorphous, crystalline.

Introduction

Oral drug delivery is the simplest and easiest way of administrating drugs because of the greater stability, accurate dosage form and easy production [1]. A number of newly synthesized chemical molecules suffer from low aqueous solubility and dissolution problems resulting in low bioavailability. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include:

1. Enhancing solubility and dissolution rate of poorly water soluble drugs.
2. Enhancing permeability of poorly permeable drugs.

Many approaches such as salt formation, solubilization and particle size reduction have been commonly used to increase dissolution rate and thereby oral absorption and bioavailability of various drugs. However all these technologies have some potential limitations therefore solid dispersion technologies are one of the promising approach for improving oral absorption and bioavailability of BCS Class II drugs.[2] In the last few years, the use of semi-synthetic hydrophilic polymers used as carriers to enhance the dissolution rate and bioavailability of poorly water soluble drugs. But many of these polymers also limit their application as carriers for dissolution enhancement by their high viscosity and toughness. Hence development of carriers with high swelling and low viscosity may offer better alternative to overcome this problem. The usage of natural polymers as drug carriers is on

increasing side because of their low cost, biocompatibility and biodegradability. [3]

Gum karaya (GK) is a natural exudate of Sterculia urens, a tree native to India belongs to family 'Sterculiaceae'. It is widely used in food industry as it is approved food additive. The wider applications of gum karaya is due to its unique features such as high swelling and water retention capacity, high viscosity properties, inherent nature of antimicrobial activity and abundant availability. Gum karaya also acts as fat replacer. [4] It is also evidenced from the literature that the gum karaya was used as a laxative due to its high swelling ability and formation of discontinuous mucilage. Our research reported that the preparation of modified form of gum karaya (MGK) and its swelling capacity are beneficial properties which overcome the processing and handling problems occurred during the preparation of solid mixtures, the present investigation aimed to study the influence of MGK on dissolution rate of poorly water soluble drug. The drug selected for the evaluation of MGK as carrier for solubility and dissolution enhancement is atorvastatin calcium as a synthetic lipid lowering agent, is an inhibitor of 3-hydroxy-3-methyl glutaryl –coenzyme A (HMG CoA) reducatase which catalyzes the conversion of HMG-CoA to mevalonate which is a rate limiting step in cholesterol biosynthesis. Atorvastain calcium is insoluble in aqueous solution of pH- 4 and below, it is very slightly soluble in water and pH-7.4 of phosphate buffer. The intestinal permeability of atorvastatin calcium is high at the physiologically relevant intestinal pH. Hence it is reported that the absolute bioavailability of atorvastatin calcium is 12 %. [5].

In this study, the influence of concentration of gum and the method of preparation of solid dispersions on the dissolution rate was also studied. Apparent solubility, in vitro dissolution study, infrared spectroscopy, differential scanning calorimetry (DSC), and X- ray diffraction (XRD) study were used to explain the phenomenon. Release data was subjected to various release kinetics models to know the type and order of drug release. The similarity factor was calculated for comparison of the dissolution profile before and after stability studies. *In vivo* studies were conducted on healthy albino rats to know decrease in total cholesterol level. [6]

Materials and methods

Atorvastatin calcium was a gift sample from Cadila Healthcare (Ankleshwar, India). Rajesh Chemicals Pvt. Ltd., Mumbai gum karaya (Grade 1).All other materials were of analytical reagent grade.

Methods

Preparation of modified gum karaya

Powdered gum was taken in a porcelain bowl and subjected to heating using sand bath for different time periods at different temperatures. Hence in the preparation of modified gum karaya, samples were heated at 120ºC for 2 hours. The prepared modified gum karaya was finally re-sieved (100 mesh) and stored in an air tight container at 25ºC [7].

Characterization of GK/MGK

Viscosity measurement

The viscosity of 1% (w/v) GK/MGK solution was measured according to the US Pharmacopoeia (USP) specification, using Brookfield DV-E Viscometer.

Swelling and water retention capacity [6,7]

Swelling index

About 1.0 gm of GK powder was accurately weighed and transferred to a 100 ml stopper measuring cylinder. The initial volume of the powder in measuring cylinder was noted. The volume was made up to 100ml mark with distilled water. The cylinder was stoppered and was shaken gently and set aside for 24 h. The volume occupied by the gum sediment was noted after 24 h. Swelling capacity of GK/MGK was expressed in terms of swelling index as follows. Swelling index (SI) was expressed as a percentage and calculated according to the following equation.

Equation no: - 1

$$Si=[(xt-xo)/xo]x100$$

where

X_0 is the initial height of the powder in graduated cylinder

X_t denotes the height occupied by swollen gum after 24 hrs.

Hydration capacity

Weighed quantity of powdered GK/MGK (1.0 g) was taken in the 15-ml tare centrifuge tube. Then, 10 ml of distilled water was added to it and allowed to centrifuge for 10 min at 1,000 rpm. After the centrifugation process, the tare centrifuge tube was taken out and inverted to remove the supernatant. The decanted tube then weighed on digital balance and the hydration capacity was calculated using the following equation.

Equation no:- 2

HC = Weight of hydrated sample/Weight of dry sample

Angle of repose

The angle of repose was determined by the funnel method. Accurately weighed powder was taken in a funnel. The height of a funnel was adjusted in such a way that its tip just touches the apex of the heap of powder. The powder was allowed to flow through funnel freely on to the surface. The diameter of the powder heap was measured and angle of repose was calculated using the following equation. [8]

Equation no: - 3

$$\tan\theta = \frac{h}{r} \qquad ; \theta = \tan^{-1}\left(\frac{h}{r}\right)$$

where
H is the height of powder heap
R is the radius of powder heap **[9]**

Table 1: Angle of repose as an indication of powder flow properties

Angle of repose(º)	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Moisture sorption capacity

Moisture sorption study was performed using programmable environmental test chamber. One gram of powdered GK/MGK was taken in a Petri dish of 9 cm in diameter and spread uniformly. Then, it was kept in programmable environmental test chamber at 37±1℃ and 100% relative humidity for 2 days. The moisture sorption was calculated by recording weight difference of the sample before and after exposure to programmable environmental test chamber.

Density

The loose bulk density (LBD) and tapped bulk density (TBD) of GK/MGK powder were determined. Powdered gum (2 gm) was poured into calibrated measuring cylinder (10 ml capacity) and noted initial volume. Then, the cylinder was allowed to fall under its own weight onto the hard surface from the height of 2.5 cm. The tapping was then continued until no further change in volume was noted. LBD and TBD were calculated using the following equation. [8]
Equation no: - 4
LBD = Weight of the powder/Volume of the packing
Equation no: - 5
TBD = Weight of the powder/Tapped volume of the packing

Compressibility

Compressibility index (Carr's index) was determined by using the following equation:
Equation no: - 6
Carr's index (%) = [(TBD – LBD) x 100] / TBD

Determination of volatile acid content

About 1 gm was accurately weighed, transferred to a 700 ml long necked flask.100 ml of water and 5 ml orthophosphoric acid was added and allowed to stand for 6 h until the gum was completely swollen. Then it was boiled for 2 h under a reflux condenser, and then steam distilled until 80 ml of the distillate was obtained. The distillate was titrated with N/10 sodium hydroxide using phenolphthalein as indicator. The procedure was repeated omitting the sample. The difference between the two titrations represented the amount of alkali required to neutralize the volatile acid. Each ml of 0.1 N NaOH = 0.006005 g of $C_2H_4O_2$ [10].

Preparation of sample

Preparation of physical mixture of atorvastatin calcium

Physical mixtures of atorvastatin calcium and modified gum karaya was obtained by simple blending the drug and carrier in ratios 1:1, 1:3, 1:5, 1:7, 1:9 with spatula and then passed through a 100 mesh screen and then weighed physically.

Kneading method

The Atorvastatin calcium and MGK were triturated in1:1, 1:3, 1:5, 1:7, 1:9 ratios using 1.5 times the amount of 70% v/v of methanol to give a thick paste, which was needed for 20 minutes and then dried at 40 ^{0}C in an oven. The dried mass was then pulverized, passed through mesh 30, stored in vacuum desiccators (48 h). The prepared solid dispersion was then grounded by using a mortar and pestle, sieved through a mesh 100 and stored over a fused calcium chloride in a desiccators for further use. When methanol alone was used for kneading; the thick paste got dried immediately. To avoid drying of the solvent during kneading, methanol was previously mixed with water (1:1) and then used for the kneading method [11].

Solvent evaporation method

To a solution of atorvastatin calcium (200 mg) in methanol (10 ml) was added appropriate amount of MGK, earlier dissolved in methanol in1:1, 1:3, 1:5, 1:7, 1:9 ratios. This solution was continuously stirred using magnetic stirrer and the solvent was evaporated and then stored over night in a desiccators. Solid dispersion thus obtained was grounded by using a mortar and pestle and sieved through a 100 mesh screen. [12].

Solvent wetting method

Atorvastatin calcium was dissolved in an appropriate amount of methanol to its saturation solubility in1:1, 1:3, 1:5, 1:7, 1:9 ratios. The amount of methanol used was 1.5 times the total weight of drug and polymer. After complete dissolution of atorvastatin calcium, solutions were dropped into MGK. Then, solvent was removed at room temperature. The solid dispersions obtained were grounded in a mortar and sieved through 100 mesh screen. [13].

Characterization of solid dispersions

Scanning electron microscopy (SEM)

The SEM images of pure drug, MGK, physical mixture and solid dispersions prepared by kneading method was analyzed by scanning electron microscope (JSM 6390, JEOl, Peabody MA, USA) with 10-kV accelerating voltage.

X-ray diffraction (XRD)

Powder XRD patterns of pure drug, MGK, physical mixture and solid dispersion prepared by kneading method were recorded using diffractograms using Philips PW 1729 X-ray generator (computer 1710). Diffractograms were run at a scanning speed of 2^0/mm and a chart speed of 2^0/2 cm per 2θ.

Differential scanning calorimetry (DSC) analysis

DSC curves of pure drug, MGK, physical mixture and solid dispersion prepared by kneading method were obtained by differential scanning calorimeter (DSC 60 Shimazdu, Japan) at a heating rate of 10 ^{0}C/min from 30 ^{0}C to 300 ^{0}C in a nitrogen atmosphere.

Determination of percentage yield and drug content

Drug content was calculated by dissolving solid dispersions equivalent to 20 mg of atorvastatin calcium in a suitable quantity of methanol (10 ml), filtered using 45 µm whatman filter paper, suitably diluted with methanol and analyzed by using UV spectrophotometer against methanol as blank. Similarly, the percentage yield of each formulation was determined according to the recoverable final weight of solid dispersions and the total original weight of atorvastatin calcium and carrier used.
Equation no: - 7

$$Yield = \left(\frac{a}{b+c}\right) \times 100$$

where, a is the weight of the solid dispersion sifted through a#120 sieve, b is the weight of atorvastatin calcium taken for solid dispersion preparation, and c is the weight of MGK taken for solid dispersion preparation[14].

Determination of solubility of solid dispersions

Atorvastatin calcium, physical mixture or solid dispersions equivalent to 20 mg were added to 10 ml of phosphate buffer pH 6.8 in screw capped vials. The vials were capped properly and shaken at 37 ^{0}C in a temperature controlled water bath for 48 hrs. Resultant samples containing undissolved solid dispersions suspended in the screw capped vials were filtered through 0.45µm filters, suitably diluted with phosphate buffer pH 6.8 and analyzed by UV spectrophotometer at 246 nm [14].

