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Characterization Of Atorvastatin Calcium And Excipients

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ABSTRACT:

Characterization of Atorvastatin Calcium and excipients, Characterisation such as Assessment of Organoleptic properties of viz. colour, appearance, Melting pointdetermination, Spectral characteristics- Ultraviolet spectroscopy (UV), Infrared spectroscopy (IR), Determination of saturation solubility: Powder X-ray diffraction study parameters are performed

KEYWORDS: A torvastatin Calcium,Powder X-ray diffraction,organoleptic properties

INTRODUCTION:

Over 60% of new chemical entities that are poorly soluble qualify either as BCS Class II or Class IV and they provide challenges as well as opportunities to scientists working in formulation development. The conventional solubilization approaches such as physical modifications of drug crystals (surface alteration of API, micronization or micro-milling) usually lead to a limited dissolution and solubility enhancement, but when developing a medium or high dosed formulation, the non-conventional formulation approaches are often required particularly when dealing with almost water-insoluble compounds usually characterized by a high melting point and/or very high lipophilicity .Dosage requirements in the drug development also introduce opportunities to explore the other non-conventional formulation approaches for enhanced solubilization . Liquid and solid dispersions, especially, are widely considered the alternative methods, which may require a range of factors for

selecting one versus the other. Most importantly, the factors considered are: polymers, surfactants and solubilizers types, thermal stability, aqueous and organic solubility and compatibility, pH dependent invariability, and solubilization capability among others.Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states. Several methods have been employed to improve the solubility of poorly water soluble drugs. A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs .The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi. Atorvastatin Calcium is HMG COA Reductase inhibitor

Characterization of Atorvastatin Calcium

The characterization of drug was carried out by conducting various tests as follows;

i. Assessment of Organoleptic properties of viz. colour, appearance

ii. Melting point determination

iii. Spectral characteristics- Ultraviolet spectroscopy (UV), Infrared spectroscopy (IR)

iv. Determination of saturation solubility:

v. Powder X-ray diffraction study

Organoleptic properties:

Organoleptic properties:

Colour: - White

Odour: - Odourless

Determination of melting point:

Melting point of Atorvastatin Calciumwas determined by glass capillary method. The programmable melting point apparatus was used. Drug filled capillary was placed in the melting point apparatus containing silicon oil as a heating medium and the melting point

was noted. The stirrer was kept on while recording the melting point so as to ensure uniform heat transfer. Reading was recorded in triplicate.

Melting Range:

Melting point of Atorvastatin Calcium was found to be 156-158^{0}C.The reported range for Atorvastatin Calcium was between 156-158^{0}C. Hence, observed melting point values are in good agreement with the reported value.

Spectral characteristics:

Determination of λ max in UV range:

10mg of Atorvastatin Calcium was accurately weighed and transferred to 100ml volumetric flask. It was dissolved in methanol and volume was adjusted with methanol to get stock solution (100µg/ml). This was diluted with methanol to give solutions of variousconcentrations. The solutions were scanned in the range of 400 to 200 nm and respective λ max values were recorded.

Preparation of calibration curve of Atorvastatin Calcium

10mg of Atorvastatin Calcium was accurately weighed and transferred to 100ml volumetric flask. It was dissolved in methanol and volume was adjusted with methanol to get stock solution (100µg/ml). It was further diluted with methanol to give concentrations 4, 8,16,32,40 µg/ml. Absorbance was measured at 247 nm and calibration curves were plotted.

Spectral analysis:

) Spectral characterisation of Atorvastatin Calcium in Methanol:

Determination of λ_{max}:-

The UV spectrum of Atorvastatin Calcium taken in Methanol is shown in figure. The λ_{max} was 246 nm.

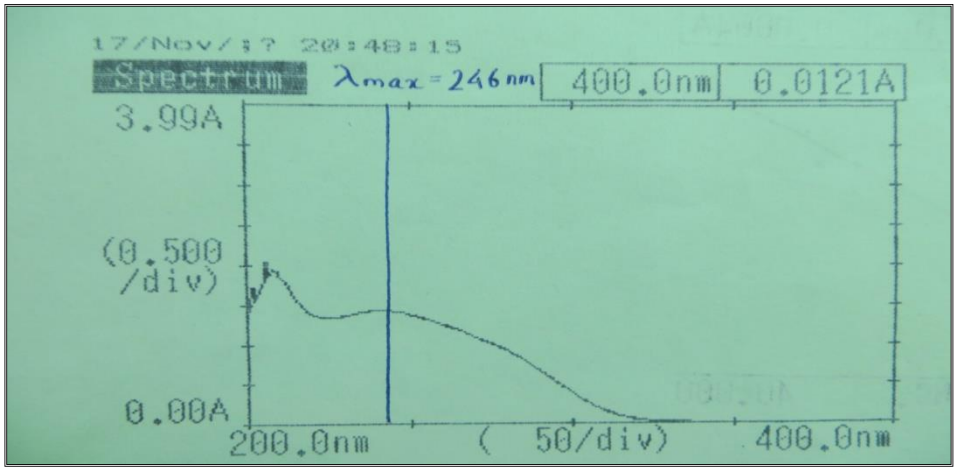

Figure: UV absorption spectrum of Atorvastatin Calcium in Methanol

Standard calibration curve of Atorvastatin Calcium Methanol:

The UV absorption data at 246 nm for various concentrations of Atorvastatin Calcium showed good linearity (r^2- 0.998) over the concentration range of 4-40µg/ml. Hence, the sample of Atorvastatin Calcium was found to obey Beer- Lambert's law over this range.

Table: Calibration curve of Atorvastatin Calcium in Methanol

Sr. no	Concentration (µg/ml)	Absorbance
1	0	0
2	4	0.212
3	8	0.3704
4	16	0.6585
5	32	1.4026
6	40	1.724

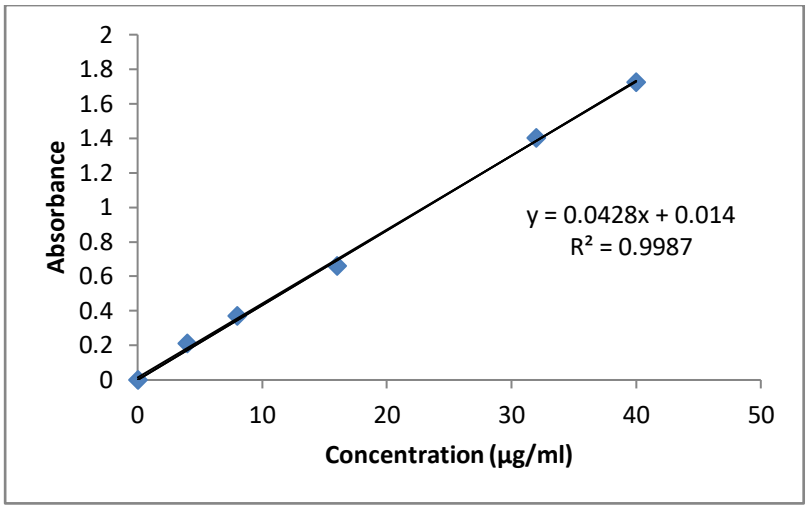

Figure: Calibration curve of Atorvastatin Calcium in Methanol

Spectral characterisation of Atorvastatin Calcium in 0.05 M Phosphte Buffer.

