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Solubility Enhancement of Poorly Soluble Drug Atorvastatin by using Complexation and Solid Dispersion techniques

Ankitha A, Yeshavantha Kumar, Avinash Patil, Dr Sathish Kumar
Department of Pharmaceutics, Sri K V college of Pharmacy,
Dept. of Pharmaceutics, Neelsaroj Institute of pharmacy,
Department of Pharmaceutics, Mallige college of Pharmacy,
Department of Pharmaceutics, Sri K V college of Pharmacy.

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ABSTRACT

Background and objective: The prime requirement of any drug therapy is Bioavailability. At present most of the new chemical entities have low aqueous solubility and high lipophilicity therefore enhancement of solubility has been major challenge in formulation development. Hence the work was carried out with the objective of formulating and evaluating the solid dispersion and inclusion complexes of Atorvastatin with an aim to increase hydrophilicity and bioavailability of Atorvastatin.

Methods: Solid dispersions and inclusion complexes of Atorvastatin were prepared using hydrophilic carriers PEG-6000, P188, β-CD and lactose in different ratio of 1:2, 1:4, 1:6 by fusion, solvent evaporation, kneading and co-precipitation methods. The formulations were evaluated for drug release, drug content and drug-polymer interactions by using various techniques like *in-vitro* dissolution, UV-Visible Spectroscopy and Fourier Transform Infrared (FTIR) Spectroscopy.

Results: All the formulation showed marked increase in drug release. The solid dispersion prepared by solvent method showed better release compared to that of fusion method. The inclusion complexes prepared by kneading method showed better release than co-precipitation method. Solid dispersion of Atorvastatin with P188 of ratio (1:6) showed higher drug release. The formulation which showed better release was again formulated using additional functional Excipients Lactose , which showed much better release than the before formulation. Inclusion complexes prepared by kneading method with ratio of (1:6) showed higher drug release. The formulation which showed high drug release was again formulated using functional Excipients lactose, this showed better release than the drug and hydrophilic polymer.

Key Words: Atorvastatin, Solid dispersion, Inclusion complexes, PEG6000, P188, β-CD, lactose, Solvent Evaporation, Kneading method, Fusion method, Co-precipitation method.

I. INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and solubility of drugs molecules. The poor solubility and low dissolution rate of poorly water-soluble drugs in aqueous gastrointestinal fluids often causes insufficient bioavailability. Therefore, it is necessary to enhance the solubility and dissolution of these drugs to ensure maximum therapeutic efficacy. The most promising method for promoting solubility is the formation of solid dispersion and inclusion complexes by using hydrophilic carriers. The solid dispersion and inclusion complexes reduce the particle size and therefore increases solubility and absorption of drugs.

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by fusion and solvent evaporation method.

The term inclusions complexes refer to molecular compounds having the characteristic structure of adduct, in which one compound (host molecule) spatially encloses another within(guest molecule).

Carriers commonly used in solid dispersions (SDs) are PEG600, P188, Lactose and carriers used in inclusion complexes are β-CD, Lactose.

Atorvastatin (ATR) is a beta-blocker used to treat high blood pressure and heart failure. ATR is partially insoluble in water. The solubility of ATR is limited because of its protonation, resulting in situ

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hydrochloride saltformation which exhibits less solubility in acidic medium.

Atorvastatin, an anti-hypertensive drug. **Atorvastatin** belongs to BCS Class II (low solubility and high permeability)which exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility and dissolution rate it possesses challenging problems in its formulation development. It needs enhancement in the dissolution rate in its formulation development to derive its maximum therapeutic efficacy. Among various techniques Cyclodextrin Complexation, Solid dispersions and Solvent deposition, use of surfactants and super disintegrants are widely accepted in industry for enhancing the dissolution rate of poorly soluble drugs from the solid dosage forms[1]. In solid dispersion and Complexation, the poorly soluble drug is dispersed in an inert water-soluble carrier such as urea, polyethylene glycol, poly vinyl pyrrolidone and surfactants at solid state.

The aim of the present work was to enhance aqueous solubility of Atorvastatin by solid dispersion techniques and inclusion complexes using carriers such as PEG 6000, Poloxamer 188, β-CD, Lactose.

Hence in the present study, an attempt has been made to develop solid dispersion and inclusion complexes Atorvastatin by adding hydrophilic polymers in different ratios with functional excipients for increasing the solubility and to see an increase in bio-availability.

