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Role Of Nano Encapsulation And Inclusion Complexation In Mouth Dissolving Strips Of Atorvastatin

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ABSTRACT

Atorvastatin calcium is a class II drug, with low oral bioavailability (14%), primarily used for the treatment of dyslipidemia and also for unstable angina, coronary heart disease, stroke and multiple risk factors for myocardial infarction. The purpose of this research is to formulate Atorvastatin as oral dissolving films to provide an immediate release of drug and fast onset of action, thereby improving the bioavailability. The films are prepared by solvent casting method using polymers such as HPMC, PVA and PVP in different composition in addition with propylene glycol as plasticizer. The formulated films are assessed for their physicochemical parameters such as weight, thickness, folding endurance, percentage moisture absorption, surface pH and drug content uniformity. The in-vitro release studies are done in USP dissolution apparatus maintained at the temperature of 37±1^{o}C and the stirring speed of 100 rpm. The optimized films were characterized using thermal analysis by DSC, interaction studies by FTIR and surface morphology by SEM. To increase the percentage of drug release at minimum duration, the drug with β cyclodextrin is prepared as, inclusion complex by kneading method and nanoparticles by emulsification solvent evaporation method, and are incorporated into the films, and further optimized by the evaluation studies.

Keywords: Atorvastatin, fast dissolving films, kneading method, nano particles.

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INTRODUCTION

Atorvastatin, classified under statins, reduces the cholesterol level by inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG - CoA) reductase which catalysis the conversion to mevalonate. It is also used as prophylaxis for the occurrence of many cardiovascular diseases. To treat hypercholesterolemia this drug was given in the form of calcium salt. Absolute bioavailability of the drug is 12% for an oral administration at 40mg dose. The low oral bioavailability of Atorvastatin is mainly due to the most critical factors like first pass effect, poor membrane permeability, low aqueous solubility and dissolution rate of the drug, etc [1]. Several approaches have been developed recently to overcome these factors, which includes salt formation, solid dispersion, inclusion complex, micro emulsion micronization, etc. These methods results in reduction of particle size which in turn increases the surface area, wet ability and solubility. For an immediate release of this drug and to improve its bioavailability, a novel dosage form is developed by formulating strips containing inclusion complex of drug with β-CD or the nano encapsulated drug [2]. Mouth dissolving strips are recently developing for both immediate and controlled release drug delivery system out of which immediate release is of special importance due to its significant advantages. The strip made for immediate release dissolves or disperses in the mouth without need of drinking water or chewing. This type of formulation helps to improve the bioavailability of drugs and is mainly focused for the ease of administration especially for patients who are mentally ill and in coma state. The ability to mask the taste helps in administering these drugs to non co-operative patients. The rapid disintegration or dissolution leading to quick effect is very important especially in the patients suffering from acute or chronic conditions like hypertension, myocardial infarction (heart attacks), heart failure, peripheral arterial disease and chronic kidney disease [3, 4].

The work here concentrates on developing fast dissolving strips by a solvent casting method using various polymers. Also the effect of kneading inclusion complex and nanoparticles of drug using β cyclodextrin for incorporating into the strips was compared to understand the raise in bioavailability due to decreasing particle size and increasing the solubility of the drug.

MATERIALS AND METHODS

Atorvastatin (Glukem Pharma, Hyderabad) HPMC (5cps, 15cps, 50cps) (SDFCL, Mumbai), Polyvinyl alcohol (Fisher scientific, USA), Polyvinyl pyrolidone (LOBA Cheme, India), Propylene glycol (Chemspure, Chennai), β cyclodextrin (SDFCL, Mumbai), methanol (Himedia, Mumbai), dicholoro methane (SDFCL, Mumbai)

Preparation of mouth dissolving strips of Atorvastatin

Mouth dissolving strips were prepared by solvent casting method using film forming polymers with respective amounts of HPMC (5cps, 15cps, and 50cps), polyvinyl pyrolidone, polyvinyl alcohol and propylene glycol with different composition as shown in table 1 and 2. The accurately weighed polymers and plasticizers were dissolved in 15mL of warm distilled

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water to get a clear viscous solution. Then the viscous solution was poured into a petriplate and kept in oven for 3hr at 40-50^{o}C for drying. After drying the strips were removed from the petriplate and further evaluation parameters were carried out, from which suitable composition was selected for further studies [5, 6, 7].

Table 1: Preparation of mouth dissolving strips of ATV with 0.3% of PVA

Ingredients (g)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PVA	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
PVP	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Propylene glycol	3	3	3	3	3	3	3	3	3	3
HPMC 15cps	_	0.15	0.45	0.75	_	_	_	_	_	_
HPMC 5cps	_	_	_	_	0.15	0.45	0.75			
HPMC 50cps	_	_	_	_	_	_	_	0.15	0.45	0.75

Table 2: Preparation of mouth dissolving strips of ATV with 0.5% of PVA

Ingredients (g)	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20
Drug	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PVA	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PVP	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Propylene glycol	3	3	3	3	3	3	3	3	3	3
HPMC 15cps	_	0.15	0.45	0.75	_	_	_	_	_	_
HPMC 5cps	_	_	_	_	0.15	0.45	0.75			
HPMC 50cps	_	_	_	_	_	_	_	0.15	0.45	0.75

Preparation of inclusion complex:

The drug-β cyclodextrin (β-CD) inclusion complexes were prepared in the ratio of 1:0.5, 1:1 and 1:2 (table 3) by kneading method for the purpose of increasing the dissolution rate at minimum duration. 50% methanol-water with dichloro methane was added to β-CD and triturated well to form slurry. Then the drug was added to the slurry and triturated for 1 hour to obtain the complexed powder and it was air dried [8].

Table 3: Preparation of ATV- β CD inclusion complex

Ingredients	KC1	KC2	KC3
Drug : βCD	1:0.5	1:1	1:2
Methanol (ml)	0.5	0.5	0.5
Dichloromethane (ml)	2	2	2

Table 4: Preparation of strips with ATV- β CD nanoparticles

Ingredients	KN1	KN2	KN3
Drug : βCD	1:0.5	1:1	1:2
Pluronic F (g)	1	1	1
Dichloromethane (ml)	3	3	3

Preparation of nanoparticles:

The drug-βCD complexed polymeric nano formulation was prepared through emulsification solvent evaporation method by dispersing an organic phase into aqueous phase (table 4). The preparation of aqueous phase was done by adding 1g of pluronic F68 dissolved in 100mL of distilled water. Then the organic phase was prepared with β CD and drug in three different ratios (1:0.5, 1:1, and 1:2) by dissolving in 3 mL of dichloromethane. The organic phase was dispersed in aqueous phase and sonicated for 30mins. After sonication the samples were stirred for 30mins in magnetic stirrer and it was centrifuged at 8000rpm for 15min. The centrifuged nano suspension was lyophilized by freeze drying method to obtain the dry nanoparticles [9].