Determination of λ_{max} :-

The UV spectrum of Atorvastatin Calcium taken in 0.05 M Phosphate buffer. The λ_{max} was 242 nm.Calibration curve as shown in Figure

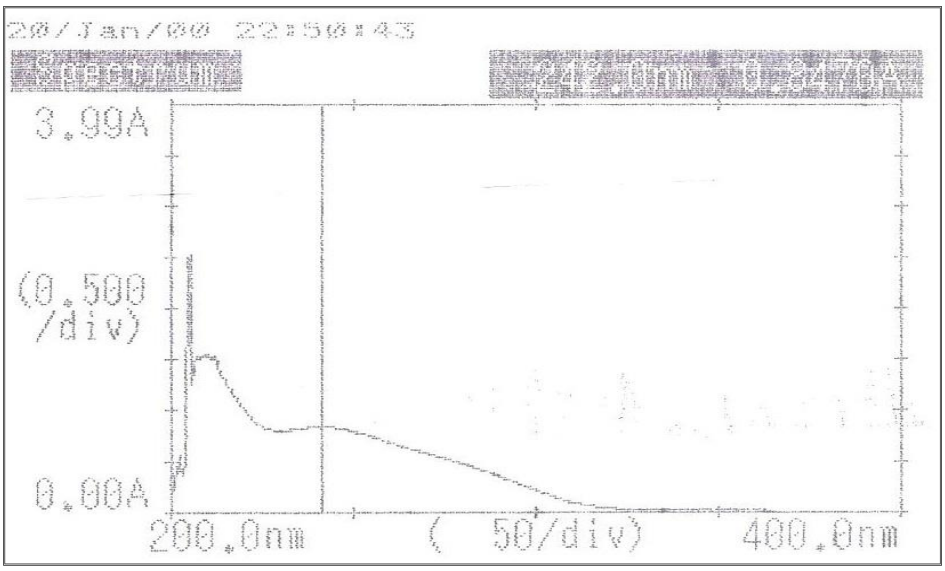

Figure: UV absorption spectrum of Atorvastatin Calcium in 0.05 M Phosphate buffer

Table: Calibration curve of Atorvastatin Calcium in Phosphate Buffer

Sr. no	Concentration (µg/ml)	Absorbance
1	0	0
2	4	0.204
3	8	0.419
4	16	0.798
5	32	1.378
6	40	1.895

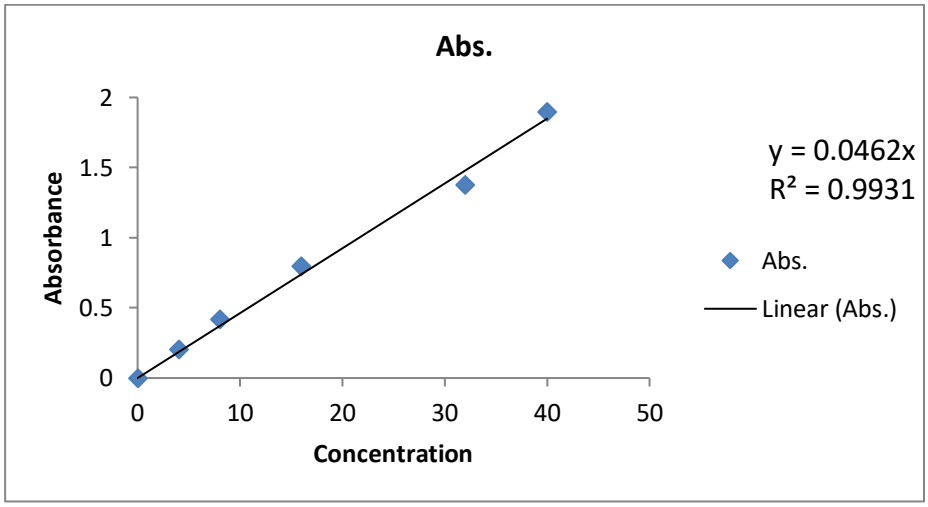

Figure: Calibration curve of AtorvastatinCalcium in Phosphate Buffer.

Determination of infrared spectrum:

IR absorption spectrum of Atorvastatin Calciumwas recorded by using FTIR spectrophotometer (FTIR-8400s) wherein 1-2 mg of drug sample was used. The baseline correction was carried out using dried potassium bromide. Subsequently, the spectrum of mixture of drug and potassium bromide was recorded and the peaks belonging to major functional groups were identified.

Infrared Spectrum ofAtorvastatin Calcium:

FTIR spectrum has been successfully used for identification and structural analysis of organic compounds. IR spectrum of Atorvastatin Calcium was taken and show in figure

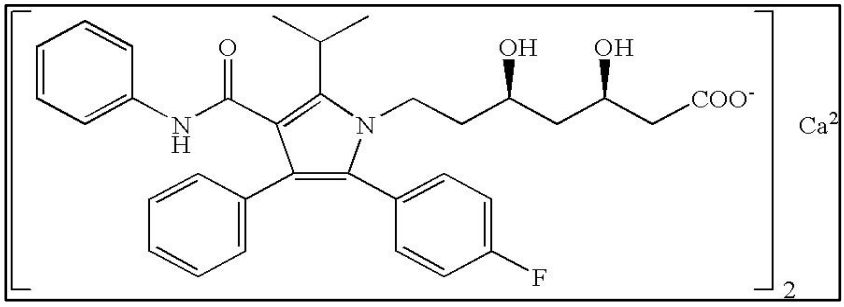

Figure: Structure of Atorvastatin Calcium

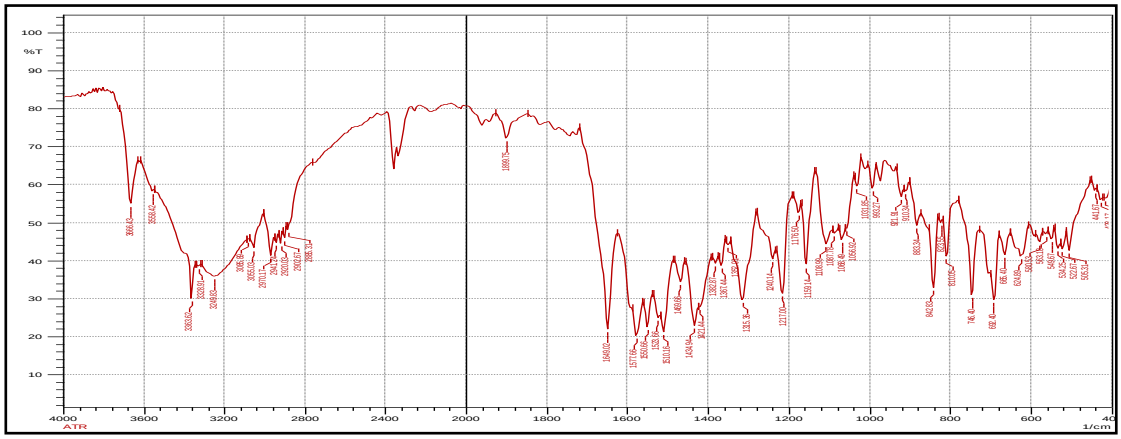

Figure: Infraredspectrum of Atorvastatin Calcium

Interpretation of Infrared spectrum of sample of Atorvastatin Calciumshown in Table

Table: Interpretation of IR Spectrum of Atorvastatin Calcium

IR Frequency (CM^{-1})	Corresponding functional group and type of molecular vibration
3085.89	Aromatic group
2970.17	-CH_3 Stretching
2930.58	CH2 Stretching
1610.67	C=N

1579.56	C-C Aromatic
768.38	C-F

Atorvastatin Calcium IR spectrum is shown in Figure.The IR spectrum of Atorvastatin Calcium reveals the presence of major functional group in the structure of Atorvastatin Calcium supporting its identity.

Determination of saturation solubility:

For this excess quantities of Atorvastatin Calciumwere added into each of 3ml of distilled water, contained in glass vials. The solutions were shaken for 48 h using orbital shaker incubator (temperature maintained at 37^0C ±1^0C). The solutions were filtered through membrane filter 0.45µ and the filtrate was diluted properly with respective solvents and the absorbance was recorded.

Determination of saturation solubility:

Saturation solubility of Atorvastatin Calcium in distilled water was found to be 7.21±0.03µg/ml at 37^0± 2^0C. Saturation solubility of Atorvastatin Calcium in 0.05 M Phosphate buffer was found to be 7.26±0.12µg/ml at 37^0± 2^0C

Powder X-ray diffraction pattern study

X-ray powder diffraction patterns were recorded on a Philips PW 17291 powder X-ray diffractometer using Ni-filtered, Cu Kα radiation, a voltage of 40 kV and a 25mA current. The scanning rate employed was 1◦ min−1 over the 7–70◦ 2θ range. The physical mixture of drug and colloidal silicon dioxide was made in the ratio of 1:25 for comparison.

Powder X-ray diffraction pattern:

The X-ray powder diffraction analysis was done for Atorvastatin Calcium. It shows that Atorvastatin calcium exhibited numerous intense and sharp peaks corresponding to crystalline nature of Atorvastatin calcium.