II. MATERIALS AND METHODS:

Materials:

ATR was obtained as a gift sample from Zydus Cadila Healthcare, Ahmedabad, India, PEG6000. Poloxamer 188, β-CD was procured from Himedia laboratories, Lactose was procured from Thermo fisher scientific India. Pvt. Ltd. All other chemicals used were of analytical grade.

PREPARATION OF SOLID DISPERSIONS AND INCLUSION COMPLEXES OF ATROVASTATIN[57]

Solid dispersions and inclusion complexes of Atorvastatin and carrier (PEG 6000and Poloxamer 188/β-cyclodextrin and lactose) were prepared in different ratios by Kneading method, Co-precipitation method and Solvent evaporation method, Fusion methods.

Solvent evaporation method [1, 26,27,30]

Atorvastatin and the polymer [polyethylene glycol-6000(PEG-6000)/Poloxamer 188] of solid dispersion containing three different ratios (1:2, 1:4 and 1:6 w/w) were prepared by solvent evaporation method and were dissolved in a minimum amount of methanol. The solvent was removed by evaporation on magnetic stirrer at the temperature 40°C for 1 h. The resulting residue was dried in oven, ground in a mortar, passed through sieve no. 60 and then stored in desiccators.

Fusion method[28, 29, 31]

The fusion or melting method includes the preparation of physical mixture of a drug and a water-soluble carrier and heating directly whenever the mixture is melted. The melted mixture is then solidified quickly in an ice-bath under stirring. The final solid mass is crumpled, pulverized and sieved.

Kneading method [45.60]

Atorvastatin and the polymer (β-cyclodextrin) of inclusion Complexation containing three different ratios (1:2, 1:4, and 1:6 w/w) were prepared by kneading method. Thick slurry was prepared by adding one third water by weight to excipients. Under stirring the appropriate quantity of drug was added to it and then dried in an oven at 45°C until dry. The dried mass was pulverized and sieved through mesh # 60.

Co-precipitation

In this method the active drug and suitable polymer are mixed with different molar ratios. Then it is dissolved in solvent and distilled water at a room temperature. The mixture is stirred for one hour at room temperature and the solvent will be evaporated. The precipitate obtained as a crystalline powder is pulverized and sieve through sieve #80 and stored in desiccators.

CHARACTERIZATION OS SOLID DISPERSIONS AND INCLUSION COMPLEXES

UV Spectrophotometric methods for determination of Atorvastatin

Preparation of standard plot of Atorvastatin for quantitative determination in various solubilizers by UV Spectrophotometry: Solvent like 0.1N Hcl was selected to dissolve Atorvastatin and the solution (1-40µg/ml) was scanned for λmax.

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Preparation of Standard Calibration Curve of atorvastatin: Standard stock solution of Atorvastatin: 100 mg of Atorvastatin pure drug was accurately weighed and transferred to 100ml volumetric flask and dissolved in 0.1 N Hcl. Again, 1 ml of this solution was transferred to 10 ml volumetric flask. It was diluted up to the mark with 0.1 N Hcl to give stock solution containing 100 µg/ml.

The standard stock solution was then serially diluted with 0.1 N Hcl to get a concentration of 2, 4, 6, 8, 10 µg/ml of Atrovastatin. Absorbance of these resultant solutions was measured at 244 nm against 0.1 N Hcl as blank. Observed absorbance was plotted against the corresponding concentration (µg/ml).

Percent Practical Yield (PY)

Practical yield (%) was calculated to know about percent yield or efficiency. Solid dispersions and inclusion complex were collected and weighed to determine practical yield (PY) from the following equation.

PY (%) = [Practical Mass (Solid dispersion) / Theoretical Mass (Drug + Carrier)] × 100

Solubility studies:

Solubility studies were carried out according to the method of Higuchi and Connors, 1965. An excess of Atorvastatin (10mg) was placed in a 25 ml glass vial containing various concentrations of each carrier in 10 ml distilled water. All glass vials were closed with stopper and cover sealed to avoid solvent loss. The content of the suspension was equilibrated by shaking in a thermostatically controlled magnetic stirrer at 25°C for 24hrs.