In vitro drug release studies

Dissolution rates from different solid dispersions were determined in 900ml of pH 6.8 phosphate buffer at 37±0.5°C with a stirrer rotation speed of 50 rpm using the USP dissolution test apparatus employing type II Paddle type apparatus. A 5-ml aliquot of dissolution medium was withdrawn at 5, 10, 20, 30, 45, 60, 90 and120 mins. The samples were suitably diluted and assayed spectrophotometrically at 246 nm. Each dissolution rate test was repeated three times. A model independent approach, dissolution efficiency (DE) was employed to evaluate the dissolution rate of atorvastatin calcium from different solid dispersions. DE is defined as the area under the dissolution curve up to the time t,(measured using trapezoidal rule) expressed as a percentage of the area of the rectangle described by100% dissolution in the same time.DE_{30} and DE_{120} were calculated from the dissolution data and used for comparison[15].

Equation no: - 8
$DE\% = {}^{t}_{o}\int y.dt \,/\, y100.dt \times 100$

Formulation of blends

ATV-Ca 2 solid dispersions and excipients like Ac-di-sol, Avicel pH 102, lactose were co-grounded in pestle mortar (except talc and magnesium stearate) and were passed through mesh no. 60. Finally talc and magnesium stearate were added and mixed for 5 minutes [9].

Characterization of blends

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. The characterization of mixed blend done for the flow property of powder that are bulk density, tapped density, Hausner's ratio, Compressibility index, angle of repose[8,9].

Bulk density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of powder (M) was determined. The bulk density was calculated using the formula [9]
Equation no:-9

$$\rho_b = \frac{M}{V_b}$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped 100 times using density apparatus. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the formula
Equation no: - 10

$$\rho_t = \frac{M}{V_t}$$

Compressibility index

The simplest way for measurement of flow of powder is its compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows·
Equation no: - 11

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Where, ρ_t = Tapped density
ρ_b = Bulk density

Table 2: Compressibility index as an indication of powder flow properties

Carr's index	Type of flow
15.0-21	Excellent
12.0-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner Ratio

Hausner ratio (HR) is an indirect index of ease of powder flow. It is calculated by the following formula.
Equation no:-12

$$Hr = \frac{\rho t}{\rho b}$$

Where, ρ_t is tapped density and ρ_b is bulk density.
Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones
(> 1.25).

Angle of repose

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula.
Equation no:-13

$$\tan\theta = \frac{h}{r} \qquad ; \qquad \theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where, θ is angle of repose; h is height of cone; r is radius of cone

Table 3: Angle of repose as an indication of powder flow properties

Angle of repose	Type of flow
<25	Excellent
25-40	Good
30-40	Passable
>40	Very poor

Formulation of atorvastatin calcium solid dispersion tablets

Atorvastatin calcium solid dispersion tablets of ATV-Ca 2 formulation were prepared by direct compression method using single punch machine (Cadmach, Ahemadabad) 9mm concave punch. 20 mg equivalent solid dispersion was taken for each formulation. Tablets were prepared with or without using Ac-di-sol as superdisintegrant. The concentration of superdisintegrant varied from 2-5 % in tablet formulations. The mixed blend of drug and excipients was compressed using a single punch tablet machine to produce flat faced tablet weighing 250 mg.

Table 4. Composition of atorvastatin calcium solid dispersion tablets

Ingredients	T1	T2	T3	T4	T5
ATV-Ca 2	120	120	120	120	120
Ac-Di-Sol	0	5	7.5	10	12.5
Avicel pH 102	90	90	90	90	90
Lactose	30	25	22.5	20	17.5
Talc	5	5	5	5	5
Magnesium stearate	5	5	5	5	5

Characterization of atorvastatin calcium solid dispersion tablets

After compression of powder, the tablets were evaluated for organoleptic characteristics like color, odor, taste, diameter, thickness and physical characteristics like hardness, friability, content uniformity, disintegration time, and *in vitro* dissolution studies.

General appearance [6]

Visual identification and over all 'elegance' were performed such as color, presence or absence of an odour, taste, surface texture and physical flaws.

Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by suing filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of weight

USP procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be satisfactory method of determining the drug content uniformity.

In vitro dissolution test

In vitro dissolution studies of formulation were carried out using USP paddle method at 50 rpm in 900 ml of phosphate buffer (pH 6.8) as dissolution media, maintained at 37±0.5^{0}C. 5 ml of aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and analyzed spectrophotometrically at 246 nm. An equal volume of fresh medium, which was prewarmed at same condition, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test [16].

Fitting of various kinetic models

The mechanisms of dissolution of atorvastatin calcium from various preparations of solid dispersions were studied. The data were treated to study the best linear fit for the following equations [13].

a) Zero order : %R = Kt.

b) First order : Log % unreleased = Kt/ 2.303

c) Matrix (Higuchi matrix) : % R = Kt$^{0.5}$

d) Korsmeyer- Peppas equation : $\frac{\text{Amount of drug released at time t}}{\text{Amount of drug released at time '∞}}$

e) Hixson-Crowell equation : (% unreleased) $^{1/3}$ = Kt

Where 'n' is the diffusion coefficient, which is indicative of transport mechanism [17].

Stability studies

The accelerated stability studies of T5 formulation was checked as per ICH guidelines at 40 ºC and 75± 5% RH upto 1 month. Periodically (initial, 7 days, 14 days, 21 days and 30 days) samples were removed and analyzed for physical characterization, hardness, drug content, disintegration time and in vitro dissolution studies. The similarity factor (f_2) was used as a basis to compare dissolution profiles. The dissolution profiles are considered to be similar when f_2 is between 50 and100. The dissolution profiles of T5 formulation before and after stability testing were compared using a similarity factor (f_2) which is calculated from the following formula:

$$f_2 = 50 \times \log \{[1 + (1/n) \sum_{j=1}^{n} | R_j - T_j |^2]^{-0.5} \times 100\}$$

Where, n is the dissolution time and Rj and Tj are the reference and test dissolution values at time t [18, 19].

In vivo studies

The Hypolipidemic activity of prepared T5 formulation of atorvastatin calcium solid dispersion tablets was determined in comparison with pure atorvastatin calcium in healthy albino rats (Wistar strain) of either sex or weighing between150 and 200g will be taken and animals will be divided into 3 groups of 4 animals each. General and environmental conditions were strictly monitored. Animal handling routines were performed according to Good Laboratory Practice. Animals were procured from central animal house Bela (Ropar). The research protocol of the animal experimentation was approved by CPSCEA the Institutional Animal Ethics Committee, Bela (Ropar) India. Each group daily will receive 2 ml of coconut oil orally. Reference and Test groups additionally will receive orally aqueous suspensions of pure atorvastatin calcium and solid dispersion (equivalent to 10 mg/kg body weight) respectively, prepared using 2% w/v gum acacia as a suspending agent. Blood samples will be collected under light ether anesthesia by retroorbital puncture; initially, after 7 days and after 14 days. The serum samples will be analyzed for total cholesterol, triglycerides (TG) and high density lipoprotein (HDL) cholesterol levels by the in vitro diagnostic kit (Transasia- Erba,Sem-Autolyser,Chem 5X model, India). The statistical analysis for the determination of differences in lipid profiles of treatment and control groups was done by unpaired t-test and p <0.001was taken as significant[20].

Results and discussion

The viscosity of GK is directly proportional to its volatile acetyl content. Hence, it is assumed that the removal of volatile acetyl content in the gum will reduce the viscosity of gum. Results of characterization of the GK and MGK are given in Table 5.7 respectively. The results indicated that the viscosity of MGK was markedly lower when compared to that of GK. It is also found that volatile acetyl content of MGK significantly less than that of GK. Due to swelling nature of carrier, the extensive surface of the carrier is increased during dissolution and dissolution rate of deposited drug is markedly enhanced. Water retention capacity of the carrier is the amount of water retained in it indicates ability of carrier towards hydrophilic nature.

Table 5: Characterization of gum karaya and modified gum karaya

Parameters	Gum Karaya	Modified Gum Karaya
Viscosity (cps)	600 ± 56	250 ±35
Swelling index (%)	1010.66 ± 95.84	888.66 ± 19.62
WaterRetentionCapacity(ml)	28.54± 2.28	26.62± 2.96
Hydration capacity	1.208±0.030	1.092±0.08
Volatile acid content	14± 2.309	11± 1.00
Angle of repose(Θ)	36±0.00	35±0.606
Carr's Index (%)	18± 0.309	18.34± 0.425

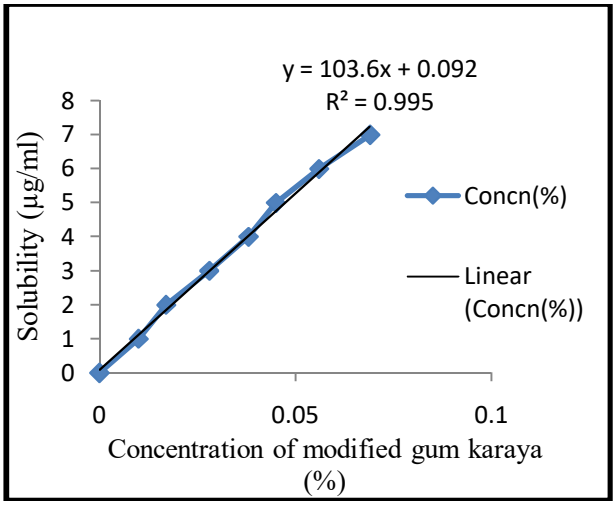
The solubility of atorvastatin calcium increases with the increase in polymer concentration, which shows a linear increase in drug

solubility with increased carrier level, with R^2 values of 0.995, indicating A_L type solubility diagram. Solubility data of atorvastatin calcium in various concentration of modified gum karaya is shown in Table 6 respectively and graph is represented in Figure 1 respectively.

Table 6: Solubility of atorvastatin calcium in modified gum karaya

S.No.	Concentration of MGK (%)	Solubility(µg/ml)
1	1	0.010±0.004
2	2	0.017±0.002
3	3	0.028±0.002
4	4	0.038±0.002
5	5	0.045±0.001
6	6	0.056±0.004
7	7	0.069±0.004

Data are expressed as mean ± S.D. (n=3)



Figure;1

Solubility data of Atorvastatin calcium, physical mixtures and solid dispersions are shown in Table 7 respectively. Solubility of drug increased with the increment in ratio of polymer. But the solubilising effect of solid dispersions prepared by kneading method showed more promising results.