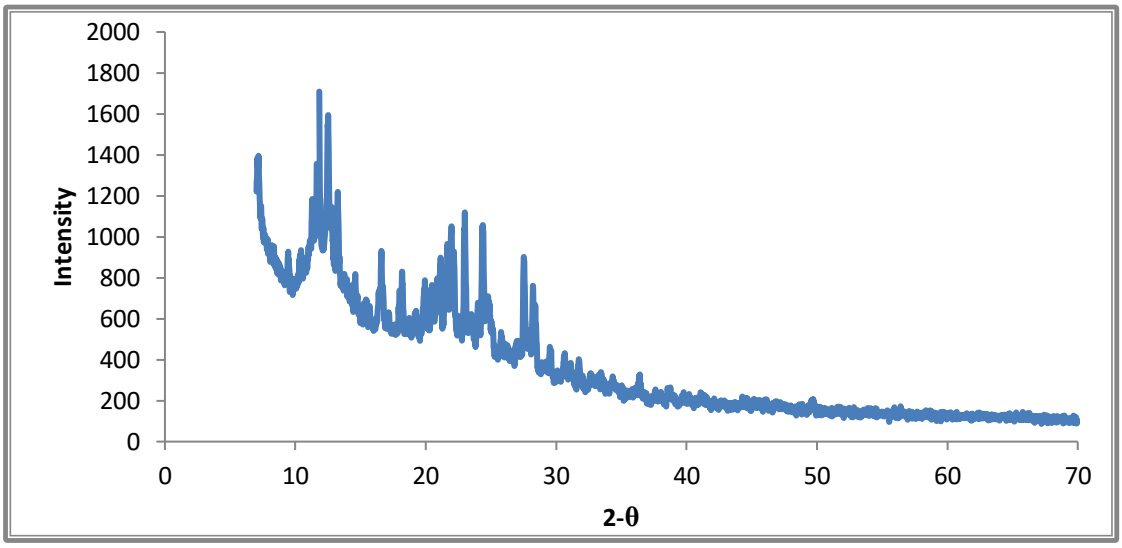

Figure: XRPD of Atorvastatin calcium

XRPD study of and solid dispersion of Atorvastatin Calcium:

The X-ray powder diffraction analysis was done for Atorvastatin Calcium

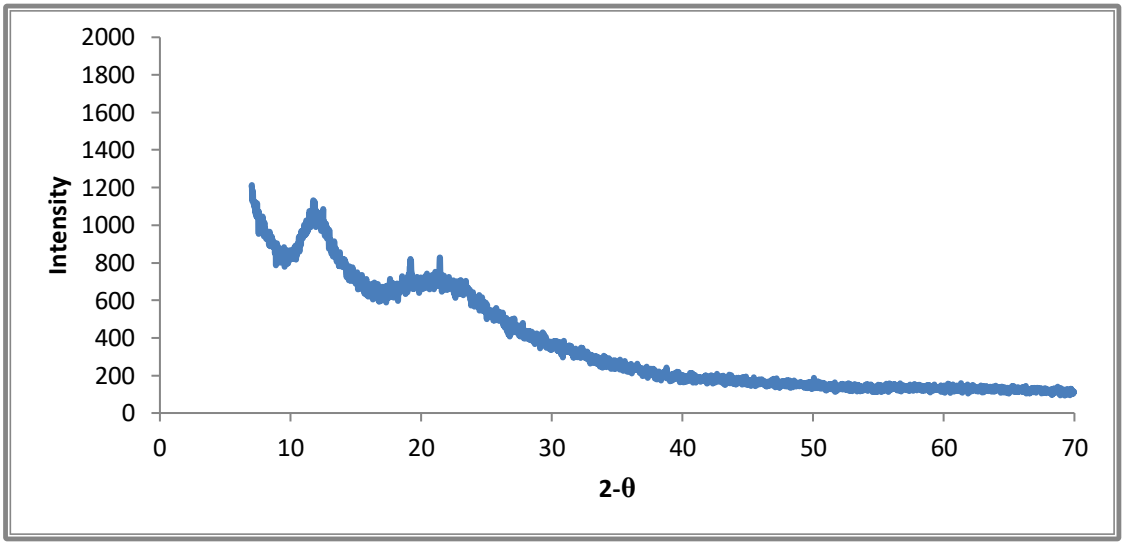

Figure: XRPD of Solid dispersion G-4

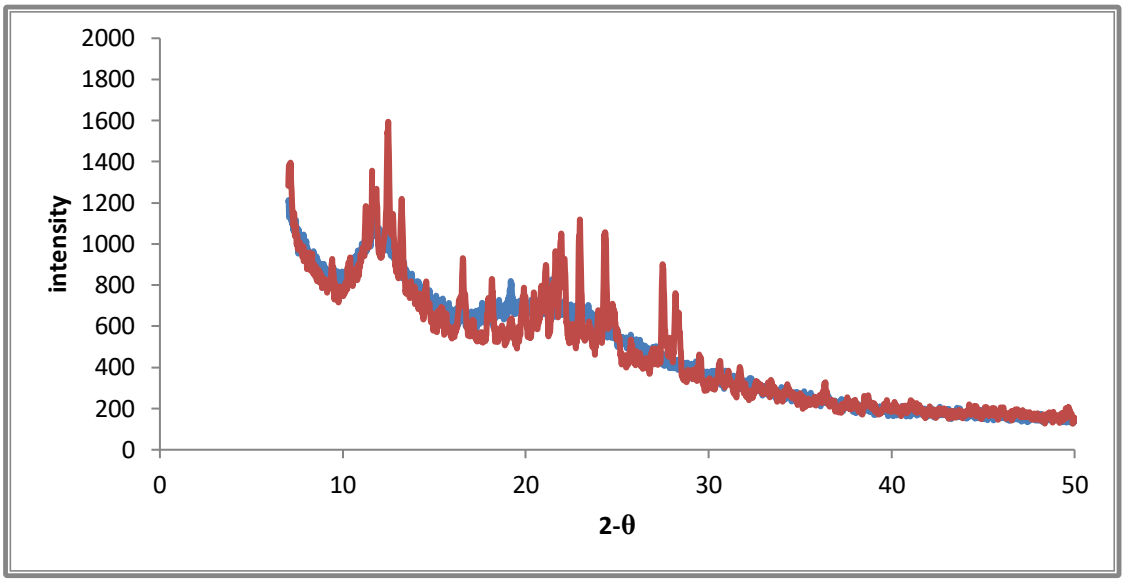

Figure: XRPD of Plain Atorvastatin Calcium and G-4

The XRPD pattern as above indicates that there was significant change in peak intensity of solid dispersion as compare to plain drug.

Characterization of excipients

Organoleptic properties:

Colour: White

Odour: Odourless

Melting point:158-160°C

Determination of melting point:

Melting points of excipients were determined by glass capillary method. The programmable melting point apparatus was used. Excipient filled capillary was placed in the melting point apparatus containing silicon oil as a heating medium and the melting point was noted. The stirrer was kept on while recording the melting point so as to ensure uniform heat transfer. Reading was recorded in triplicate.

Melting Points* of Excipients

Name of polymer	Reported Melting point	Observed Melting point
α Glucosyl Hespiridine	130°C	128-130
PVPK-30	150^0C	148-150^0C

Preparation of solid forms and solid dispersion

Preparation of solid dispersion

a. By Spray drying
b. By Kneading Method
c. By Solvent evaporation Method

Preparation of solid dispersion

In this the two types of solid dispersion were prepared.

1) Drug and α Glucosyl Hespiridine.
2) Drug and PVPK-30.

Three different methods were used for the preparation of solid dispersion of drug and α Glucosyl Hespiridine.

These methods include

1) Spray drying
2) Kneading Method
3) Solvent evaporation.

Each method has its own advantages and disadvantages.

These prepared batches are tested and analysed to get the optimized batch.

A. By spray drying method

In this method, drug and α Glucosyl Hespiridine were used to prepare the solid dispersion. As α Glucosyl Hespiridine is highly soluble in water it forms the complex with the drug and helps for its solubilisation.