Preparation of strips with inclusion complex and nanoparticles:

Inclusion complex mixture and powdered nanoparticles containing drug of appropriate amount was incorporated into the selected film forming polymeric solution, separately and kept in an oven for drying at 40-50^{o} C.

Physicochemical properties of the strips:

The appearance of the prepared films was examined for their transparency or opaqueness. Then the films were weighed individually and the thickness was measured by vernier caliper**.** The folding endurance test of the films was performed to determine the flexibility of the film. The film was folded n number of times at the same place till there was a tear or crack observed at that specific point. The pH determination was performed by cutting the prepared films into small pieces and placing in a petri dish with 2mL of distilled water. The pH probe was kept in contact to the surface of the film in petri dish for few minutes and the pH was noted. The uniformity of the drug in the film was determined by cutting the film into pieces of 1x1 cm^2 and dissolving in distilled water diluted suitably, and the absorbance of the solution was measured at 240nm (λmax) using UV-visible spectrophotometer. The concentration of the drug in the sample was determined using the standard calibration data. The entire physico-chemical evaluation tests were carried out in triplicates [10-13].

Evaluation of inclusion complex:

Phase solubility:

The phase-solubility technique was adopted to determine the affinity between ß-CD and the drug Atorvastatin in aqueous media. Phase-solubility studies were performed by Higuchi and Connors method. Atorvastatin was taken in test tubes, in amounts that ensure saturation (i.e.) 5 mg was taken in 10 mL of methanol water solution at a ratio of 20:80. At a concentration of 0mM, 2mM, 4mM, 6mM, 8mM and 10mM, β-cyclodextrin was taken for a total of 10 mL with the saturation amount of drug in it. The test tubes were sealed with paraffin and shaken for 72 hrs at room temperature (25-28°C) with 100 rpm speed. After the solutions have

attained equilibrium the aliquots were filtered using 90mm Ø X 100 circles of Whatman filter paper (Whatman International Ltd Maidstone England). The filtrated solution was centrifuged for 10 min at 3000 rpm and the obtained supernatant was measured at 240 nm. The solubility constant (Kc) according to the 1:1 stoichiometric ratio determine the concentration of complexes were calculated from the phase-solubility diagrams using Equation (1). The slope and intercept was obtained from the initial straight-line portion of the plot of Atorvastatin concentrations against ß-CD concentration in aqueous media [14].

$$K_C = \frac{\text{Slope}}{\text{Intercept } (1-\text{slope})}$$ Equation 1

Evaluation of nanoparticles:

Particle size distribution and surface charge analysis:

The formulated nano particles were analyzed for particle size and surface charge using zeta sizer (Malvern Nano Series ZS, UK), based on the principle of dynamic light scattering and charge conductivity, respectively. The particle size and its distribution and the zeta potential of the nano suspension was measured to ensure the monodispersity and also to predict their stability [15].

Entrapment efficiency:

The nano particle suspension formulated with the drug and polymer was ultra centrifuged at 18,000 rpm for 30 minutes. The supernatant solution was diluted suitably to measure the absorbance, from which the concentration of drug in supernatant was calculated using the standard calibration data. The entrapment efficiency of the extract in the polymeric nano particles was calculated using the formula [16],

$$\%\ \text{Entrapment Efficiency} = \frac{\text{Total drug content} - \text{Drug content in supernatant}}{\text{Total drug content}}$$

***In vitro* drug release studies:**

The *in vitro* drug release studies were carried out in USP basket dissolution apparatus using phosphate buffer (pH 6.8) as the media. The films were cut into pieces of 1x1 cm^2 and placed in baskets. Then the baskets were immersed in vessel containing 300mL of media, kept at 37±0.5^oC and were rotated at 100 rpm. The 10mL of samples were withdrawn at 5, 10,15,30,45 and 60 min time intervals and replaced with fresh media. The samples were analyzed for their percentage drug release using UV- visible spectrophotometer at the 240nm [17].

***In- vitro* drug release kinetics:**

The mechanism of drug release from the formulation was studied by fitting the obtained dissolution data to various mathematical kinetic models such as zero-order, first order, Higuchi, Korsmeyer-Peppas and Hixon-Crowell models, the criteria for selecting the most appropriate model are chosen on the basis of goodness of fit test. R^2 values obtained from the respective plots were noted and also the slope value obtained from the Korsmeyer-Peppas kinetics model, and the mode of drug release from the dosage form was predicted [18].

Thermal analysis (TG-DSC):

Differential Scanning Calorimetry (DSC) and Thermo gravimetry (TG) were used to check the modifications in physical, chemical properties or heat capacity of the component involving endothermic or exothermic processes with respect to change in heat flow, temperature and weight changes. The thermal behavior of pure drugs, polymer mixture and selected formulation (KF2) was studied using DSC (TA instrument, Q100, USA) to confirm the complex formation and possible interactions in the formulation. Around 5 mg of the samples were placed in an alumina pan and heated at the rate of 10ºC /min up to 500ºC and the results were represented as weight loss and heat flow against temperature [19].

Infrared Spectroscopy (IR):

Infrared spectroscopy (IR) was used to identify the drug excipients interaction in the selected formulation. The IR spectra of the selected β-cyclodextrin were analyzed by ATV method in the region between 4000-400 cm^{-1}. The spectral analysis was also performed for pure drug Atorvastatin, polymer mixture and pure β-Cyclodextrin and the results were compared to confirm the presence of specific functional groups of the molecules [20].

SEM analysis:

Scanning Electron Microscopy was performed to view the microscopic aspects of the guest and the host molecule obtained by the process of kneading mixture and lyophilized nano encapsulated powder mixture which was compared with the pure sample of drug and β cyclodextrin to study the difference in surface morphology and crystallization state. The morphology of the binary systems was examined at different magnification by Scanning Electron Microscope (JSM 6701F, JEOL, Japan) after they were sputter coated with gold using auto fine coater (JFC 1600, JEOL, Japan) [21].

X-ray diffractometry:

X-ray diffraction study was done to detect the change in crystalline behavior of drugs within the inclusion complex and the nano encapsulated particles. The process was performed by a Powder X-ray diffractometer (D8 FOCUS, BRUKER, USA) using Cu-Kα radiation at 1.5418 Å, for the pure drug sample (Atorvastatin), β cyclodextrin and compared to the diffractogram of

the selected formulations. The analysis was performed at 2θ values from 10° to 60° with a step size of 0.02º/min [22].