The *in vitro* release profile of atorvastatin calcium, physical mixtures and solid dispersions (prepared by kneading method, solvent evaporation method, solvent wetting method) ATV-Ca 1, ATV-Ca 2, ATV-Ca 3, ATV-Ca 4, ATV-Ca 5, ATV-Ca 6, ATV-Ca 7, ATV-Ca 8, ATV-Ca 9, ATV-Ca 10, ATV-Ca 11, ATV-Ca 12, ATV-Ca 13, ATV-Ca 14, ATV-Ca 15 is shown in Table 8to 11 and graph for the comparison of cumulative percent drug release versus time is shown in Figure 2 to 5. In all the cases,

Table 7: Solubility data of atorvastatin calcium from physical mixtures and
solid dispersions in comparison with pure atorvastatin calcium

Formulation Number	Solubility(µg/ml)
Pure drug	0.120 ± 0.002
ATV-Ca 1	0.240 ± 0.003
ATV-Ca 2	0.351 ± 0.002
ATV-Ca 3	0.423 ± 0.002
ATV-Ca 4	0.470 ± 0.001
ATV-Ca 5	0.484 ± 0.006
ATV-Ca 6	0.218 ± 0.001
ATV-Ca 7	0.321 ± 0.002
ATV-Ca 8	0.375 ± 0.003
ATV-Ca 9	0.422 ± 0.003
ATV-Ca 10	0.482 ± 0.001
ATV-Ca 11	0.201 ± 0.002
ATV-Ca 12	0.298 ± 0.004
ATV-Ca 13	0.354 ± 0.002
ATV-Ca 14	0.395 ± 0.001
ATV-Ca 15	0.438 ± 0.001
PM 1	0.156 ± 0.001
PM 2	0.171 ± 0.003
PM 3	0.184 ± 0.002
PM 4	0.191 ± 0.006
PM 5	0.199 ± 0.002

cumulative percent release was much greater than pure atorvastatin calcium. Hence it is apparent that as the percent of carrier is increased, the dissolution rate also increased. Pure atorvastatin calcium yielded the slowest percent release due to its hydrophobic property causing the powder to float on the surface of the dissolution media and prevented its surface to make contact with medium for initial time intervals. Hence the enhancement of the atorvastatin calcium dissolution rate by solid dispersion technique compared with that of the pure drug, could presumably be explained by the following factors :1) swelling ability of the carrier 2) low viscosity of the carrier 3) a decrease in crystallinity

and size of the drug crystals in the solid dispersion. 4) Increased solubility 5) an improved drug wettability.

When the mixture comes in contact with water, the polymer particles might have hydrated rapidly into polymer solution solubilizes the adjacent drug particles and subsequently releases the drug into the medium.

Dissolution efficiency of pure atorvastatin calcium, physical mixtures and all solid dispersions at 30 and 120 minutes were calculated which is shown in Table 12 respectively. As the dissolution time was increased from 30 to 120 minutes, the dissolution efficiency was increased in all solid dispersions. Among the formulations ATV-Ca 2 has shown maximum dissolution efficiency of 24.77% and 44.16 % at thirty minutes (DE_{30}) and one twenty minutes (DE_{120}) respectively. Improvement in dissolution rate of atorvastatin calcium in solid dispersions compared with pure drug might be due to the solubilization effect and wetting ability of modified gum karaya on atorvastatin calcium. On the basis of results obtained, the method of preparation of solid dispersion also influences the rate of dissolution. The reason for higher dissolution rate of solid dispersion prepared by kneading method is due to, synergistic effect of trituration and solubilization effect of used solvent further reduced the crystallinity leading to improvement in dissolution rate. Furthermore, kneading results in uniform distribution of drug in the polymer crust in a highly dispersed state. Thus, Solvent wetting method enhances the dissolution rate of atorvastatin calcium due to wetting effect of solvent. It was also proved that as the viscosity of carrier decreased, the dissolution rate also increased. During the process of dissolution, as soon as the drug carrier particles comes in contact with dissolution fluid, seeping in of dissolution medium in to the drug carrier particle is taking place, which initiated the formation of gel layer of carrier around the particle. The diffusion of dissolved drug through the gelatinous layer is determining factor in the enhancement of dissolution rate.

SEM images of atorvastatin calcium, modified gum karaya, physical mixtures and solid dispersions are shown in Figure 6 to 9 respectively. It was observed that atorvastatin calcium is present as irregular shaped crystals and modified gum karaya as multifaceted, slippery surfaced granules. It is clearly visible that in ATV-Ca 2 formulation (1:3 solid dispersion prepared by kneading method) does not show any crystalline material. The SEM also supports data obtained from XRD and DSC.

The X-ray Diffractograms of pure atorvastatin calcium, modified gum karaya, physical mixtures, and solid dispersion is shown in Figure 10 to 13 respectively. Hence it is evident from Figure 5.19 that characteristic diffraction peaks of atorvastatin calcium is at 2Θ = 9.12, 9.44, 10.23, 10.54, 11.82, 12.16, 16.97, 19.45, 21.59, 22.62, 23.22 and 23.68. However modified gum karaya exhibited characteristic single peak at 28º with low intensity indicating their amorphous nature as shown in Figure 5.20. The XRD of physical mixtures of atorvastatin calcium and modified gum karaya and atorvastatin calcium 2 solid dispersion show peaks corresponding to atorvastatin calcium and also the peaks related to modified gum karaya persists respectively. But in Figure 5.22 the atorvastatin calcium peaks with reduced peak height and area were observed, suggesting reduced crystallinity of atorvastatin calcium in ATV–Ca 2 formulation prepared by kneading method.

The DSC runs for atorvastatin calcium, modified gum karaya and solid dispersions are shown in Figure 14-16.The DSC curve for atorvastatin calcium showed a sharp melting endotherm at 150ºC.The DSC curve for modified gum karaya exhibited a broad endothermic peak owing due to amorphous nature. Further the solid dispersion (ATV-Ca 2) showed no endothermic peak corresponding to the melting point of atorvastatin calcium indicating that drug is dispersed amorphously in modified gum karaya matrix.

From the above characterization of solid dispersions the ATV-Ca 2 (solid dispersions of atorvastatin calcium with modified gum karaya in ratio 1:3prepared by kneading method) found to be more approachable for incorporation in tablets due high saturation solubility and higher dissolution efficiency.

Total five formulations were formulated and designated as T1, T2, T3, T4 and T5.

The characterization of mixed blend was performed for determination of mass volume relationship parameters. The evaluated parameters are bulk density, tapped density, hausner ratio, compressibility index and angle of repose. The bulk density of mixed blend varied between 0.564 ± 0.002 to 0.682 ± 0.009 (g/cm^3). The tapped density was found in the range of 0.619±0.004 to 0.745± 0.001(g/cm^3). The hausner ratio was found in range of 1.116± 0.803 to 1.128± 0.496.The powder blends of all the prepared formulations had hausner ratio of less than 1.14 indicating the good flowability .The compressibility index was found in range of 11.496± 0.006 to 12.447±0.014 (%). The compressibility –flowability correlation data indicating a good flowability of the powder blend. The angle of repose was found to be 20.055±0.876 to 24.280±0.446 (º).The angle of repose is below than 30º range indicating good to excellent flow properties of blend.

The results for characterization of blends of solid dispersion tablets are shown in Table 13. After compression of blend, the tablets were evaluated for their physical properties like color, odour, physical, shape and texture) and quality control parameters like diameter, thickness, hardness, friability and disintegration time and *in vitro* dissolution studies. All the tablets were grayish in color, flat in shape with smooth surface having zero defects. The prepared tablets were elegant and have lot to lot tablet uniformity and also free from any surface texture problems.

The thickness of the tablet was found 3.14± 0.02 to 4.31± 0.03mm.The weight of the prepared tablets was found to be in the range of 248 ± 3.0 to 252 ± 6.1 mg. So it was predicted that all the tablets exhibited uniform weight with low standard deviation values with acceptable variation as per IP. The results are shown in Table 5.20.The hardness of the prepared tablets varied from 2.3 ± 0.28 to 3.3± 0.28 (Kg/Cm^2). The tablets have satisfactory strength to withstand the applied mechanical shocks.

The friability of all the tablets was found to be less than 1.0% which shows the durability of the prepared tablets and resistance to loss of weight indicating the tablet's ability to withstand abrasion in handling, packaging and shipment.

In the formulation of atorvastatin calcium solid dispersion tablets, Ac-di-sol was used as a superdisintegrant. T5 formulation shows better disintegration properties when compared to T1 formulation in which no superdisintegrant was added. The disintegration time of these tablets varied from 6 to 27 minutes (Table 14).

The drug content of all the tablet formulations was determined spectrophotometrically at 246 nm as shown in Table 15. It varied from 19.012 ± 0.011 to 20.943 ± 0.034 mg per tablet. Low values of standard deviation indicated uniformity of the drug content in the prepared tablets.

The results *in vitro* drug release of atorvastatin calcium solid dispersion tablets indicated that as the concentration of the superdisintegrant (Ac-di–sol) was increased the dissolution rate increased and also the drug was released faster. The maximum drug release was found in formulation T5 (69.41 %) as shown in Table 16. The disintegrant Ac- di- sol shows the faster disintegration as its concentration was increased. So the order of drug release was found to be in the following order

T5 > T4 >T3 > T2 > T1 > M

Dissolution efficiency of all the atorvastatin calcium tablets was calculated at 30 to 120 minutes and data is shown in Table 17. Among the formulations T5 has shown maximum dissolution efficiency of 22.14 at 30 minutes (DE_{30}) and 42.19 at 120 minutes (DE_{120}).

Release data of T5 tablet was subjected for kinetic treatment to know the type and order of drug release Table 18 lists the regression parameters obtained after fitting various release kinetics models to *in vitro* dissolution data. The goodness of fit for various models investigated for binary systems ranks in the order of Korsemeyer-Peppas>Hixson–Crowell cube root law >zero-order >first-order >Higuchi. The Korsemeyer-Peppas model describes drug release kinetics in the most be fitting manner. The value of diffusional exponent "n" was obtained from the slopes of the fitted Korsemeyer-Peppas model. The solid dispersion tablets tended to exhibit Fickian diffusional characteristics, as the corresponding values of n were lower than the standard value from declaring Fickian release behavior, the results point out the prevalence of diffusional mechanistic phenomena. Hence results of various kinetic models are shown in Figure 18 to 22 respectively.

All the formulations showed no significant variation in all the parameters under the test period at different conditions i.e.(40ºC (75±5 % RH). The results are shown in Table 19 respectively. The similarity factor was calculated for comparison of the dissolution profile before and after stability studies. The f_2 value was found to be more than 50 (~ 90.9) thereby indicating a close similarity between both the dissolution profiles.

Hence, the results of the stability studies confirmed that the developed formulation is very stable which can be seen in Figure 23.