The ratio for both Polymer and the Drug were varied and spray dried at optimized instrumental parameter. Drug and α Glucosyl Hespiridine in the ratio of 1:1, 1:2, 1:3, and 1:4

were added to the solvent Ethanol. This solution is then stirred for 10 min. The resultant solution was spray dried using the Lab Spray Dryer (Labultima LU 222 advanced). The following batches of spray drying were prepared

Table: Spray drying parameter

Sr. no.	Parameter	Value
1	Inlet temperature	70^0C
2	Outlet temperature	60^0C
3	Inlet High	80
4	Outlet High	70
5	Cool temperature	45^0C
6	Aspirator Flow Rate	45 Nm^3/hr
7	Feed Pump Flow	1 ml/min
8	De Block On	1 sec
9	De Block off	20 sec
10	Total cycle time	280 min

Batches of solid dispersion of Atorvastatin Calcium with PVPK 30 prepared using spray drying method:

Table: batches for solid dispersion of PVPK-30 by spray drying method

Sr. no.	Drug (mg)	PVPK-30	Batch code

1	500	250	P-1
2	500	500	P-2
3	500	1000	P-3
4	500	1500	P-4

Table: Batches of solid dispersion of α Glucosyl Hespiridine by Spray drying method

Sr. no.	Drug (mg)	α Glucosyl Hespiridine	Batch code
1	500	500	G-1
2	500	1000	G-2
3	500	1500	G-3
4	500	2000	G-4

B. **By Kneading Method**

In this method, α Glucosyl Hespiridineand the drug were mixed in a porcelain dish.then little quantity of solvent was added and triturated the particular mixture until it gets the paste like consistency.Then it was vacuume dried at temp. 40℃ for the 60 minutes. After drying particular formulation triturated again to form the fine powder.Then that powder was passed from the 60 mesh screen.The filterd preparation was ready for the further evaluation. By this method, the different ratios of drug and

α Glucosyl Hespiridine were made

Table: Batches for solid dispersion with α Glucosyl Hespiridineby Kneading Method

Sr.	Drug (mg)	α Glucosyl Hespiridine	Batch code

no.			
1	500	250	G-5
2	500	500	G-6
3	500	1000	G-7
4	500	1500	G-8

C. Solvent Evaporation Method

In this method the the drug and the α Glucosyl Hespiridine were mixed in the ethanol and the solution was poured in the petri dish. Different ratios of the drug and the polymer were mixed and kept for the drying.

Table: Batches for solid dispersion of α Glucosyl HespiridinebySolvent Evaporation Method.

Sr. no.	Drug (mg)	α Glucosyl Hespiridine(mg)	Batch code
1	500	500	G-9
2	500	100	G-10
3	500	1500	G-11
4	500	2000	G-12

Characterisation of solid dispersion:

Determination of melting point:

Melting point was determined using glass capillary method. The programmable melting point apparatus (Make- Veego) was used. Due care was taken to maintain the uniform heating of silicon bath, in which the capillary containing solid forms was placed.

Physico- mechanical properties determination:-

Atorvastatin Calcium, its solid form and solid dispersion were evaluated for the following parameter:

a) Bulk density and Tapped density
b) Compressibility index
c) Hausner's ratio

Bulk and tapped density

Both bulk density (BD) and tapped density (TD) of powder blends were determined. A quantity of 1gm of powder from each formula was lightly shaken to break any agglomerates formed and it was introduced into a 10 ml measuring cylinder and apparent volume were measured (V_0). The cylinder containing the samples were tapped 500 times and the tapped volume (V_t)were measured .The tapping was continued until no further change in volume was noted. BD and TD were calculated using the following formulae

.

$$\textbf{BD} = \frac{\textbf{Weight of the powder}}{\textbf{Volume of the packing}}$$

$$\textbf{TD} = \frac{\textbf{Weight of the powder}}{\textbf{Tapped volume of the packing}}$$

Carr's index(% Compressibility)

The values of compressibility indicates for each of the powder samples were determined using formula

$$\textbf{Carr's index} = \frac{\textbf{Tapped Density- Bulk Density}}{\textbf{Tapped Density}} \textbf{ X 100}$$

Table: Relationship between % compressibility and Flowability

% Compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very poor
> 40	Very very poor

Hausner's ratio

Hausner's ratio was determined for characterization of flow of powder blend. A Hausner's ratio greater than 1.25 is considered as to be an indication of poor flowability. Formula used as follows:

$$\textbf{Hausners ratio} = \frac{\textbf{Tapped Density}}{\textbf{Bulk Density}}$$

Spectrophotometric characterisation:

a) Determination of λ_{max}

Solid dispersion equivalent to 10mg of Atorvastatin Calcium was accurately weighed and transferred to 100ml volumetric flask. It was dissolved in methanol and volume was adjusted with methanol to get stock solution (100µg/ml). This stock solution was again diluted 10 times to get solutions of 10µg/ml concentration. The solutions were scanned in the range of 400 to 200 nm and respective λ max values were recorded.

Infrared spectrophotometry:

Infrared spectrum:

IR absorption spectrum of solid form of Atorvastatin Calcium and its solid dispersion was recorded by potassium bromide dispersion technique in which dry samples and potassium bromide and drug sample were placed in sample holder and infrared spectrum was recorded using FTIR spectrophotometer.

Saturation Solubility:

The saturation solubility of solid forms and solid dispersion was measured in distilled waterand Phosphate Buffer. 3 ml of distilled water and 3 ml of 0.05 M Phosphate Buffer were taken in vial of 5 ml capacity. The drug was added in small increments with stirring until saturation level exists. The vials were kept at 37^0C in orbital shaker incubator for 48 hrs. The resulting solution was filtered by whatman filter paper, diluted and absorbance was recorded at 247 nm.

X-Ray Diffraction Study:-

X-ray powder diffraction patterns were recorded on a Philips PW 17291 powder X-ray diffractometer using Ni-filtered, Cu Kα radiation, a voltage of 40 kV and a 25mA current. The scanning rate employed was 1◦ min−1 over the 7–70◦ 2θ range.

Percent Drug Content

The pre weighed solid dispersion (equivalent to 10 mg of Atorvastatin Calcium) was dissolved in 10 ml methanol. This stock solution was filtered by using whatman filter paper and necessary dilutions were made. Atorvastatin Calcium content in methanol was analyzed UV-spectrophotometrically (UV 1700 Shimadzu) at 247 nm using methanol as blank.

Drug release studies

Drug release studies from solid dispersion were performed using USP dissolution apparatus II using 900 ml of 0.05 M Phosphate buffer as medium at 37 ± 0.5^0C. The speed of the paddle was adjusted to 75rpm. The details of the dissolution parameters are given in Table

Table: Dissolution test details for dissolution study

Sr. No.	Specification	Standard values
1	Apparatus	USP dissolution apparatus II
2	Paddle Speed	75 rpm
3	Volume of medium	900 ml
4	Dissolution Medium	0.05 M Phosphate Buffer at pH 6.8
5	Aliquot taken at each time interval of 5 min.	5ml
6	Temperature	37± 0.5^{o} C.

Pure drug and solid dispersion (equivalent to 10 mg of Atorvastatin Calcium) was taken in muslin cloth and tied to the paddle. An aliquot (5 ml) of sample was collected at an interval of minutes and analyzed for the content of Atorvastatin Calcium by UV-spectrophotometer at 247 nm. An equivalent volume (5 ml) of fresh dissolution medium was added to compensate for the loss due to sampling and results of drug release study were reported.

Scanning electron microscopy study:

The scanning electron microscopic analysis of drug and their solid dispersion were carried out by JSM- 6360A scanning electron microscope operated at acceleration of voltage 15 KV. Prior to estimation samples were coated with 20 nm thin platinum layer by auto fine coater to render them electrically conductive.

Evaluation of solid dispersion of A**torvastatin Calcium**

Atorvastatin Calcium solid dispersion was prepared by following methods.

i) By Spray drying method

ii) By Kneading Method

iii) By Solvent evaporation method

Morphology of solids plays a valuable role in pharmaceutical processing and product development of solid dosage forms. Differences in morphologies may strongly influence the particle orientation, flow ability, packing, compaction, compressibility and dissolution characteristics of drug powder and which then influence the bioavailability of the dosage form. Physicomechanical properties are as shown in Table

Table: Physico-mechanical properties for solid dispersion with PVPK 30 (P-P4) and α Glucosyl Hespiridine (G1-G4) by spray drying method.