RESULTS AND DISCUSSION

Physicochemical characterization of ATV strips:

The results obtained for the physico chemical evaluation of the ATV strips and the inclusion complex or nanoencapsulated drug strips were shown in table 5 and table 6, respectively. The thickness of the strips were observed using vernier caliper which was found to be in the range between 0.3 ± 0.14mm to 0.7 ± 0.07mm and strip weight measured using weighing balance were in the range of 2.681 ± 0.25g to 4.210 ± 0.43g. Weight and thickness of ATV-βCD inclusion strip was within the range of 3 to 4 ± 0.01g and 0.3mm respectively. For ATV-βCD nano strip, weight and thickness were 4.626 ± 0.03 and 0.4 ± 0.07 respectively. Folding endurance of all the formulation were evaluated to check the integrity of the strip with buccal mucosa, all the formulations showed > 100 times as folding endurance, which proved that the strip was acceptable for using in the mouth. Surface pH of the strips lied in the neutral range of 6.5 to 7.1. Drug content of all the formulations was within the limit of 90-11-% except for the three formulations F7, F13 and F15 [10-13].

Size charge and stability of nanoparticles:

The physico chemical properties of the nanoparticles, which include the size, surface charge and drug entrapment level were shown in the table 7. Surface charge measured in terms of zeta potential plays a significant role in the stability of nanoparticles. Zeta potential greater than +25mV and less than -25mV correlates to a greater stability of the nano particles. The prepared nano particles of Atorvastatin using β-cyclodextrin in different ratio as1: 0.5, 1:1 and 1:2 had zeta potential as -13.7, -16.3 and -0.778 mV respectively. The nanoparticles prepared with low concentration of β-CD were found to show better stability than the higher ratio. This may be due to the aggregation of the nano particles formed because of higher affinity of the hydrophilic polymer surface and other attractive forces in the nano suspension. This was also evident from the size of the particles, which was found to increase with respect to increase in the polymer level [15].

Table 5: Physicochemical properties of ATV mouth dissolving strips

Formulation code	Weight (g ± S.D)	Thickness (mm ± S.D)	Folding endurance	Surface pH	Drug content (% ± S.D)
F1	2.767 ± 0.17	0.3 ± 0.14	>100	6.5 ± 0.18	105.44 ± 0.42
F2	3.025 ± 0.23	0.3 ± 0.10	>100	6.8 ± 0.22	107.2 ± 0.22
F3	3.065 ± 0.22	0.5 ± 0.17	>100	6.7 ± 0.16	116 ± 0.31
F4	3.402 ± 0.16	0.4 ± 0.13	>100	7.0 ± 0.14	110.3 ± 0.11
F5	3.522 ± 0.23	0.5 ± 0.09	>100	6.9 ± 0.36	118.61 ± 0.55
F6	3.480 ± 0.17	0.5 ± 0.12	>100	7.0 ± 0.19	92.601 ± 0.26
F7	3.666 ± 0.18	0.5 ± 0.08	>100	6.7 ± 0.27	77.02 ± 0.45
F8	2.681 ± 0.25	0.4 ± 0.15	>100	7.1 ± 0.35	100.37 ± 0.36
F9	3.716 ± 0.32	0.6 ± 0.07	>100	6.8 ± 0.44	112.50 ± 0.62

F10	3.599 ± 0.24	0.4 ± 0.19	>100	6.9 ± 0.27	111.37 ± 0.55
F11	3.676 ± 0.27	0.5 ± 0.17	>100	6.7 ± 0.37	98.56 ± 0.39
F12	4.030 ± 0.77	0.5 ± 0.10	>100	7.0 ± 0.24	114.78 ± 0.28
F13	3.525 ± 0.52	0.4 ± 0.13	>100	7.1 ± 0.18	77.60 ± 0.67
F14	4.096 ± 0.37	0.6 ± 0.18	>100	6.9 ± 0.55	111.06 ± 0.29
F15	3.653 ± 0.19	0.7 ± 0.07	>100	7.1 ± 0.25	72.11 ± 0.27
F16	3.715 ± 0.24	0.5 ± 0.09	>100	7.0 ± 0.32	101.22 ± 0.25
F17	3.910 ± 0.74	0.5 ± 0.10	>100	6.5 ± 0.15	115.67 ± 0.74
F18	3.832 ± 0.32	0.5 ± 0.13	>100	6.9 ± 0.37	111.76 ± 0.23
F19	3.643 ± 0.55	0.5 ± 0.07	>100	7.0 ± 0.44	112.11 ± 0.48
F20	4.210 ± 0.43	0.6 ± 0.12	>100	6.9 ± 0.43	108.4 ± 0.72

Table 6: Physicochemical properties of Strips containing ATV-βCD inclusion complex / ATV-βCD nanoencapsulated particles

Formulation code	Weight (g ± S.D)	Thickness (mm ± S.D)	Folding endurance	Surface pH	Drug content (% ± S.D)
KF1	3.594 ± 0.72	0.3 ± 0.02	>100	7.0 ± 0.04	90.91 ± 0.55
KF2	3.371 ± 0.43	0.3 ± 0.05	>100	6.9 ± 0.09	93.96 ± 0.23
KF3	3.884 ± 0.22	0.3 ± 0.03	>100	7.1 ± 0.10	107.33 ± 0.82
NF1	4.262 ± 0.31	0.4 ± 0.07	>100	6.8 ± 0.07	90.41 ± 0.42
NF2	4.222 ± 0.23	0.4 ± 0.04	>100	7.0 ± 0.12	90.85 ± 0.45
NF3	4.360 ± 0.34	0.4 ± 0.03	>100	7.1 ± 0.05	91.22 ± 0.22

Table 7: Physicochemical properties of ATV-βCD nanoparticles

Formulation code	Drug : β-cyclodextrin	Size (nm)	Zeta potential (mV)	Entrapment efficiency (% ± S.D)
NL1	1:0.5	891	-13.7	38.41 ± 0.25
NL2	1:1	941	-16.3	62.5 ± 0.41
NL3	1:2	1071	-0.778	60.13 ± 0.32

Entrapment Efficiency of the ATV- βCD nanoparticles:

Among the prepared formulations, the entrapment efficiency of NL2 and NL3 was observed to be 62% and 60% respectively when compared to NL1 showing the lowest entrapment efficiency of 38.41% only. This clearly evidenced that increase in the ratio of the carrier used in the formulation as 1:1 increased the entrapment efficiency as compared to 1:0.5 level. Also further increase in its concentration did not show significant difference in entrapment efficiency, which may be due to the saturation level of inclusion being achieved at 1:1 ratio.