Table 8: Dissolution profile of pure atorvastatin calcium and solid dispersions prepared by kneading method

Time (min)	Cumulative Mean Percent Released ± Standard Deviation					
	Pure Drug	ATV-Ca 1	ATV -Ca2	ATV-Ca 3	ATV –Ca 4	ATV-Ca 5
5	0.32±0.45	10.60±0.50	19.60±0.74	16.39±0.38	18.32±0.34	18.64±0.19
10	4.18±0.12	15.76±0.25	29.91±0.92	18.98±0.26	22.48±0.22	23.84±0.68
20	6.10±0.36	19.63±1.05	35.73±0.58	24.78±0.46	25.43±0.67	26.72±0.58
30	11.90± 0.73	26.72±0.68	40.27±0.66	32.53±0.78	32.86±0.45	33.82±1.07
45	16.09±0.40	32.54±1.34	52.53±0.94	36.42±1.46	42.86±0.50	43.50±0.65
60	20.93 0.80	38.36±0.59	60.30±1.26	49.32±0.83	51.26±0.36	52.55±0.78
90	24.95±0.64	46.76±0.87	66.47±0.54	53.23±0.35	56.46±0.58	58.39±0.33
120	28.49±0.49	48.10±0.60	72.65±0.48	58.43±0.56	62.31±1.28	66.17±0.21

Data are expressed as mean ± S.D. (n=3)

Table 9: Dissolution profile of pure atorvastatin calcium and solid dispersions prepared by solvent evaporation method

Time (min)	Cumulative Mean Percent Released ± Standard Deviation					
	Pure Drug	ATV-Ca 6	ATV –Ca7	ATV-Ca 8	ATV–Ca 9	ATV-Ca 10
5	0.32±0.45	9.32±0.47	16.39±0.36	12.53±0.91	14.46±0.80	16.39±0.91
10	4.18±0.12	13.83±1.30	26.05±0.28	17.04±0.46	19.62±0.45	20.91±0.60
20	6.10±0.36	20.91±1.26	34.44±0.44	21.56±0.38	25.43±1.50	25.43±0.46
30	11.90±0.73	26.08±0.56	42.83±0.27	29.94±0.94	30.60±0.47	32.53±1.26
45	16.09±0.40	35.75±0.38	52.52±0.75	36.41±0.44	43.27±1.38	43.49±0.65
60	20.93 0.80	40.29±0.22	57.08±0.34	42.88±0.89	50.65±0.87	51.26±1.40
90	24.95±0.64	44.19±0.35	66.14±0.36	51.28±0.62	54.52±0.51	56.46±0.39
120	28.49±0.49	46.81±1.57	70.07±0.52	52.62±0.98	60.35±0.65	64.23±0.41

Data are expressed as mean ± S.D. (n=3)

Table 10: Dissolution profile release of pure atorvastatin calcium and solid dispersions prepared by solvent wetting method

Time (min)	Cumulative Mean Percent Released ± Standard Deviation					
	Pure Drug	ATV-Ca 11	ATV –Ca12	ATV-Ca 13	ATV–Ca 14	ATV-Ca 15
5	0.32±0.45	7.39±0.32	15.10±0.68	7.71±1.32	10.92±0.30	12.53±0.36
10	4.18±0.12	11.90±1.48	24.12±0.73	11.96±0.67	13.83±0.29	17.69±0.48
20	6.10±0.36	14.48±0.67	32.50±0.92	16.43±0.89	20.27±0.51	25.92±0.30
30	11.90± 0.73	18.35±1.20	41.54±0.31	20.94 ±0.94	26.72±0.64	35.13±0.27
45	16.09±0.40	23.52±0.49	49.94±0.58	26.75±0.47	35.11±0.30	40.92±0.45
60	20.93 0.80	29.97±0.30	56.43±0.39	31.91±1.43	43.51±0.56	44.82±0.52
90	24.95±0.64	32.58±0.32	65.49±0.20	39.66±0.54	48.05±0.34	50.66±0.41
120	28.49±0.49	43.54±1.70	66.20±0.10	45.49±0.38	52.61±0.64	60.03±0.20

Data are expressed as mean ± S.D. (n=3)

Table 11: Dissolution release profile of physical mixtures

Time (min)	Cumulative Mean Percent Released ± Standard Deviation					
	Pure Drug	PM 1	PM 2	PM 3	PM 4	PM 5
5	0.32±0.45	8.03±0.43	10.3±0.59	9.54±0.31	8.35±1.58	9.03±0.59
10	4.18±0.12	9.96±0.37	12.52±0.91	11.4±0.59	10.8±0.43	11.98±0.1.31
20	6.10±0.36	12.52±0.67	15.75±0.48	14.76±0.38	13.82±0.50	15.19±0.92
30	11.90± 0.73	14.71±0.20	18.96±0.31	18.43±0.51	16.93±0.36	17.4±0.30
45	16.09±0.40	17.32±0.19	20.89±0.63	20.00 ±0.32	18.64±0.58	18.72±0.58
60	20.93 0.80	19.28±0.22	23.42±0.34	22.38±1.46	21.21±0.42	22.27±0.41
90	29.95±0.64	22.14±1.82	26.62±0.40	25.52±0.36	23.4±0.18	24.1±0.24
120	34.49±0.49	23.1±0.38	29.17±1.29	27.4±0.91	24.42±1.53	26.36±0.31

Data are expressed as mean ± S.D. (n=3)

Table 12: Determination of dissolution efficiency of solid dispersions

Formulation Number	DE_{30} %	DE_{120} %
Pure drug	5.18	18.28
ATV-Ca 1	13.83	28.97
ATV-Ca 2	24.77	44.16
ATV-Ca 3	18.39	34.03
ATV-Ca 4	19.89	37.12
ATV-Ca 5	19.90	37.69
ATV-Ca 6	13.88	27.84
ATV-Ca 7	24.02	43.03
ATV-Ca 8	14.63	32.34
ATV-Ca 8	17.64	36.28
ATV-Ca 10	18.39	37.69
ATV-Ca 11	10.13	21.93
ATV-Ca 12	24.02	42.47
ATV-Ca 13	11.26	24.47
ATV-Ca 14	13.88	30.37
ATV-Ca 15	16.89	34.31
PM 1	9.94	15.32
PM 2	12.19	18.17
PM 3	12.80	17.29
PM 4	10.69	16.25
PM 5	10.62	16.62

Table 13: Characterization of blends

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner Ratio	Compressibility index (%)	Angle of Repose(°)
T1	0.643±0.005	0.745±0.001	1.120±1.236	12.447±0.014	24.280±0.446
T2	0.578±0.008	0.619±0.004	1.127±0.782	11.496±0.006	24.221±0.728
T3	0.626±0.008	0.727±0.001	1.116±0.803	12.411±0.003	23.405±0.449
T4	0.564±0.002	0.628±0.009	1.122±0.552	12.318±0.006	20.055±0.876
T5	0.682±0.009	0.656±0.011	1.128±0.496	12.224±0.018	23.715±0.336

Table 14: Characterization of atorvastatin calcium solid dispersion tablets

Formulation code	Thickness (mm)	Weight uniformity (mg)	Hardness (Kg/Cm^2)	Friability (%)	Disintegration time (Minutes)
T1	3.21 ± 0.04	250 ± 2.0	3.3± 0.28	0.44 ± 0.011	27
T2	3.14± 0.02	252 ± 6.1	3.0 ± 0.11	0.67 ± 0.008	20
T3	3.22 ± 0.06	248 ± 2.0	3.0 ± 0.60	0.52 ± 0.027	15
T4	3.74 ±0.04	249 ± 3.0	3.3 ± 0.15	0.56 ± 0.013	13
T5	4.31± 0.03	250 ± 0.28	2.3 ± 0.28	0.37 ± 0.091	6

Table 15: Drug content of T1-T5 solid dispersion tablets

Formulation code	Drug content (mg per tablet)	Drug content (%)
T1	19.91 ± 0.017	99.56 ± 0.24
T2	19.53 ± 0.034	97.65 ± 0.34
T3	20.12 ± 0.041	100.6 ± 0.41
T4	19.42 ± 0.011	97.12 ± 0.11
T5	20.17 ± 0.024	100.85 ± 0.45

Table 16: Dissolution profile of atorvastatin calcium from marketed product andsolid dispersion tablets

Time (min)	Cumulative Mean Percent Released ± Standard Deviation					
	MP	T1	T2	T3	T4	T5
5	4.17±0.11	9.32±0.48	10.60±0.82	10.92±0.26	15.75±0.23	18.96±0.67
10	6.11± 0.28	10.61±0.63	12.59±0.71	14.47±0.45	18.98±0.35	24.12±0.28
20	10.61±0.24	18.98±1.25	18.99±0.62	24.13±1.45	22.21±1.57	30.58±0.27
30	14.48±0.46	26.72±0.97	28.65±0.53	33.16±0.40	36.38±0.58	39.65±0.58
45	19.00±0.84	32.53±0.81	34.47±0.48	40.27±0.31	38.35±0.46	46.13±0.26
60	20.31 ±0.96	40.28±0.59	42.86±1.34	48.02±0.47	53.82±0.90	56.46±1.35
90	23.54±0.45	46.76±0.64	54.80±0.56	55.79±0.64	59.02±0.27	64.84±0.96
120	24.21±0.54	48.09±0.96	56.47±0.41	62.28±0.82	66.13±0.38	69.41±0.46

Data are expressed as mean ± S.D. (n=3)

Table 17: Dissolution efficiency of marketed product and solid dispersion tablets

Formulation Number	Dissolution efficiency (%)	
	DE_{30}	DE_{120}
MP	6.71	13.13
T1	12.76	28.97
T2	13.51	33.47
T3	16.89	35.72
T4	17.64	38.53
T5	22.14	42.19

Table 18: Fitting of drug release from T5 tablet to various release kinetic models

S. No.	Mech.	Slope	R^2
1	Zero order	0.446	0.930
2	First order	0.003	0.976
3	Higuchi	5.971	0.972
4	Hixson Crowell cube root law	0.026	0.931
5	Korseyemer - Peppas	0.430	0.991

Table 19: Evaluation parameters after stability studies

Parameters	Conditions 40ºC (75±5 % RH)				
Time Period(days)	0	7	14	21	30
Color appearance	Grey	Grey	Grey	Grey	Grey
Hardness (kg/cm^2)	3.0	3.0	3.0	3.0	2.9
Drug Content (mg)	98.94	98.93	98.93	98.93	98.91
Disintegration Time (s)	10	10	10	10	10

Table 20: Serum lipid profiles of various experimental groups at different time intervals

S.No.	Experimental group	Time intervals	Total cholesterol (mg/dl)*	Total TG (mg/dl)*	HDL - cholesterol (mg/dl)*
1.	Control	Initial	62.7 ± 3.37	72.27 ± 0.18	22 ± 1.3
		7 days	76.8 ± 4.48	149 ± 1.92	34 ± 2.6
		14 days	91.3 ± 2.95	192 ± 2.28	39 ± 1.4
2.	Reference	Initial	54.6 ± 2.55	75 ± 2.16	20 ± 1.56
		7 days	60.2 ± 2.43	128 ± 0.42	51 ± 2.34
		14 days	57.7 ± 1.51**	144 ± 3.21**	55 ± 1.85**
3.	Test	Initial	61.23 ± 2.32	80.14 ± 1.06	21 ± 1.67
		7 days	64.3 ± 240	132 ± 2.03	54 ± 2.45
		14 days	57.8 ± 1.43**	112 ± 1.15**	58 ± 1.50**

*Mean ± SD, n=6, **p < 0.001

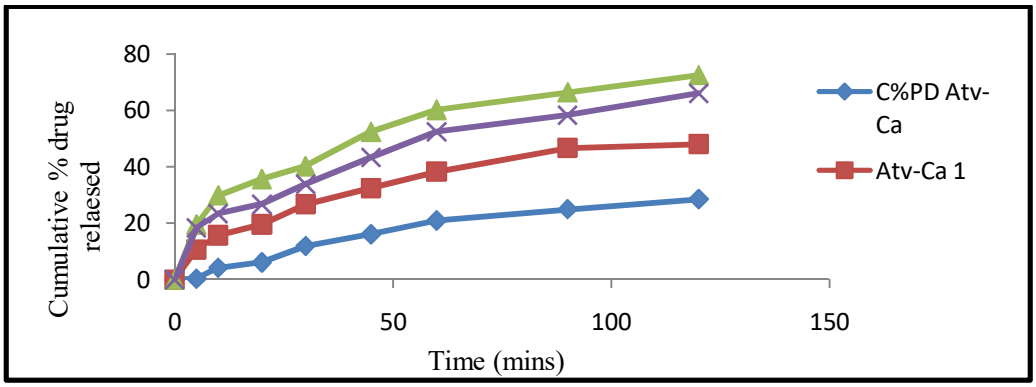


Figure: 2: *In vitro* dissolution profile of cumulative %drug released vs time prepared by kneading method