Sr. No.	Batch	Bulk density	Tapped density	Hausner's Ratio	Car's index
1	P-1	0.34	0.41	1.20	17.07
2	P-2	0.38	0.43	1.13	11.6
3	P-3	0.38	0.45	1.18	15.55
4	P-4	0.40	0.47	1.17	14.89
5	G-1	0.38	0.41	1.07	7.31
6	G-2	0.38	0.45	1.18	18.42
7	G-3	0.40	0.47	1.17	14.89
8	G-4	0.40	0.50	1.25	20.0
9	G-5	0.36	0.41	1.13	12.19
10	G-6	0.39	0.47	1.20	17.02
11	G-7	0.34	0.40	1.17	15.0
12	G-8	0.35	0.42	1.20	16.66
13	G-9	0.37	0.43	1.16	13.95
14	G-10	0.38	0.44	1.15	13.63
15	G-11	0.40	0.45	1.12	11.11
16	G-12	0.39	0.46	1.17	15.21

In all above batches, there was change in car's index and Hausner's ratio with change in ratio of drug to polymer. G1-G4 are the batches of solid dispersion with α Glucosyl Hespiridine with increase in poloxamer from 1 to 4 times of drug respectively. Batches from P1-P4 are of PVPK-30, these all batches follows the same change as in α Glucosyl Hespiridine. For all batches, Hausner's ratio is within or equal to 1.25 which indicate good flowability.

SEM of plain drug and solid dispersion:as shown in figure

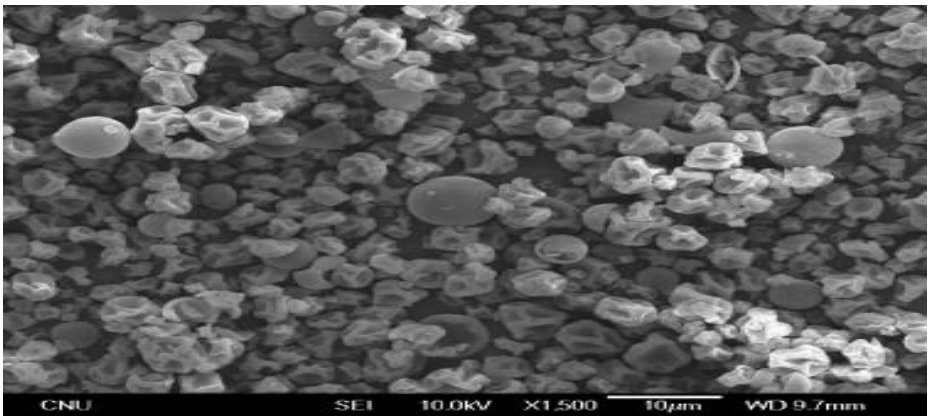

Figure :SEM of solid dispersion

SEM of solid dispersion

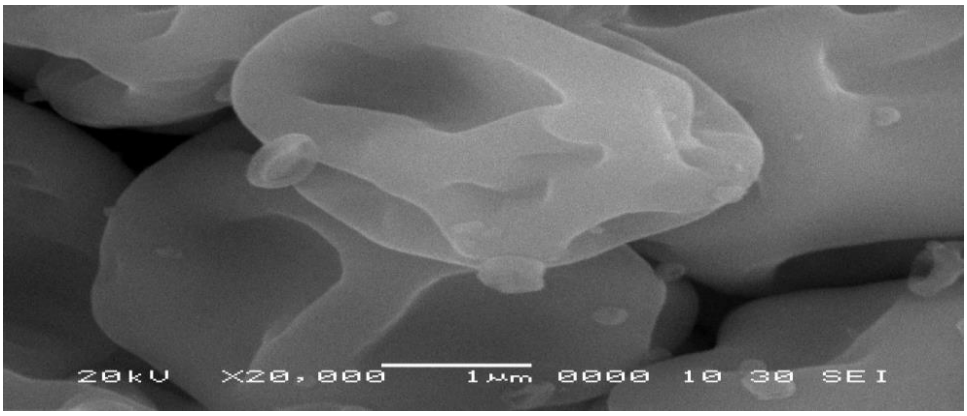

Figure: SEM of solid dispersion

From SEM of solid dispersion it was clearly observed that there was no crystalline substance in solid dispersion.

Saturation solubility studies:

Improved dissolution behaviour of solid dispersions of Atorvastatin Calcium can be attributed to increase in saturation solubility of Atorvastatin Calcium. Solid dispersion systems lead to reduction in particle size of Atorvastatin Calcium because of which there is an enhancement of saturation solubility. This change was confirmed by conducting similar saturation solubility studies on Pure Atorvastatin Calcium as control.

Saturation solubility for solid dispersion of Atorvastatin Calcium with PVP K-30 and α Glucosyl Hesperidins:

Saturation solubility of solid dispersion Batches in distilled water and 0.05 M Phosphate Buffer was found to be as follows (**Table**). among these following batches saturation solubility of spray dried batches (G1-G4),(P1-P4) and batches prepared by kneading method(G5-G8) was found to be nearly same while saturation solubility for batch prepared by solvent evaporation method (G9-G12) was less as compare to other methods Saturation solubility with PVP K-30 is shown in Table and figure

Table: Saturation solubility of solid dispersion in PVP K-30 by spray drying method.

Sr. no.	Batch code	In distilled Water (µg/ml)	In 0.05M Phosphate Buffer (µg/ml)
1	P-1	39.51±0.29	98.45±1.32
2	P-2	56.12±0.69	178.54±0.68
3	P-3	89.08±1.50	240.11±0.36
4	P-4	120.16±1.01	293.29±1.67

***n=3**

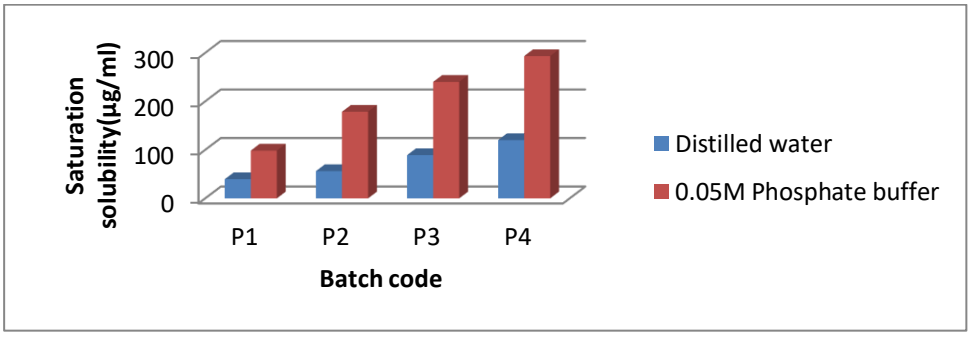

Figure: Saturation solubility of solid dispersion with PVP K-30 in Distilled water and 0.05 M Phosphate Buffer.

Saturation solubility for solid dispersion of Atorvastatin Calcium with Alpha Glucosyl Hespiridine:

Saturation solubility of solid dispersion Batches in distilled water and 0.05M Phosphate Buffer was found to be as follows (**Table**). Batches prepared by spray drying method (G1-G4) and batches prepared by kneading method (G5-G8) shows more increase in solubility as compare to batches prepared by Solvent evaporation method (G9-G12).Saturation solubility with α Glucosyl Hespiridine is shown in Table and figure

Table: Average* (±SD) Saturation solubility of solid dispersion in α Glucosyl Hespiridine by spray drying method

Sr. no.	Batch code	In distilled Water (µg/ml)	In 0.05M Phosphate Buffer (µg/ml)
1	G1	42.63±1.23	102.36±0.69
2	G2	76.80±1.56	189.95±1.34
3	G3	119.0±0.92	276.25±1.64
4	G4	127.18±1.45	339.64±0.78

***n=3**

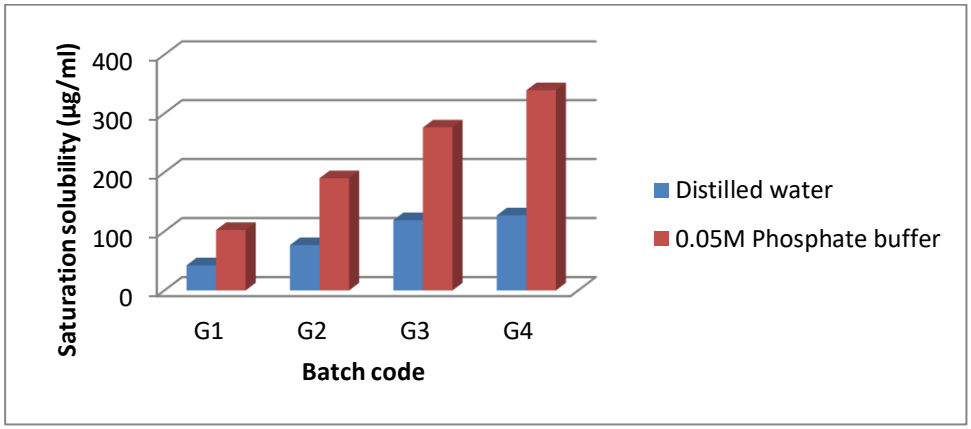

Figure: Saturation solubility of solid dispersion with αGlucosyl Hespiridine in Distilled water and 0.05 M Phosphate Buffer.