Phase solubility study for ATV- βCD inclusion complexation:

The phase solubility study was performed to understand the change in solubility of the molecule leading to a inclusion complex in hydro-alcoholic solution as a function of the host concentration. The phase solubility diagram (PSD) for the complexes with Atorvastatin: β cyclodextrin was performed to determine the solubility of the drug using a UV absorbance with

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respect to increase in concentration of ß-CD. The PSD for the drug-cyclodextrin encapsulation was classified under type A_L according to Higuchi and Connor's rule. The Atorvastatin solubility showed a linear increase with the increase in the concentration of ß-CD. (Figure1)

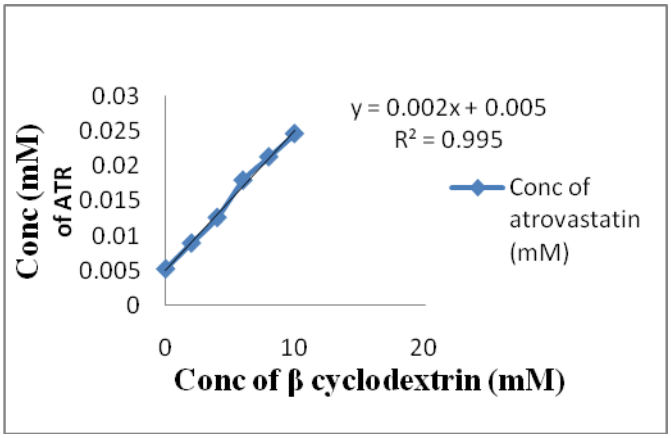

Figure 1: Phase solubility study of Atorvastatin with ß-CD

The solubility constant (Kc) of Atorvastatin was obtained from the slope of the linear phase solubility diagram and was found to be 400.8016 M^{-1}, which proved that the inclusion complex formed by Atorvastatin within ß-CD was quite stable [14].

***In-vitro* drug release studies:**

The *in vitro* drug release data of ATV strips prepared with pure drug, β-CD complexed drug and nano encapsulated drug were compared (Figure 2). The strips prepared without HPMC (F11 and F12) showed drug release up to 57-69% at the end of 1hr, whereas the HPMC incorporated strips showed significant variation in the drug release. The high viscosity grade HPMC, especially at higher concentration was found to show sustained release due to the rigid strips formed, wherein the diffusion was low. Formulation containing 0.1% of HPMC with 0.3% PVA was found to show 100% release at the end of 1hr, due to fast swelling of flexible strips and thereby higher dissolution of the drug. With same concentration of HPMC and 0.5% PVA (F12, F15, F18) the maximum drug release was 74-83% only which may be due to less swelling and inhibition of media into the strip. The formulation F6 showing least drug release of 41% was selected for incorporation of the inclusion complex and nano encapsulated form of drug, to check the improvement in dissolution rate.

The kneading mixture (KC1, KC2, and KC3) showed improved drug release of 84-99% with respect increase in the ratio of βCD (1:0.5, 1:1 and 1:2), compared to pure drug showing only 39% at the end of 1hr. This confirmed the enhancement of solubility and dissolution of the drug in the inclusion complex. The strips incorporated with complexed mixture (KF1, KF2 and KF3) also show 100% release within 45min-1hr.

In case of nanoparticles suspension, (NL1, NL2 and NL3) the maximum drug release observed was 44-49% and this nano encapsulated drug in strips (NF1, NF2 and NF3) also showed drug release only upto 55-58%. Even though, the percentage release was slightly higher than the pure drug, the overall solubility and dissolution enhancement was very low compared to the inclusion complex system, which may be due to rigid encapsulation of drug in the hydrophobic core of β-cyclodextrin and its slower diffusion into the aqueous media [17].

***In-vitro* drug release kinetics:**

The *in-vitro* drug release data of the Atorvastatin formulations fitted to various kinetic models, revealed the drug release mechanism (Table 8). The ATV strip formulation F6 containing the pure drug showed Korsmeyer-Peppas kinetics. In case of the ATV- βCD kneaded mixture filled in capsules, polymeric nano suspension and the nanoparticles incorporated strips also the similar kinetics was absorbed. The mechanism of such release can be attributed to the diffusion of water into the formulation, swelling of polymer in the strip and dissolution of the hydrophilic carrier matrix. The kinetics of the strips prepared with kneading mixture correlated to both first order kinetics and Korsmeyer-Peppas mechanism, where a specific concentration dependent profile could be obtained. The n value < 0.45 seen in most of the formulation indicated Fickian diffusion transport of drug molecules (except KC1 and KC2 showing anomalous non-Fickian diffusion mode) [18].

Thermal behavior of ATV in inclusion complex and nanoencapsulation strips:

The TG-DSC thermograms of the pure drug, polymer mixture and the inclusion complex strips were shown in figure 3. The DSC curve of pure Atorvastatin showed an endothermic peak at 168.93^{o}C corresponding to its melting point, followed by the decomposition peak at 320.86 ^{o}C. There was a gradual weight loss observed in the TG curve at 238.56 ^{o}C due to loss of water of hydration and then sudden fall at 320.86 ^{o}C confirming the decomposition state. The DSC curve of the polymer mixture containing HPMC, PVA and PVP showed the small endothermic peaks of the polymers at 193.15 ^{o}C, 330.96 ^{o}C and decomposition at 440.10 ^{o}C. The DSC of the inclusion complex showed the identical peaks of polymer mixture at 200 ^{o}C, 322.89 ^{o}C and 439.9 ^{o}C and could not reveal the endothermic peak of the drug which may be due to solid state modification and its homogeneous dispersion into the higher ratio of bulk polymeric system [19].

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Table 8: *In-vitro* Kinetics studies of formulations

Formulation Code	R^2					n value
	Zero order	First order	Higuchi	Korsmeyer-Peppas	Hixon-Crowell	
F6	0.1533	0.3801	0.8510	0.9892	0.3081	0.268
KC1	0.9233	0.9973	0.9580	0.9915	0.9939	0.678
KC2	0.6709	0.9490	0.9636	0.9661	0.9039	0.461
KC3	0.8991	0.9435	0.9346	0.9540	0.8991	0.399
KF1	0.3523	0.9945	0.9091	0.9691	0.9773	0.338
KF2	0.5738	0.9753	0.9737	0.9908	0.9514	0.406
KF3	0.0840	0.9951	0.8029	0.9656	0.9395	0.268
NL1	-0.0953	0.2775	0.7634	0.9926	0.1595	0.220
NL2	-0.3124	0.0589	0.6654	0.9963	-0.0612	0.177
NL3	0.2590	0.5002	0.8974	0.9976	0.4250	0.298
NF1	0.5111	0.7589	0.9569	0.9849	0.6870	0.383
NF2	0.0013	0.3645	0.7878	0.9874	0.2511	0.230
NF3	0.0982	0.4987	0.8358	0.9813	0.3796	0.268