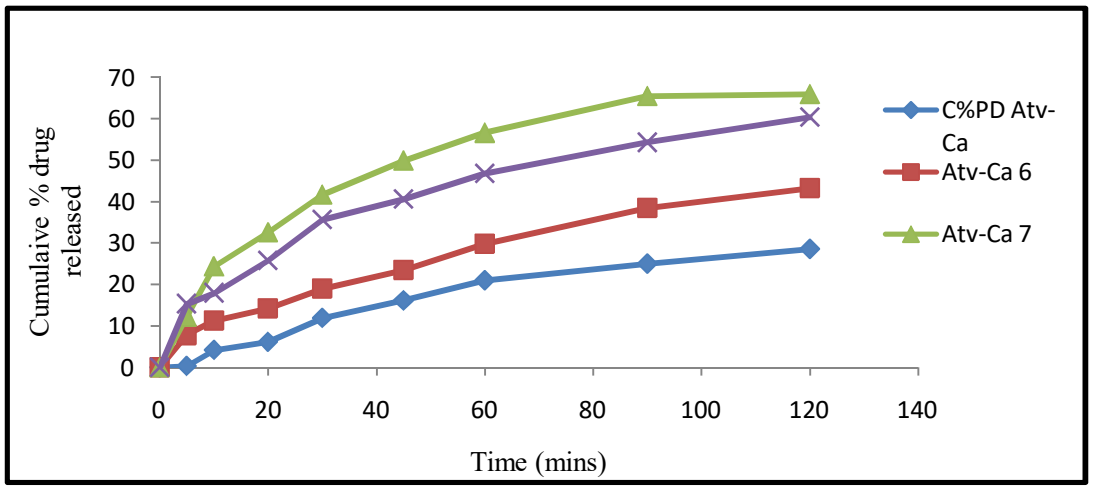


Figure: 3: *In vitro* dissolution profile of cumulative %drug released vs time prepared by solvent evaporation method

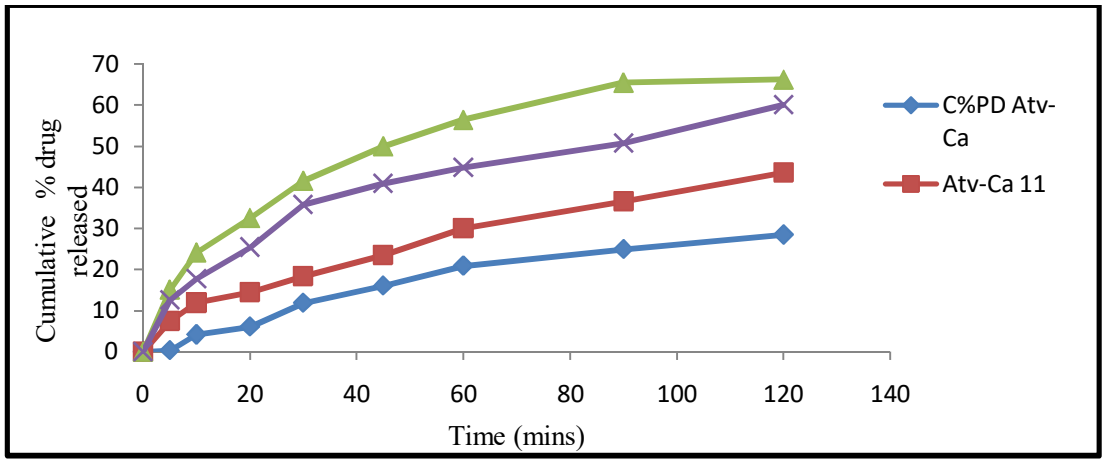


Figure 4: *In vitro* dissolution profile of cumulative %drug released vs time prepared by solvent wetting method

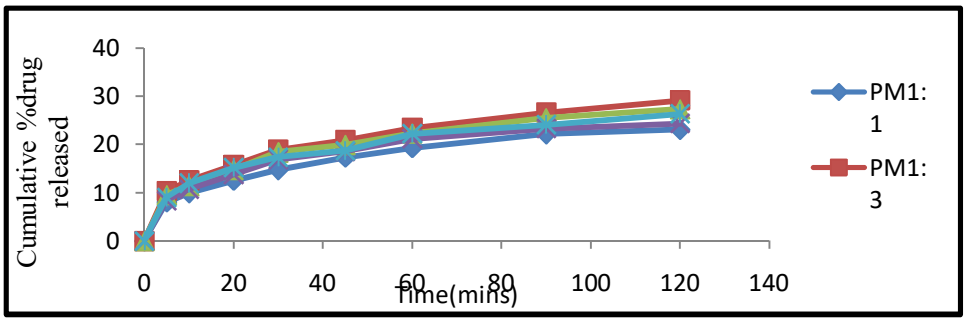


Figure: 5: *In vitro* dissolution profile of cumulative %drug released vs time prepared by physical mixing

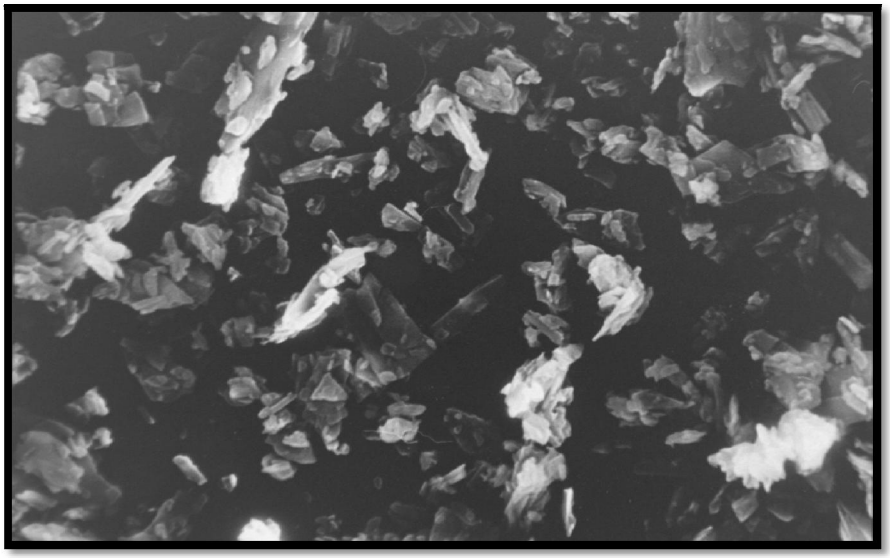


Figure 6: Scanning electron photomicrograph of atorvastatin calcium

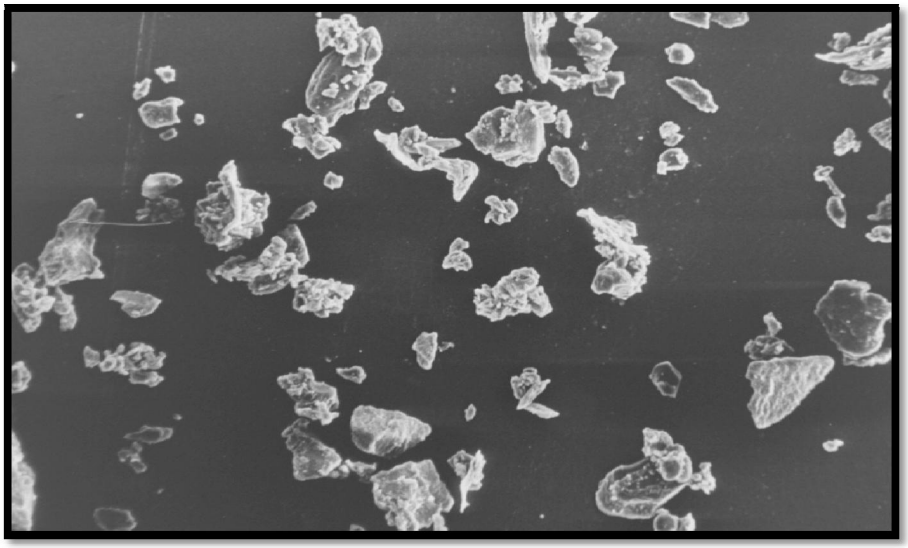


Figure 7: Scanning electron photomicrograph of modified gum karaya

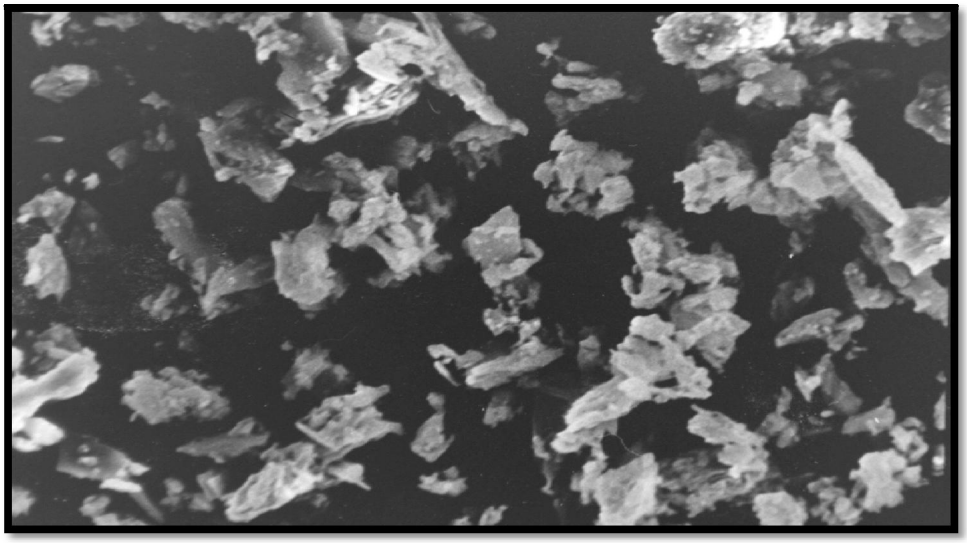


Figure 8: Scanning electron photomicrograph of physical mixtures (1:3) of atorvastatin calcium and modified gum karaya