Saturation solubility for solid dispersion of Atorvastatin Calcium with Alpha Glucosyl Hespiridine by kneading method

Saturation solubility of solid dispersion Batches in distilled water and 0.05M Phosphate Buffer was found to be as follows (**Table**). Batches prepared by Kneading Method (G5-G9) shows more increase in solubility as compare to batches prepared by Solvent evaporation method (G9-G12).Saturation solubility with α Glucosyl Hespiridine is shown in Table and figure

Table: Average* (±SD) Saturation solubility of solid dispersion in α Glucosyl Hespiridine by kneading method

Sr. no.	Batch code	In distilled Water (µg/ml)	In 0.05M Phosphate Buffer (µg/ml)
1	G5	39.20±1.87	92.23±0.37
2	G6	91.87±0.65	165.46±1.42
3	G7	107.23±1.43	248.69±1.52
4	G8	119.18±0.78	305.11±0.79

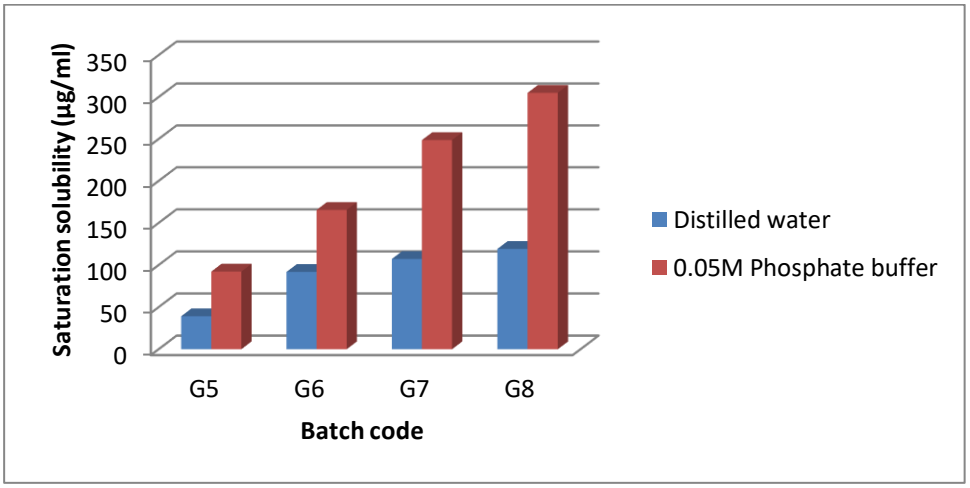

Figure: Saturation solubility of solid dispersion with α Glucosyl Hespiridine in Distilled water and 0.05 M Phosphate Buffer by kneading method.

Saturation solubility for solid dispersion of Atorvastatin Calcium with Alpha Glucosyl Hespiridine by solvent evaporation

Saturation solubility of solid dispersion Batches in distilled water and 0.05M Phosphate Buffer was found to be as follows (**Table**). Batches prepared by Solvent evaporation method (G9-G12) showsSaturation solubility with α Glucosyl Hespiridine as shown in Table and figure

Table: Average* (±SD) Saturation solubility of solid dispersion in α Glucosyl Hespiridine by solvent evaporation method.

Sr. no.	Batch code	In distilled Water (µg/ml)	In 0.05M Phosphate Buffer (µg/ml)
1	G9	26.23±0.56	82.65±0.52
2	G10	39.65±0.98	103.25±1.64
3	G11	54.98±1.54	146.67±1.21
4	G12	73.45±1.65	194.31±0.61

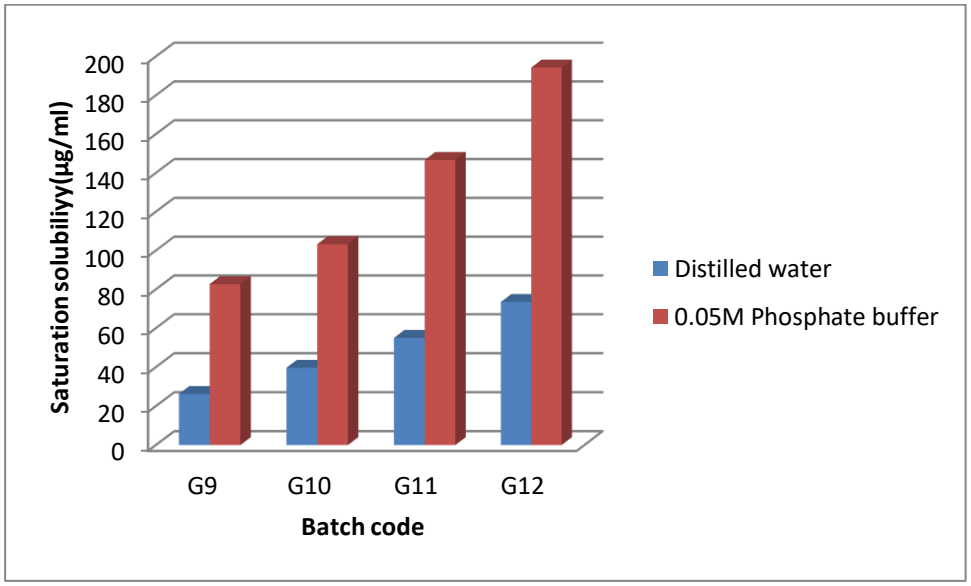

Figure.Saturation solubility of solid dispersion with α Glucosyl Hespiridine in distilled water and 0.05 M Phosphate buffer.

Saturation solubility of plain drug, and solid dispersion was determined. It shown that the solubility of the solid dispersion containing α Glucosyl Hespiridine increased more than the plain drug.Solvent evaporation is not as good as spray drying or Kneading Method.

Percent Drug Content in solid dispersion:

The percentage Atorvastatin Calcium content of various solid dispersions of Atorvastatin Calcium with α Glucosyl Hespiridine prepared by Spray drying, Kneading, Solvent evaporation method was determined and given in following table.

Table: Average* (±SD) Percent drug content in solid dispersion

Batch code	% Drug content
G-1	97.28 ± 1.45
G-2	98.12±1.09
G-3	97.45±1.81
G-4	98.09±1.68
G-5	97.34±1.68
G-6	98.16±0.98

G-7	96.47±1.31
G-8	98.34±1.49
G-9	98.88±1.31
G-10	97.40±1.84
G-11	98.14±1.56
G-12	98.15±1.18

***n=3**

In vitro dissolution study:

The impact of solid form and solid dispersion on dissolution profile was studied and comparative account of the same was done with plain drug as shown below. Cumulative percent drug release from batches obtained by spray drying method with PVP K-30 is as shown in Table No.8.11 and Figure No.8.17.

Table: Average* (±SD) Cumulative Percent Drug Release from Batches obtained by Spray drying method with PVP K-30.