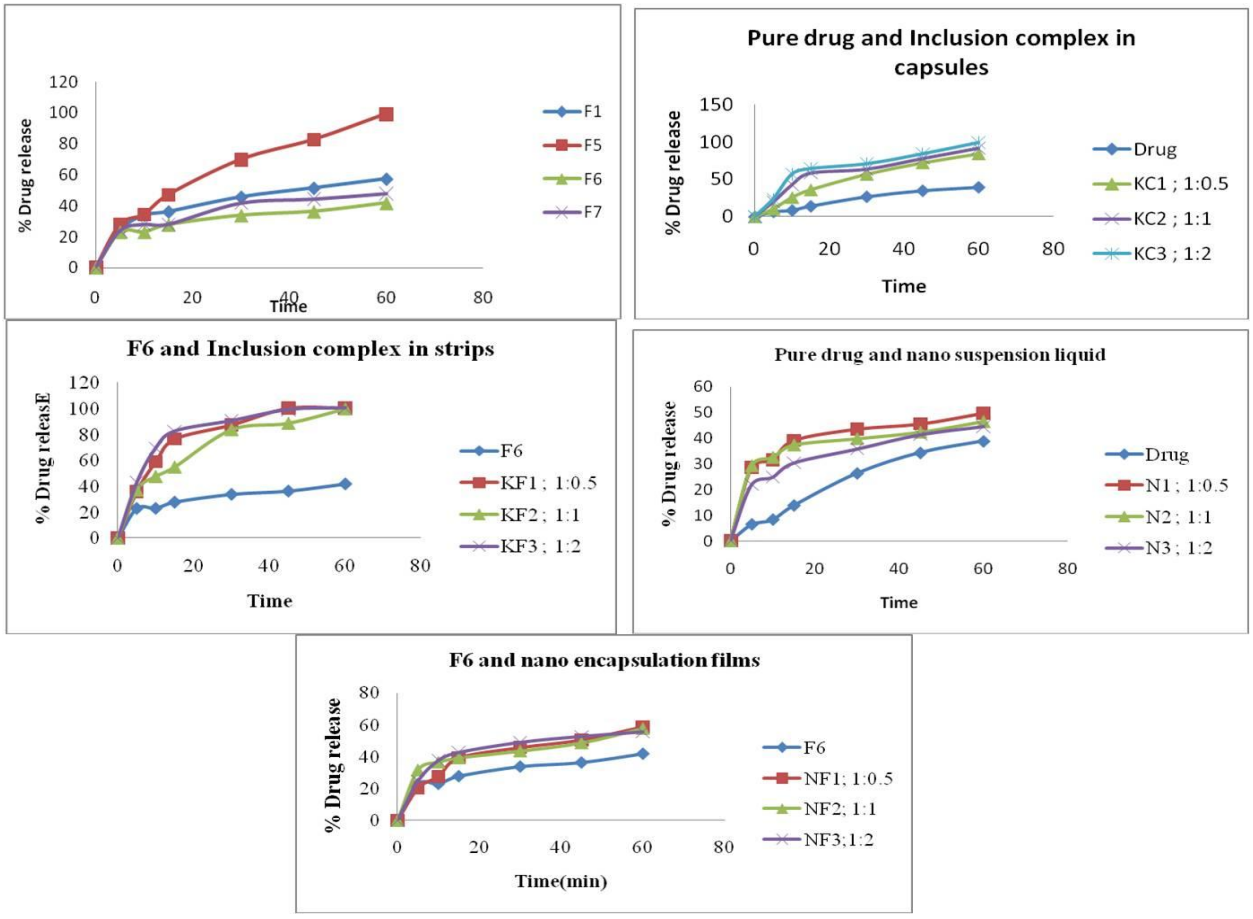

Figure 2: Drug release profile of strips containing plain drug compared to inclusion complexed and nanoencapsulated ATV-ßCD strips and pure drug

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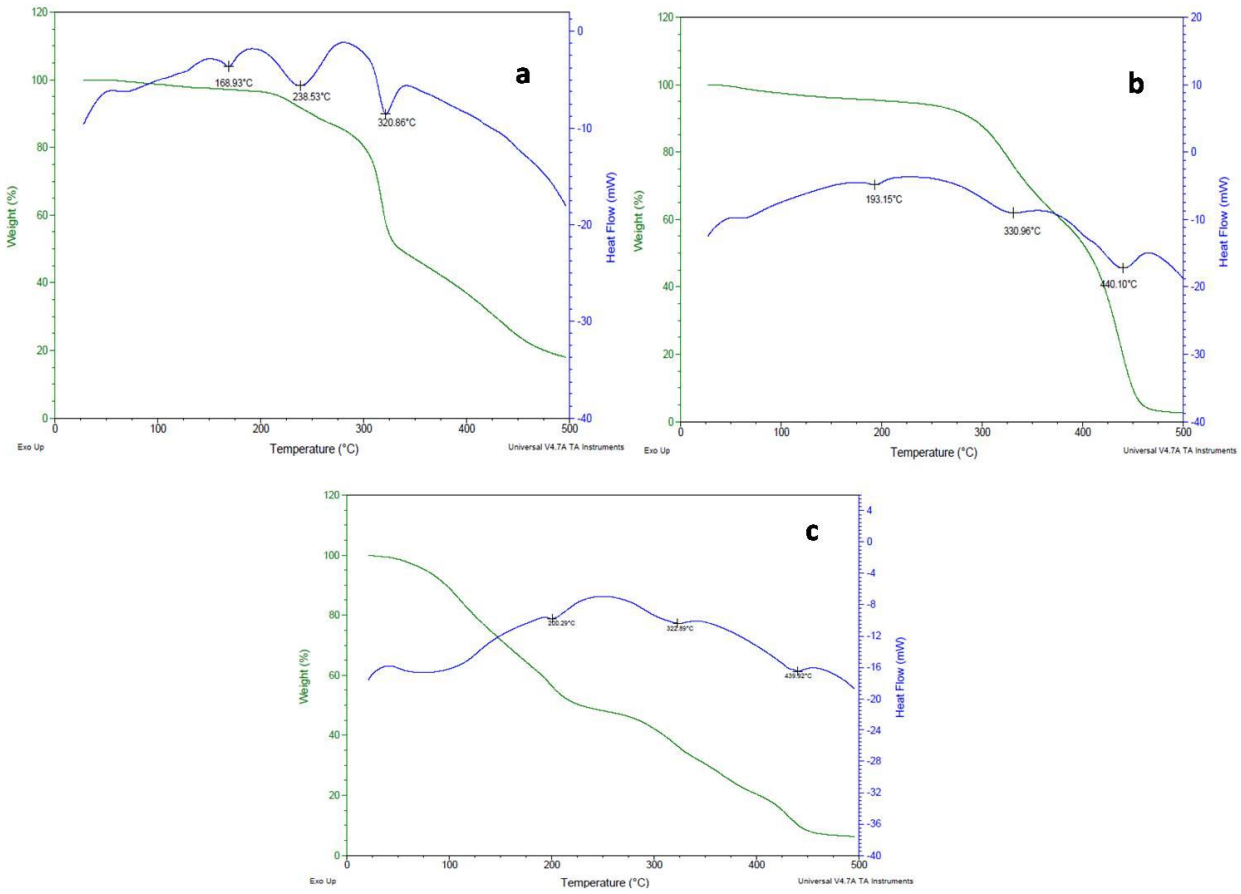