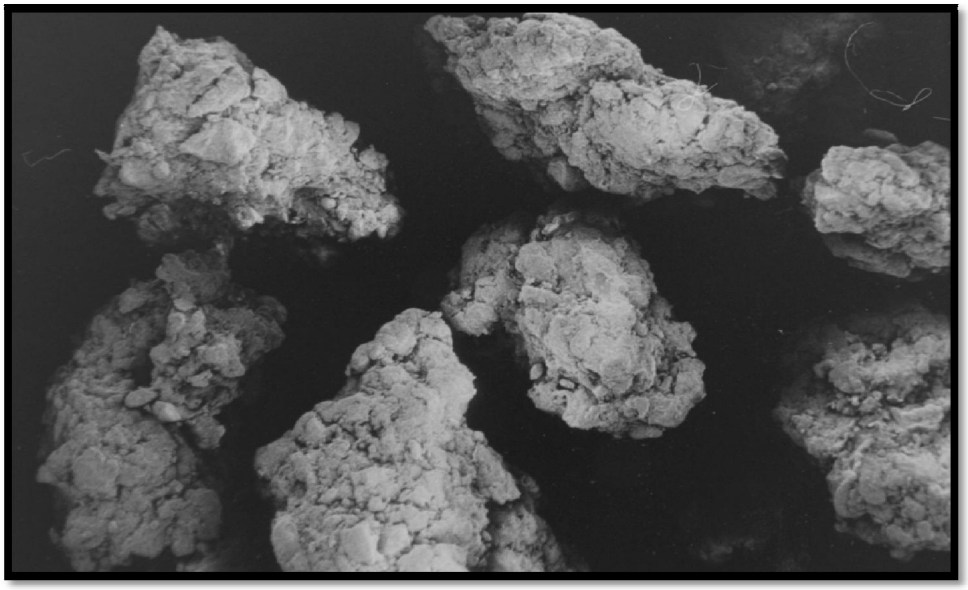


Figure 9: Scanning electron photomicrograph of ATV-Ca 2 formulation

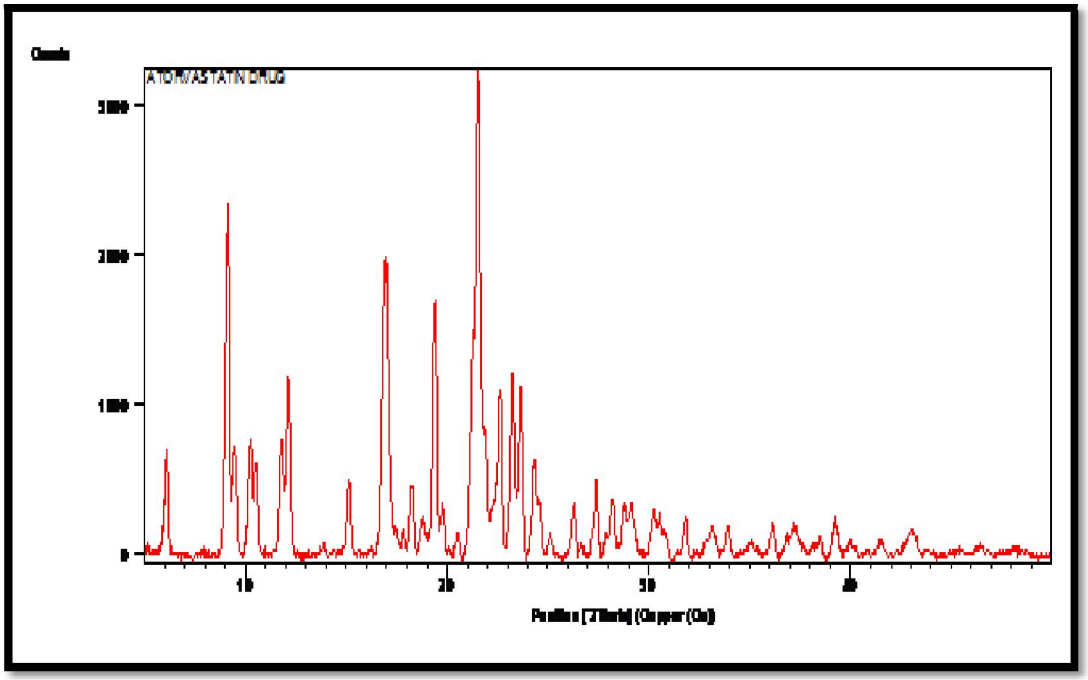


Figure: 10: X-ray diffraction of atorvastatin calcium

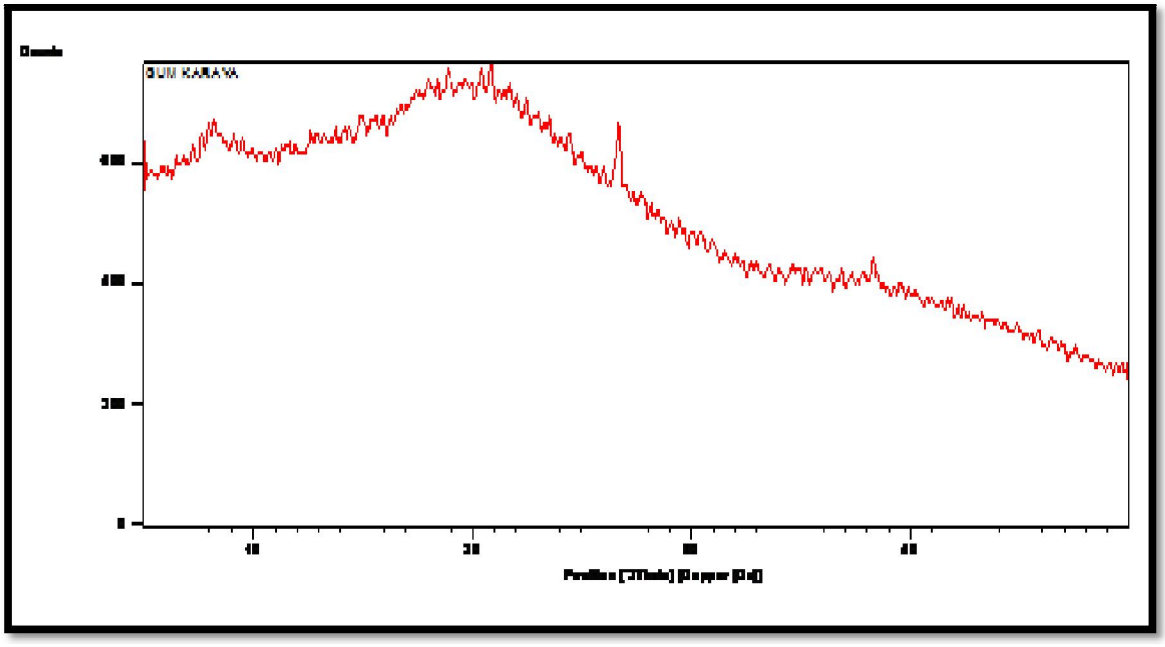


Figure: 11: X-ray diffraction of modified gum karaya

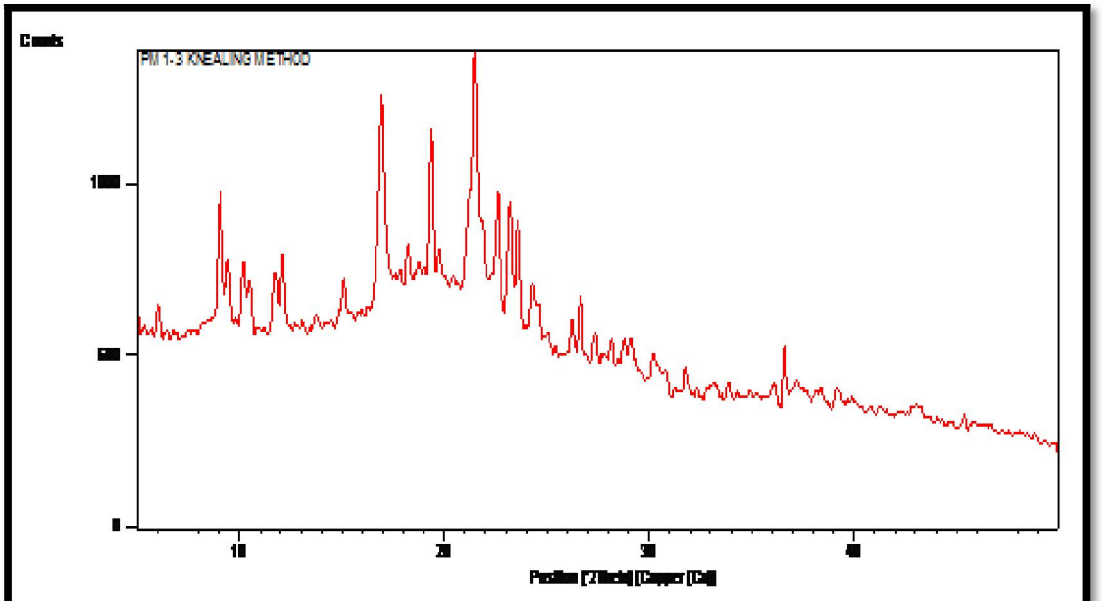


Figure 12: X-ray diffraction of physical mixtures (1:3) of atorvastatin calcium and modified gum karaya