Time (min)	Pure drug (%cumulative release)	P-1 (%cumulative release)	P-2 (%cumulative release)	P-3 (%cumulative release)	P-4 (%cumulative release)
0	0	0	0	0	0
5	6.9±1.21	8.2±0.22	13.4±0.41	16.2±0.62	21.2±0.51
10	7.9±0.23	13.2±0.34	21.0±0.59	23.6±0.58	29.2±1.20
15	11.23±0.56	18.6±0.58	29.3±1.01	33.2±1.45	39.3±1.13
20	13.8±0.34	26.4±0.77	38.7±1.56	43.3±1.39	51.02±0.99
25	15.64±1.65	34.5±0.36	43.6±1.39	51.0±0.89	60.1±1.01
30	19.52±0.24	42.7±1.10	51.3±1.12	63.26±1.18	68.2±1.26
35	23.65±1.37	51.6±1.81	61.2±0.52	69.32±1.12	77.3±1.02
40	25.31±1.24	57.8±1.13	65.2±1.28	74.52±0.99	84.6±1.21
45	29.32±0.95	63.10±1.01	69.5±1.37	81.26±0.84	89.6±1.09
50	31.25±1.56	67.3±1.33	74.2±1.13	84.02±1.05	

55	34.9±1.23	70.6±1.61	79.4±0.98		
60	38.6±1.02	77.9±0.89			

***n=3**

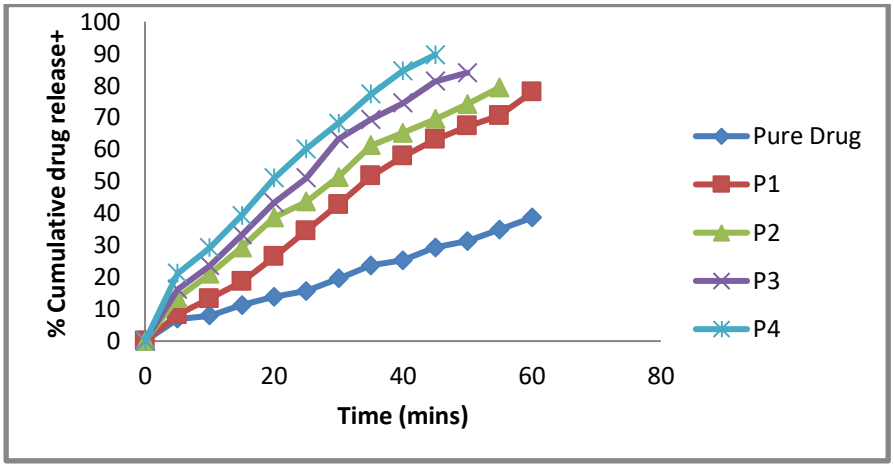

Figure: Cumulative Percent Drug Release from Batches obtained by spray drying method with PVP K-30

In this dissolution study of batch P1-P4 were studied for the in vitro drug release.Above batches dissolution was compared with the plain drug,which shown that solid dispersion of Atorvastatin Calcium prepared with PVP K-30 shown the increase in dissolution as compare to the plain drug. Dissolution of solid dispersion shown that dissolution rate increases with increase in concentration of PVP K-30. At 45 min from batch P1 was 63.10±1.01 and from batch P4 was 89.6±1.09.In these Drug:PVP K-30 ratio changed from 1:1 to 1:4, So there was four times increase in the concentration of PVP K-30.PVP K-30 has helped in increasing solubility and hence dissolution rate.

Cumulative percent drug release from batches obtained by spray drying method with α Glucosyl Hespiridine is as shown in Table No.8.12 and Figure No.8.18.

Table: Average* (±SD) Cumulative Percent Drug Release from Solid dispersion Batches obtained by spray drying method method with α Glucosyl Hespiridine.

Time (min)	Pure drug (%cumulativ	G-1 (%cumulativ	G-2 (%cumulativ	G-3 (%cumulativ	G-4 (%cumulativ

	e release)	e release)	e release)	e release)	e release)
0	0	0	0	0	0
5	6.9±1.21	7.9±0.09	14.6±0.79	19.1±0.59	22.6±0.32
10	7.9±0.23	11.39±0.69	21.6±0.53	29.5±1.1	31.3±0.46
15	11.23±0.56	19.1±0.63	33.6±1.10	41.2±1.41	43.1±1.50
20	13.8±0.34	31.5±0.16	41.3±1.56	51.1±1.02	56.3±0.89
25	15.64±1.65	38.6±1.12	49.5±1.36	62.3±0.15	65.9±0.90
30	19.52±0.24	47.1±0.13	57.2±1.51	69.2±1.44	73.9±1.11
35	23.65±1.37	52.±1.70	67.3±2.10	76.1±1.23	80.1±1.23
40	25.31±1.24	59.0±1.57	72.8±0.52	82.3±0.36	88.2±0.35
45	29.32±0.95	66.9±1.34	76.9±1.32	84.7±1.29	97.6±0.15
50	31.25±1.56	72.5±1.01	81.1±0.81	88.9±1.32	99.0±0.45
55	34.9±1.23	76.1±1.31	84.1±1.60	95.3±0.91	
60	38.6±1.02	79.3±1.09	87.6±0.75		

***n=3**

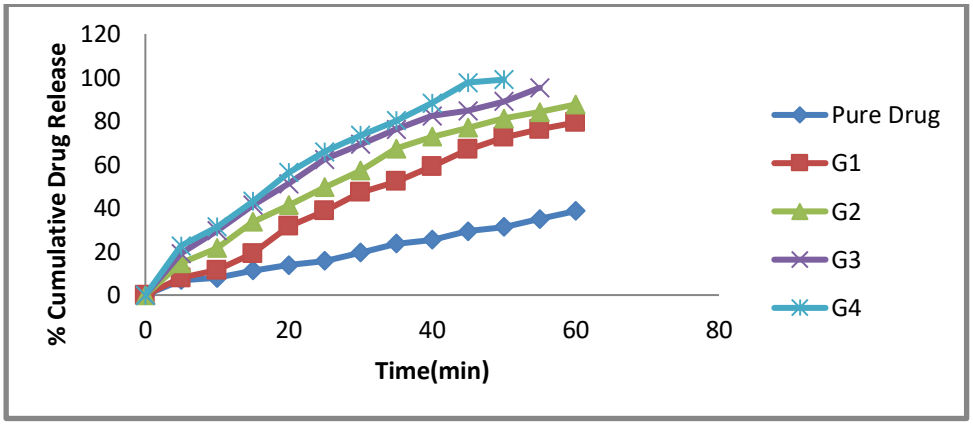

Figure :Cumulative Percent Drug Release from Batches obtained by spray drying method with α Glucosyl Hespiridine.

In this dissolution study of batch G1-G-4 were studied for the in vitro drug release.Dissolution profile of above batches shown that solid dispersion of Atorvastatin

Calcium prepared with α Glucosyl Hespiridine shown the increase in dissolution as compare to the plain drug. Dissolution of solid dispersion shown that dissolution rate increases with increase in concentration of α Glucosyl Hespiridine. At 45 min release from batch G1 was 72.5±1.01and from batch G4 was 99.0±0.45.In these Drug: α Glucosyl Hespiridine ratio changed from 1:1 to 1:4, So there was four times increase in the concentration of α Glucosyl Hespiridine. As compare to PVP K-30 there is significant increase in the dissolution rate when solid dispersion is prepared with α Glucosyl Hespiridine by spray drying method.

Cumulative percent drug release from batches obtained by Kneading method with α Glucosyl Hespiridine is as shown in Table and Figure

Table: Average* (±SD) Cumulative Percent Drug Release from solid dispersion with α Glucosyl hespiridine obtained by kneading method.

Time (min)	Pure drug (%cumulative release)	G-5 (%cumulative release)	G-6 (%cumulative release)	G-7 (%cumulative release)	G-8 (%cumulative release)
0	0	0	0	0	0
5	6.9±1.21	7.2±0.11	11.1±0.64	13.2±0.49	17.6±0.30
10	7.9±0.23	10.22±0.62	18.1±0.45	20.68±1.6	23.3±0.49
15	11.23±0.56	18.6±0.56	27.1±1.19	31.2±1.46	34.1±1.52
20	13.8±0.34	24.1±0.98	34.5±0.54	38.1±1.13	44.6±0.89
25	15.64±1.65	31.4±1.45	43.1±1.32	47.8±0.19	54.1±0.99
30	19.52±0.24	36.1±0.11	50.9±1.06	56.2±1.42	63.9±1.11
35	23.65±1.37	42.2±1.05	57.2±1.10	64.1±1.20	74.1±1.23
40	25.31±1.24	49.0±0.23	63.2±0.79	71.3±0.33	82.0±1.35
45	29.32±0.95	54.1±1.60	69.2±1.32	75.6±1.20	93.1±0.13
50	31.25±1.56	61.5±0.26	74.0±0.80	80.9±1.39	98.4±1.36
55	34.9±1.23	67.5±0.32	77.1±1.66	89.3±0.91	
60	38.6±1.02	72.1±1.19	80.6±0.71	95.8±1.76	