Figure 3: DSC thermograms of a) Atorvastatin pure drug b) Polymer mixture c) ATV-βCD inclusion strip (KF2)

Drug-Polymer interactions:

The FTIR spectra of pure drug, mixture of polymers (HPMC, PVP, PVA), pure β-CD, ATV with β-CD inclusion strips (KF2) and ATV with β-CD nano encapsulated strips (NF2) were shown in figure 4 and 5. The wave numbers represented by the FTIR spectra of pure Atorvastatin revealed the presence of functional groups corresponding to O-H and aliphatic C-H at 3365.37cm^{-1} and 2926.5 cm^{-1} respectively. The functional groups of β-CD showed a characterized vibration of the –CH_2 –CH_2 groups in 2800-3000 cm^{-1} region. The polymer mixture showed a peak at 2953.08, 1666.12, 3443.53 corresponding to functional groups =CH_2 to prove the presence of HPMC, C=O to prove the presence of PVP, -OH to prove the presence of PVA respectively. In the strip formulation containing the kneading mixture inclusion complex it was observed that the O-H peak of drug, HPMC and PVA superimposed and gave a very broad peak at 3518.06 cm^{-1}, similarly a broad peak was observed at 2908.84 cm^{-1} indicating the superimposed peaks of the functional aliphatic C-H group of drug, β-CD, HPMC and PVP. The broadening of the peak may be due to the inter-molecular H-bonding between the OH groups of drug and polymers during the inclusion complex formation. The nanoparticles strip formulation also showed the same pattern showing broad peaks of -OH at 3536.24, due to the

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encapsulation of drug in the polymers, HPMC and PVP with the formation of weak H-bonding [20].

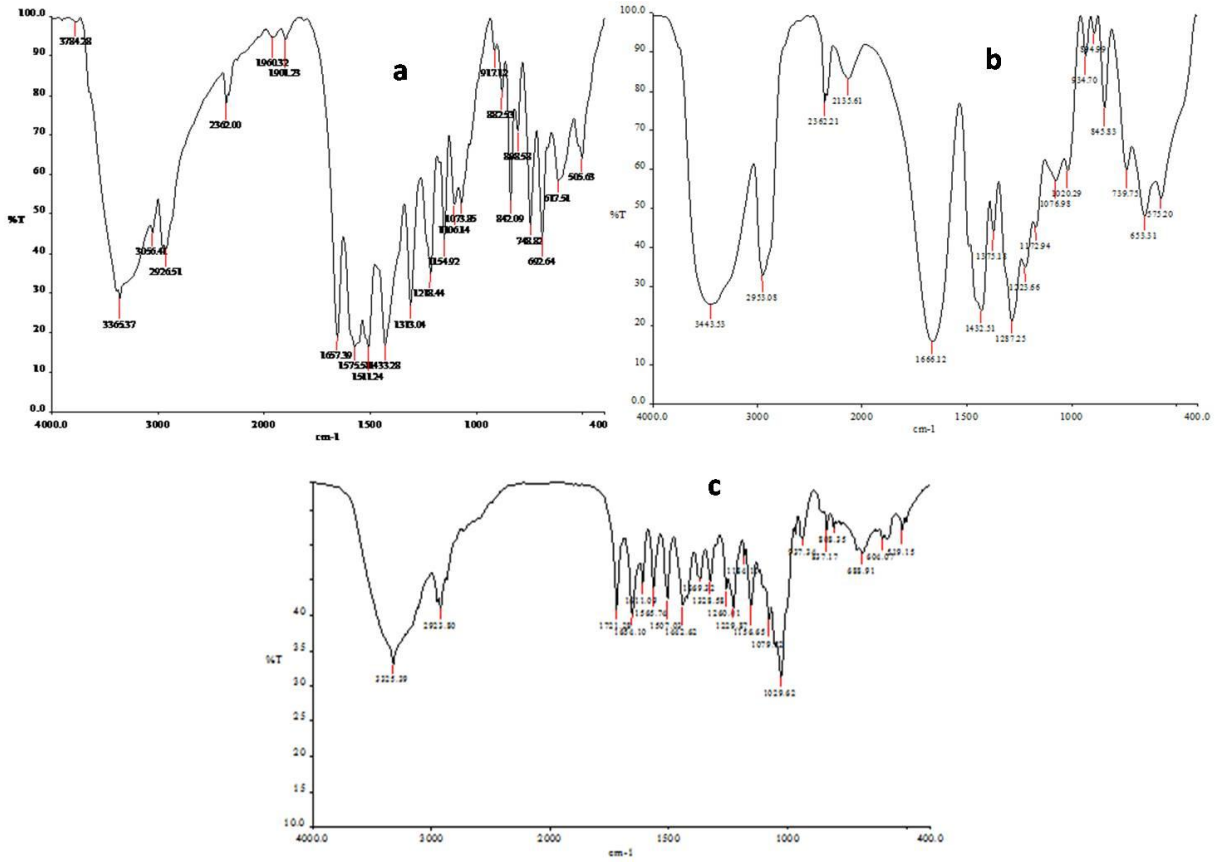

Figure 4: FT-IR Spectrum of a) Pure drug Atorvastatin b) Polymer mixture c) Pure β-cyclodextrin

Morphology of inclusion complex and nanoparticles

The scanning electron microscopy images (Figure 6) showed that Atorvastatin and β-CD are semi crystalline in nature with flakes structure. The surface morphology of the inclusion complex showed smooth small particles where change in the semi crystalline form of the particles to amorphous state was observed which contribute to the greater increase in solubility of the drug. The kneading process during complex formation has lead to size reduction of semi crystalline particles to form uniform homogeneous powder dispersion. In nano encapsulation formulation, the surface morphology showed small semi crystalline particles as in irregular shaped nano crystals which could show only slight increase in solubility of drug [21].