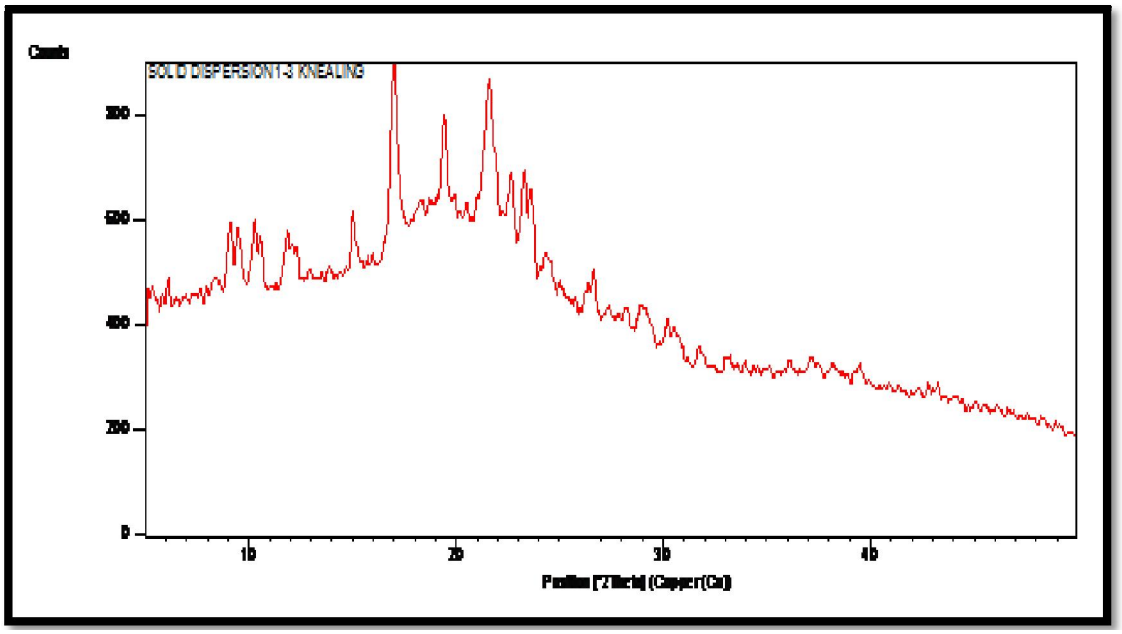


Figure 13: X-ray diffraction of ATV-Ca 2 formulation

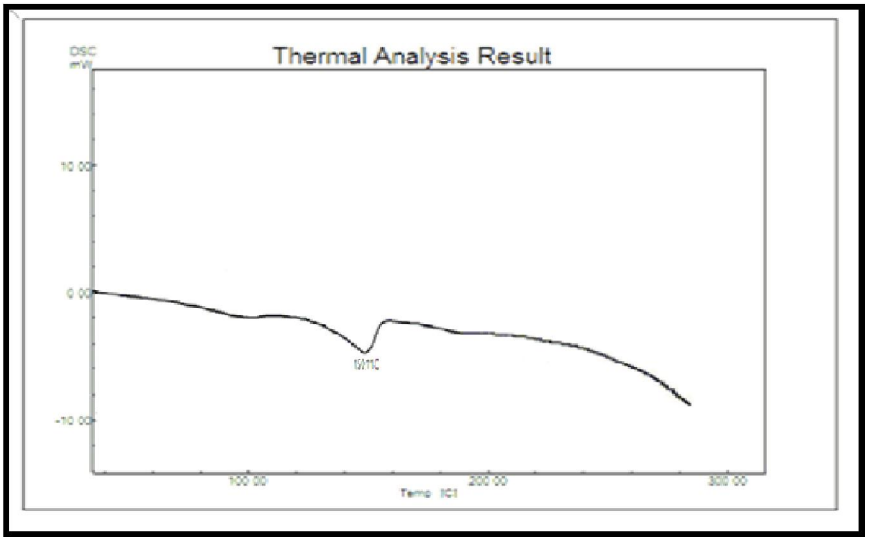


Figure 14: DSC thermogram of atorvastatin calcium

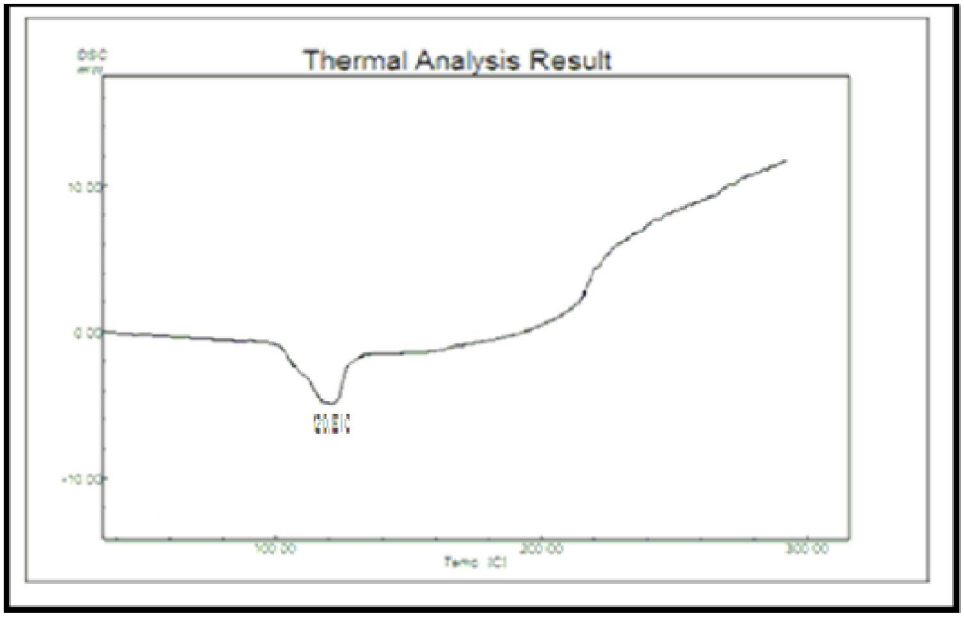


Figure15: DSC thermogram of modified gum karaya

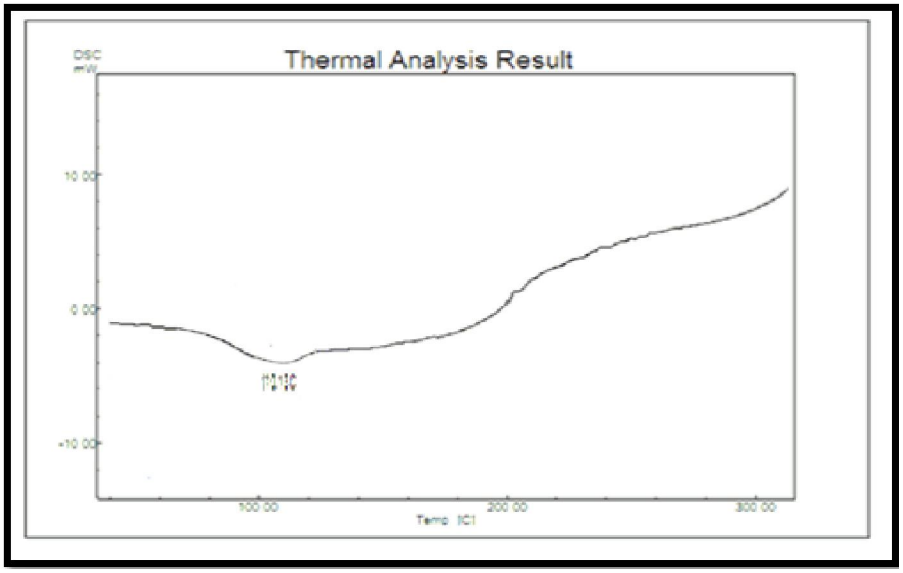


Figure16: DSC thermogram of ATV-Ca 2 solid dispersions

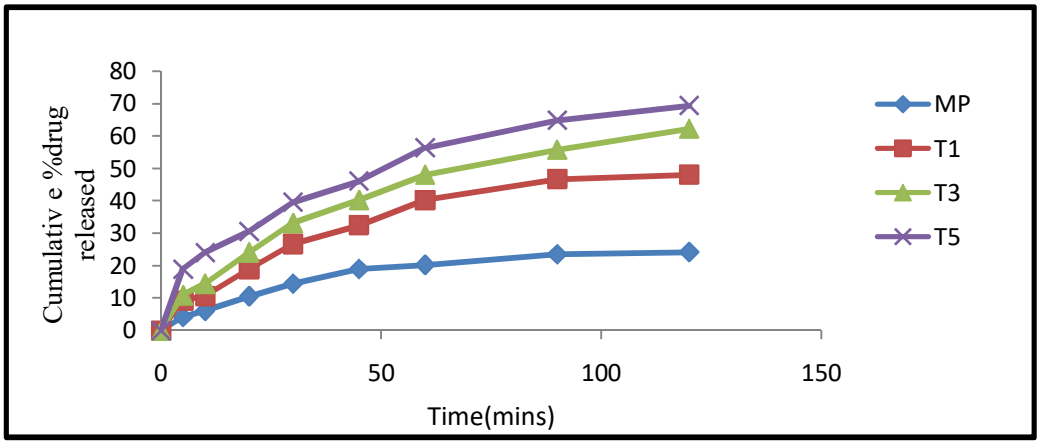


Figure 17: Plot of cumulative %drug released vs time of marketed product and solid dispersion tablets

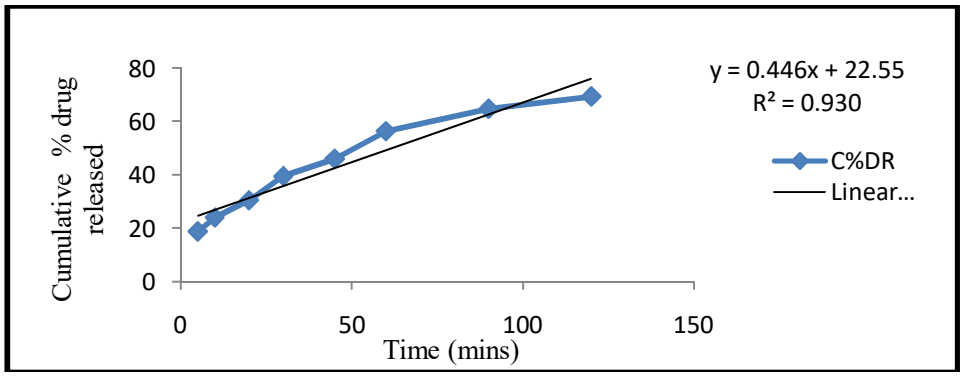


Figure 18: Zero order release profile of T5 atorvastatin calcium solid dispersion tablets

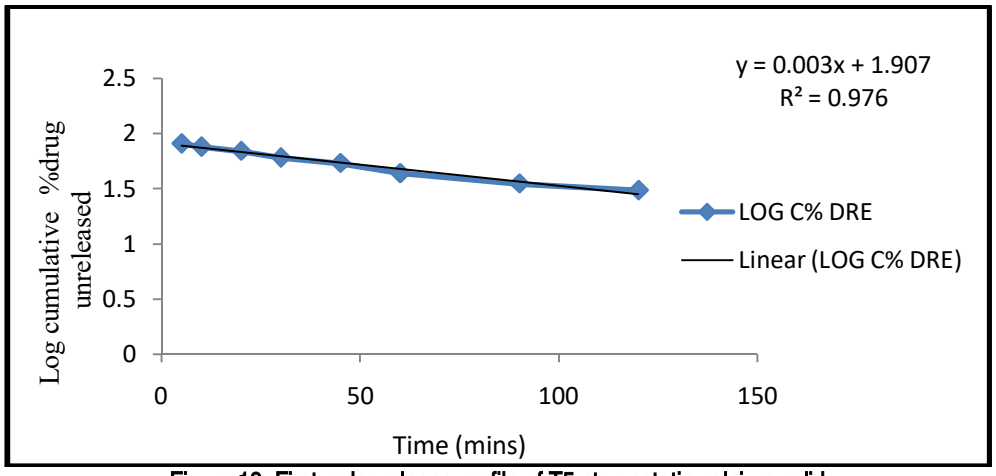


Figure 19: First order release profile of T5 atorvastatin calcium solid dispersion tablets

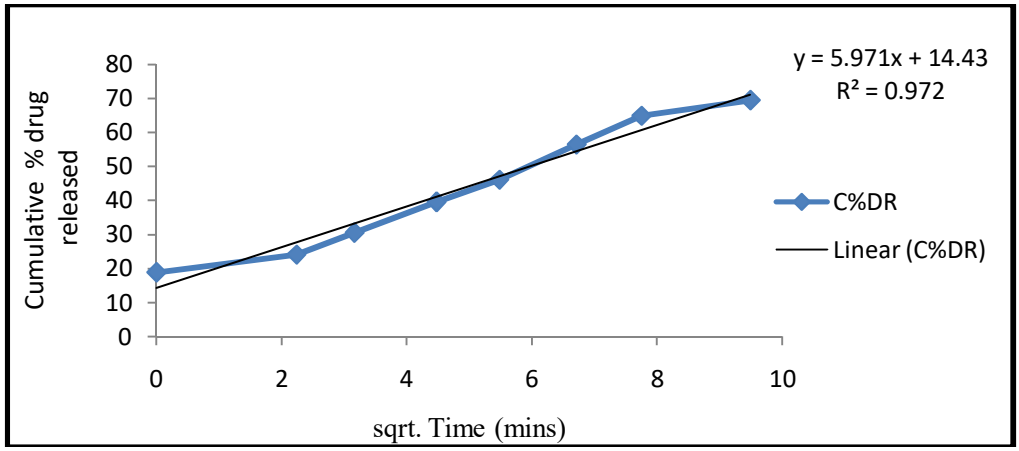


Figure 20: Higuchi release profile of T5 atorvastatin calcium solid dispersion tablets