***n=3**

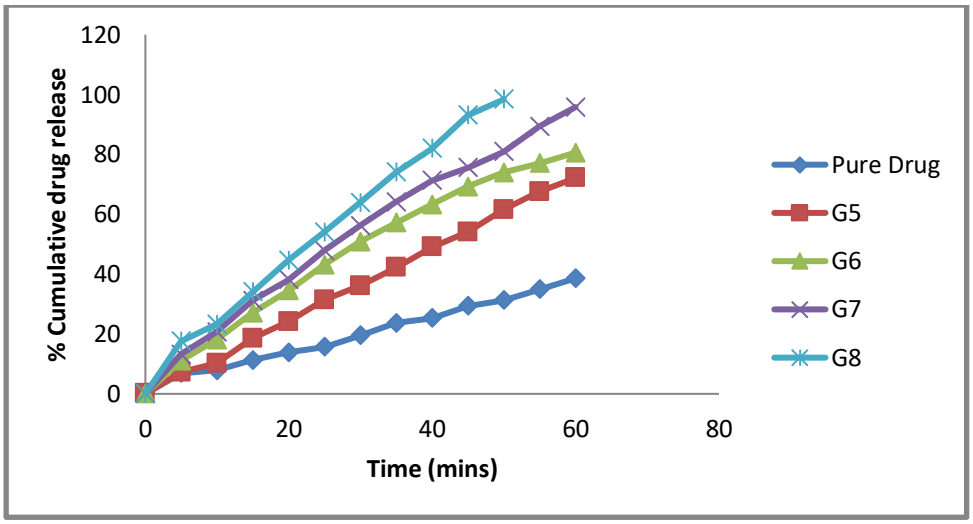

Figure: Cumulative Percent Drug Release from solid dispersions with α Glucosyl Hespiridine obtained by kneading method.

In this dissolution study of batch G-5 G-8 were studied for the in vitro drug release.Above batches dissolution was compared with the plain drug, which shown that there is increase in dissolution of solid dispersion of Atorvastatin Calcium prepared with α Glucosyl Hespiridine . Dissolution of solid dispersion shown that dissolution rate increases with increase in concentration of α Glucosyl Hespiridine. At 45 min release from batch G-5 was 54.1±1.60 and from batch G8 was93.1±0.13.In these Drug: α Glucosyl Hespiridine ratio changed from 1:1 to 1:4, so there was four times increase in the concentration of α Glucosyl Hespiridine. As compare to PVP K-30 there is significant increase in the dissolution rate when solid dispersion is prepared with α Glucosyl Hespiridine by kneading method.

Cumulative percent drug release from batches obtained by solvent evaporation method with α Glucosyl Hespiridine is as shown in Table

Table: Average* (±SD) Cumulative Percent Drug Release from solid dispersion with α glucosyl Hespiridine by solvent evaporation method.

Time (min)	Pure drug (%cumulative release)	G-9 (%cumulative release)	G-10 (%cumulative release)	G-11 (%cumulative release)	G-12 (%cumulative release)

0	0	0	0	0	0
5	6.9±1.21	7.9±0.12	7.2±0.79	7.9±0.61	7.1±0.33
10	7.9±0.23	8.6±0.41	9.2±0.11	9.36±0.91	10.1±0.44
15	11.23±0.56	11.9±0.21	11.6±1.03	12.36±0.48	13.8±1.20
20	13.8±0.34	14.1±0.11	16.2±0.66	17.23±1.89	18.2±0.88
25	15.64±1.65	15.8±1.08	21.0±1.3	22.36±0.23	23.1±1.33
30	19.52±0.24	20.2±0.11	27.9±1.65	27.36±1.84	28.1±1.25
35	23.65±1.37	24.2±0.87	31.4±0.18	32.52±1.24	35.6±1.22
40	25.31±1.24	26.0±1.57	36.0±0.93	37.25±0.34	42.1±0.31
45	29.32±0.95	29.4±1.08	39.1±1.21	40.21±1.69	51.1±0.91
50	31.25±1.56	31.5±1.84	42.1±0.68	43.25±1.33	
55	34.9±1.23	35.4±1.34	47.1±1.69	48.32±0.86	
60	38.6±1.02	39.4±1.15	51.2±1.16		

*n=3

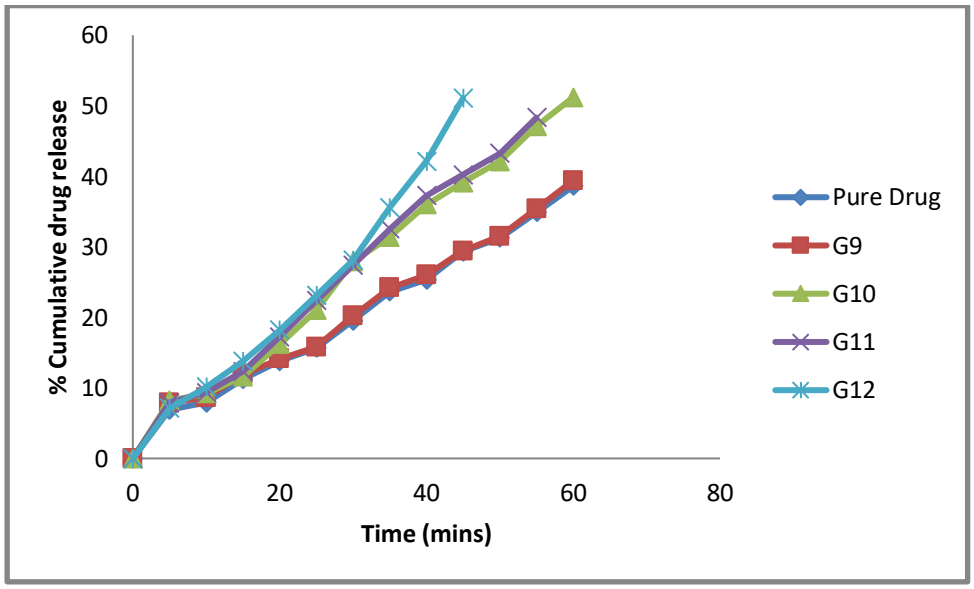

Figure: Cumulative Percent Drug Release from solid dispersion with α Glucosyl Hespiridine obtained by solvent evaporation method.

In this dissolution study of batch G-9 G-12 were studied for the in vitro drug release. Above batches dissolution was compared with the plain drug, which shown that there is slight

increase in dissolution of solid dispersion of Atorvastatin Calcium prepared with α Glucosyl Hespiridine. Dissolution of solid dispersion shown that dissolution rate slightely increases with increase in concentration of α Glucosyl Hespiridine. At 45 min release from batch G-9 was 27.2±1.08and from batch G8 was 51.1±0.91.In these Drug: α Glucosyl Hespiridine ratio changed from 1:1 to 1:4, so there was four times increase in the concentration of α Glucosyl Hespiridine.

Polymer Effect:

The release rate for plain Atorvastatin Calciumat 45 min was found to be 29.32±0.95This release rate was increased as the Drug: Polymer ratio increased from 1:1 to 1:4 proportions. For PVP K-30, it was increased from 63.10±1.01 to 89.6±1.09 at 45 min by spray drying method. For α Glucosyl Hespiridine. It wasincreased from 66.9±1.34to 97.6±0.15at 45 min by spray drying method and54.1±1.60 **to**93.1±0.13

By kneading method at 45 min and29.4±1.08 to 51.1±0.91 by solvent evaporation method**.** The improvement in the dissolution rate was greatest when polymer weight fraction was highest in the system. For both PVP K-30 andα Glucosyl Hespiridinesystems, when used in 1:1, 1:2, 1:3and 1:4 proportions, the spray drying method, resulted in slightly high dissolution rates. This enhancement in dissolution rate of Atorvastatin Calciummay be due to the formation of eutectic mixture between the drug and α Glucosyl Hespiridine,also it may be due to increase in wettability of the drug. Among the polymers employed,α Glucosyl Hespiridineshowed higher rate of dissolution than PVP K-30 which may be due to the differences in HLB values and ratio of hydrophilic units and hydrophobic units.

.**Effect of ratio:**

The drug/carrier ratio in a solid dispersion is one of the main influences on the performance of a solid dosage. If the percentage of drug increased, it will form small crystals within the dispersion rather than remaining molecularly dispersed. As the concentration of carrier increases drug is molecularly dispersed, which leads to the absence of crystallinity and thereby increase in solubility and release rate of drug.

Effect of method of preparation: Solid dispersions of Atorvastatin Calcium prepared by spray drying method showed better drug release profiles as compared to Atorvastatin Calcium solid dispersions obtained with Kneading method and solvent evaporation method.

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