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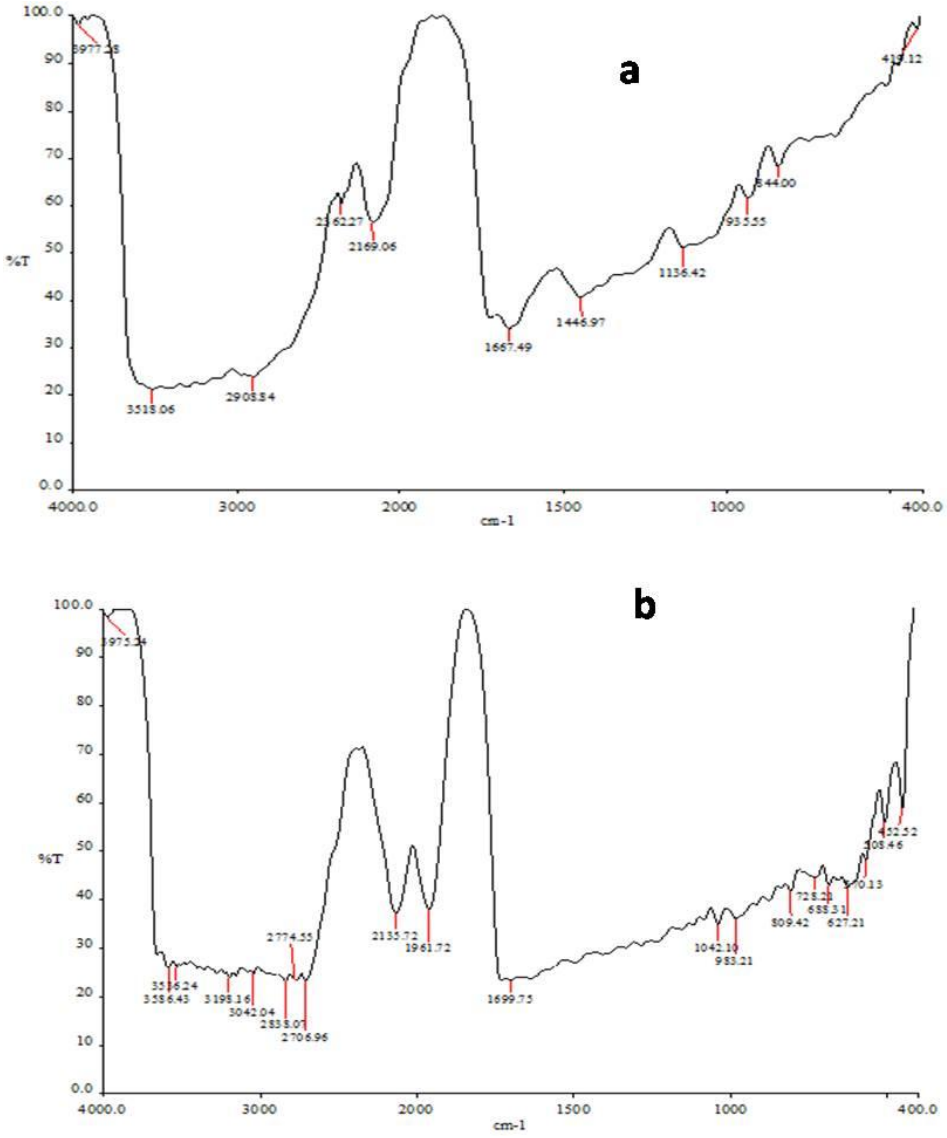

Figure 5: FT-IR Spectrum of a) ATV-βCD inclusion strip (KF2) b) ATV-βCD nano encapsulated strip (NF2)

Crystalline changes of ATV in inclusion complex and nanoencapsulation:

The XRD pattern of pure Atorvastatin, β-CD, inclusion strip (KF2) and nano encapsulated strip (NF2) were shown in figure 7. The XRD spectrum of pure drug showed sharp and highly intense characteristic peaks, indicating the crystalline and semi crystalline state. Pure β-CD was found to be semi crystalline in nature as shown by the several clustered diffraction peaks. The XRD pattern of the inclusion complex strip (KF2) showed very low intense peaks of the drug along with the β-CD, due to the conversion of semi crystalline particles into amorphous mixture which result in the improvement in the solubility of the drugs. In nano particles strip (NF2) certain intense peaks of the drug were observed along with low intense peeks of β-CD, due to the formation of nano crystals. The kneading method adapted for forming the inclusion complex involves grinding process which leads to change in crystallinity of the pure substances.

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Similarly in nanoparticles formation under sonication condition, the molecular crystal lattice structure of the drug can modify leading to different diffraction patterns [22].