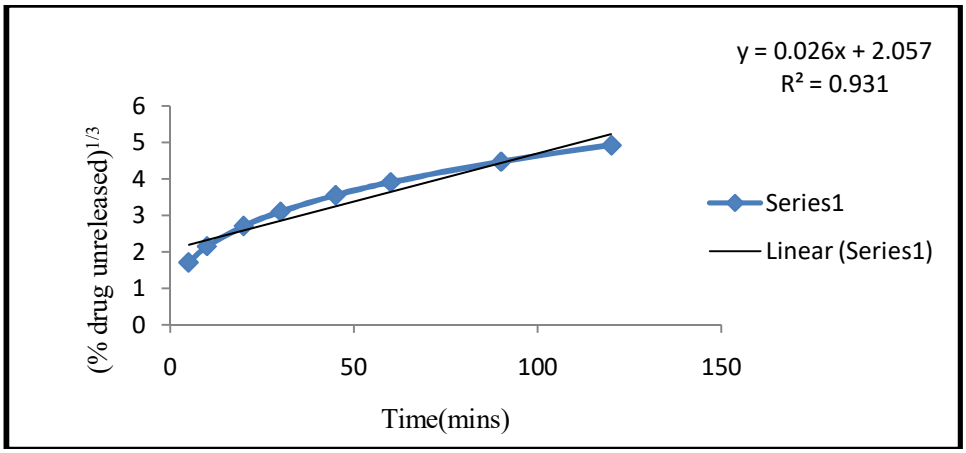


Figure 21: Hixson crowell cube root law release profile of T5 atorvastatin calcium solid dispersion tablets formulation

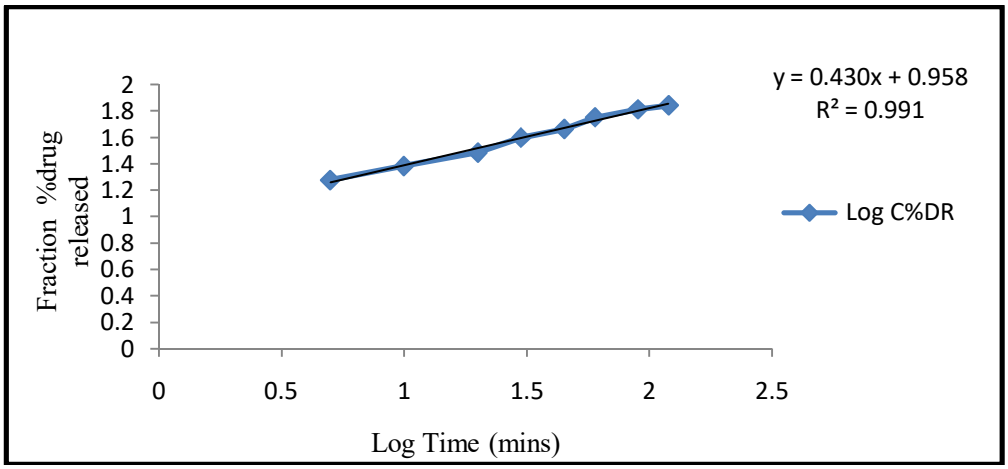


Figure 22: Korseyemer- peppas release profile of T5 atorvastatin calcium solid dispersion tablets

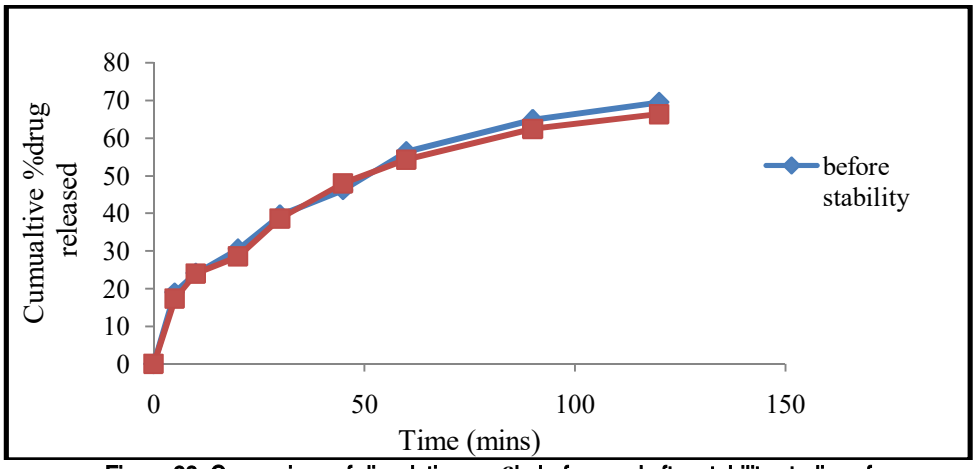


Figure 23: Comparison of dissolution profile before and after stability studies of T5 solid dispersion tablets

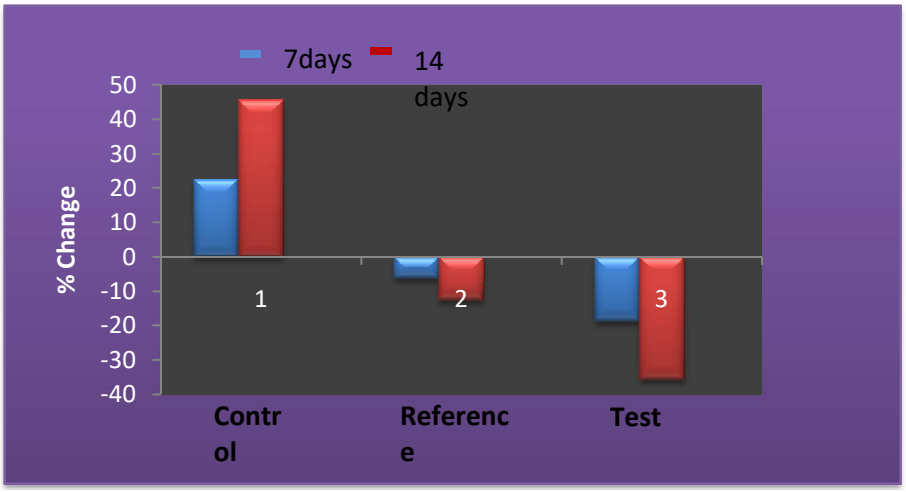


Figure 24: Percent change in serum total cholesterol levels of experimental group at different time intervals

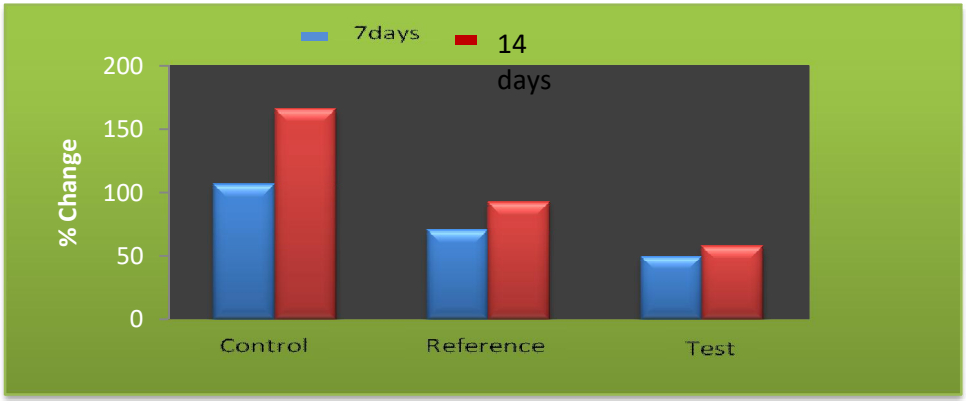


Figure 25: Percent increase in serum TG levels of experimental group at different time intervals

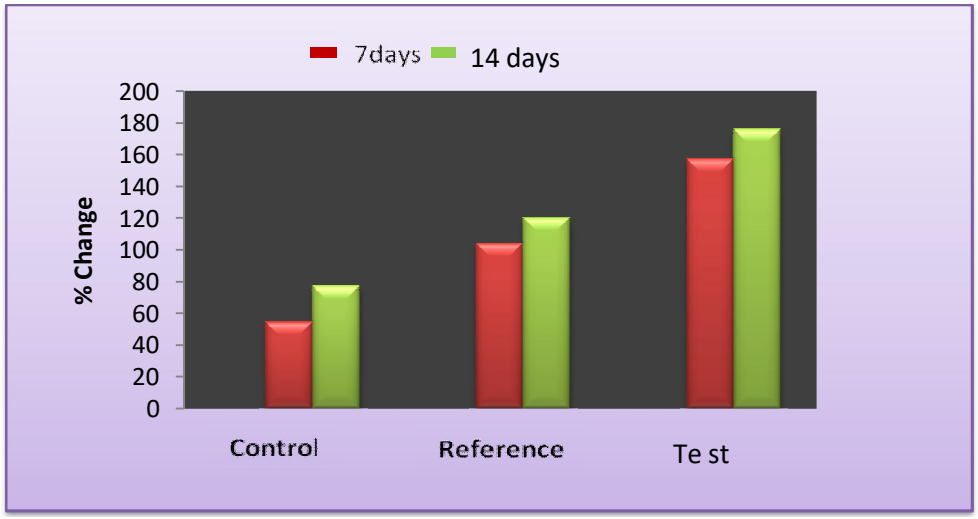


Figure 26: Percent increase in serum HDL-cholesterol levels of experimental group at different time intervals

Hypolipidemic drugs like atorvastatin calcium (HMG CoA reductase inhibitors) are known to elevate total cholesterol and TG level in blood. At the same time they cause elevation of the HDL-cholesterol levels, which promote the removal of cholesterol from peripheral cells and facilitate the delivery back to the liver. This pharmacodynamic effect is reported to be dose dependent hence was used as a comparison of the *in vivo* performance of pure atorvastatin calcium and solid dispersion 1:3. Administration of excess coconut oil, which is a rich source of saturated fatty acids, promotes biosynthesis of cholesterol in liver and leads to hypercholesterolemia. The serum lipid profiles of all the experimental groups at different time intervals are Table 20 and the % changes in lipid profiles are plotted in Figure 25 to 26. As expected, after7days of treatment with excess coconut oil, control group showed significant increase in total cholesterol, TG and HDL-cholesterol. Whereas, reference group showed around 16%decrease in total cholesterol, 21%increase in TG and17% increase in HDL-cholesterol. Interestingly, test group in comparison to reference presented three-fold decrease in total cholesterol, almost similar increase in TG and 1.4-fold increase in HDL-cholesterol.After14 days of similar treatment, control group showed further increase in all the lipid levels. The reference group showed slight further decrease in total cholesterol, significant increase in TG and negligible increase in HDL-cholesterol. Test group on the other hand, presented further two fold decrease in total cholesterol, negligible increase in TG and further1.4-fold increase in HDL-cholesterol in comparison with the reference group. Thus, at the of 14 days study solid dispersion 1:3 performed better than pure atorvastatin calcium in reducing total cholesterol and TG level and increasing HDL- cholesterol levels. This could primarily attribute to improved solubility and dissolution associated with amorphization of the drug.

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