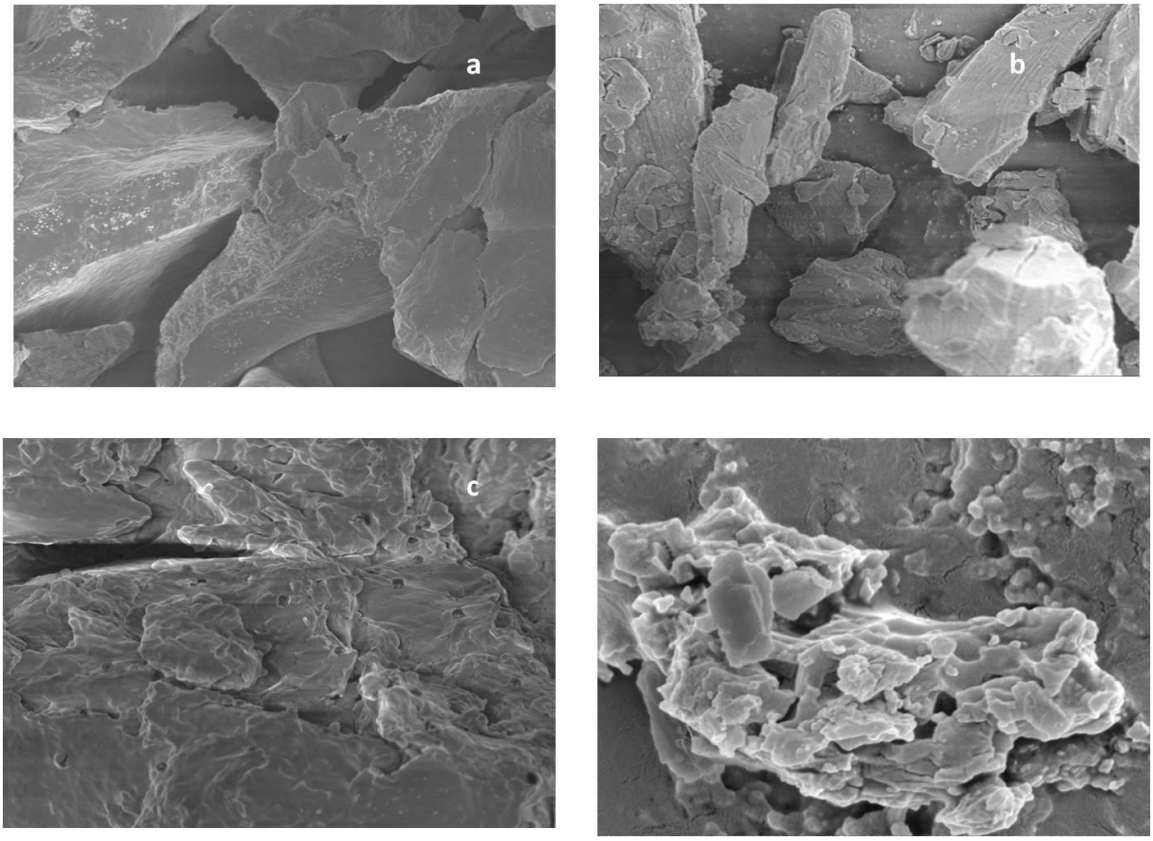

Figure 6: SEM images of a) Pure drug Atorvastatin b) Pure β-CD c) ATV- β-CD Inclusion complex d) ATV- β-CD nano encapsulated complex

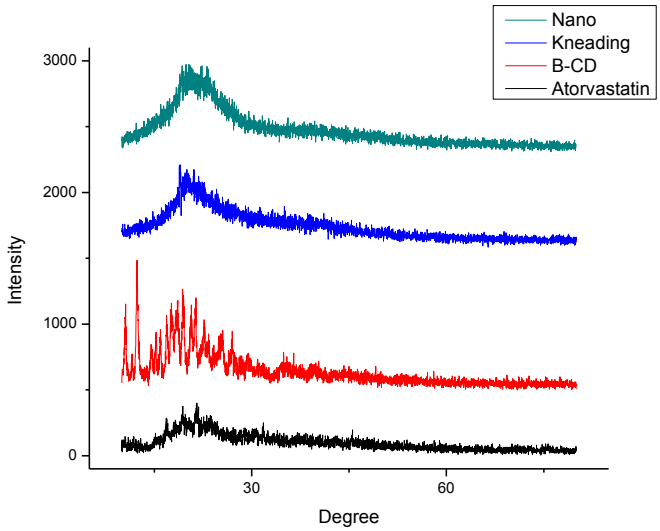

Figure 7: Comparison of XRD spectrum of a) Pure drug Atorvastatin b) Pure β-CD c) ATV- β-CD Inclusion complex d) ATV- β-CD nano encapsulated complex

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CONCLUSION

The polymer composition used in optimizing the film, showed that significant level of swellable hydrophilic polymer as 0.1% at HPMC and 0.3% PVA was necessary for easy inhibition of salivary fluid into the strips causing fast release of the drug. The nanoencapsulated particles of drug-β-CD incorporated into strips showed only slight improvement in the dissolution, as compared to the inclusion complexed drug in strips. This was identified to be due to saturation encapsulation efficiency of only 60% achieved at 1:1 and 1:2 ratio and also formation of nano crystalline mixtures during the emulsification process of nanoparticles preparation.

The inclusion complex incorporated strips (KF1, KF2 and KF3) showed improved dissolution of the drug, since kneading caused conversion of crystalline molecules to amorphous state, as evidenced by the characterization results shown by XRD, DSC and SEM. There was no significant interaction between the drug and polymers also confirmed by the FTIR interpretation.

The development of mouth dissolving strips with inclusion complexed drug improve the bioavailability of the drug Atorvastatin by providing immediate release of the maximum amount of drug from the dosage form.

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REFERENCES

[1] Panakanti PK, Panakanti G, Reddy S, Somagoni J and Yamasai MR. IOSR J Pharm 2012; 2: 23-32.
[2] Qifang W, Sanming L, Xin C, Xiaowen F, Chaojie L. Asian J Pharm 2010; 5: 188-193.
[3] Shweta K, Mayank B. International Journal of Pharm Tech Research 2012; 4: 725-733.
[4] Kulkarni AS, Deokule HA., Mane MS, Ghadge DM. J Curr Pharm Res 2010; 2: 33-35.
[5] Koland M, Sandeep VP, Charyulu NR. J Young Pharm 2010; 2: 216-22.
[6] Nappinnai M, Chandanbala R, and Balaijirajan R. Indian J Pharm Sci 2008; 70: 631–635.
[7] Kunte S, Tandale P. J Pharm Bioall Sci 2010; 2: 325–328.
[8] Suresh S, Shivakumar HN, Kiran KG. Indian J Pharm Sci 2006; 68: 301-307.
[9] Hariharan D, Ashokumar M, Dinesh S, Mohan M, Nirmal SA, Raghunath G, Srinivasrao V, Suddhasattya D. Drug Invention Today 2011; 3: 216-218.
[10] Subhash chandra bose P, Saritha RND. Indian J Pharm Sci 2011; 2: 665-672.
[11] Alka L, Neelima P and Rajeshwer KKA. Int J Pharm Sci Res 2011; 2: 2457-2462.
[12] Mona N, Mayank N, Vikram C. Der Pharmacia Lettre 2012; 4: 1221-1227.
[13] Prabhakara P, Ravi M, Marina K, Vijaynarayana K, D'Souza U, Harish NM, Shastry CS, Charyulu RN. Int J Pharm Inv 2011; 1: 99–104.
[14] Zaibunnisa AH, Rashima RNAH. Res J Pharm Tech 2011; 7: 9-14.
[15] Javier C, Jose L, Maite A, Juan M. J Chem Pharm Res 2012; 4: 232-238.

ISSN: 0975-8585

[16] Won-Tae K, Hee Chung, Il-Shik Shin, Kit LY, Donghwa Chung. Carbohydrate Pol 2008; 71: 566–573.
[17] Ilago R, Kavimani S, Mullaicharam AR, Jayakar B. J Chem Pharm 1997; 59: 232-235.
[18] Magdy IM, Mohamed H, Muaadh A. Mohamed Ali. J Chem Pharm Res 2011; 3: 665-686.
[19] Aliaa N. ElMeshad, Arwa S. Hagrasy E. Pharm Sci Tech 2011; 12: 1384–1392.
[20] Indira R, Prasanna, Uma S. Int J Pharm Inv 2012; 2: 26–33.
[21] Satishbabu BK, Srinivasan BP. Indian J Pharm Sci 2008; 70(2): 175–179.
[22] Yong-Zhong D, Jia-Guo X, Ling-Wang, Hong Y, Fu-Qiang H. Eur Polym J 2009; 45: 1397–1402.