After attaining the equilibrium, the content of each vial was then filtered through a double filter paper (Whatman 42). The filtrate was suitably diluted and assayed spectrophotometrically at 242nm to measure the amount dissolved drug. There was no interference from all used carriers at this wavelength. The solubility of Atrovastatin in water at the same temperature was also determined following the same procedure.

Drug content

Drug content of Atrovastatin in Solid dispersion with PEG 6000 and Inclusion Complexation with β-cyclodextrin was estimated UV-Spectrophotometric method. An accurately weight quantity of Solid Dispersion (equivalent to 10 mg of Atrovastatin) was taken and dissolved in 100 ml of 0.1N Hcl, from the solution 1ml of solution was diluted to 10 ml and assayed for drug content at 244nm.

% Drug content = (Actual amount of drug in solid dispersion/Theoretical amount of drug in solid dispersion) X100

In-vitro dissolution studies

The in-vitro dissolution study was conducted using USP Type I (Basket) Dissolution apparatus (Lab India, Mumbai) at 37±0.2°C using 900 ml of 0.1N Hcl buffer with pH 1.2. The samples equivalent to 100mg of Atrovastatin were added to the bowls and the Basket rotation was set to 50 rpm. 5 ml samples were withdrawn at predetermined time intervals up to one hour and the same amount of fresh medium was replaced immediately to maintain sink condition. The withdrawn samples were filtered through membrane filter (0.45µ), suitably diluted and the absorbance was measured at 244 nm by using UV spectrophotometer.

Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectra of Atrovastatin and formulations were obtained by FTIR Spectroscopy. Samples were compressed into KBr disks in a hydraulic press in order to prepare sample KBr blends. Then the pellets were characterized from 400 to 4000 cm-1.

Inclusion efficiency

All inclusion complexes of Atrovastatin and their physical mixtures were separately taken in 25ml volumetric flasks. Ten milliliters of methanol were added to it, mixed thoroughly. The volume was made up to mark with methanol. An aliquot from each of the solution was suitably diluted with methanol to get the final concentration of 10 µg/ml of drug and spectrophotometrically assayed for drug content. Inclusion efficiency was calculated using the formula.

Inclusion efficiency = (estimated % drug content/ theoretical % drug content) × 100.

Stability studies

Stability studies were done to understand how to design a product and its packaging such that

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product has appropriate physical, chemical and microbiological properties during a defined shelf-life when stored and used. The optimized tablet formulation was subjected for stability studies over a period of 3 months. The tablets were wrapped with aluminum foil and packed in amber colored screw capped container and kept for the stability study at 40±20C. Samples were taken after 3 months and analyzed for the tablet parameters like colour, drug content, and In-vitro dissolution profile. In-vitro drug release at 0 month and after 3 months of stability study was compared.

FORMULATION CHART:

Composition	Ratios	FUSION method	Solvent Evaporation Method	Kneading method	Co-precipitation Method
Atrovastatin + PEG 6000	1:2 (100:200 mg)	SDF1	SDE1	-	-
	1:4 (100:400 mg)	SDF2	SDE2	-	-
	1:6 (100:600 mg)	SDF3	SDE3	-	-
Atrovastatin + P188	1:2	SDF4	SDE4	-	-
	1:4	SDF5	SDE5	-	-
	1:6	SDF6	SDE6	-	-
Atrovastatin + P188 + lactose	1:2:0.5 (!00:200:50 mg)	-	SDE7	-	-
	1:4:1 (100:400:100 mg)	-	SDE8	-	-
	1:6:1.5 (100:600:150 mg)	-	SDE9	-	-
Atrovastatin + β-CD	1:2	-	-	CBK1	CPC1
	1:4	-	-	CBK2	CPC2
	1:6	-	-	CBK3	CPC3
Atrovastatin + β-CD + lactose	1:2:0.5	-	-	CBK4	-
	1:4:1	-	-	CBK5	-
	1:6:1.5	-	-	CBK6	-

III. RESULTS

PREFORMULATION STUDIES OF ATROVASTATIN

Melting point: Melting point of Atrovastatin was determined by capillary method and result was found to be, which complied with the standard monograph, indicating the purity of drug.

Standard calibration plot of Atrovastatin: The λmax of Atrovastatin in 0.1 N Hcl buffer was found to be 244 nm. The absorbance values are tabulated in the table. Atrovastatin obeyed Beer Lamberts law in the concentration range of 1-10 µg/ml with regression co-efficient 0.999.

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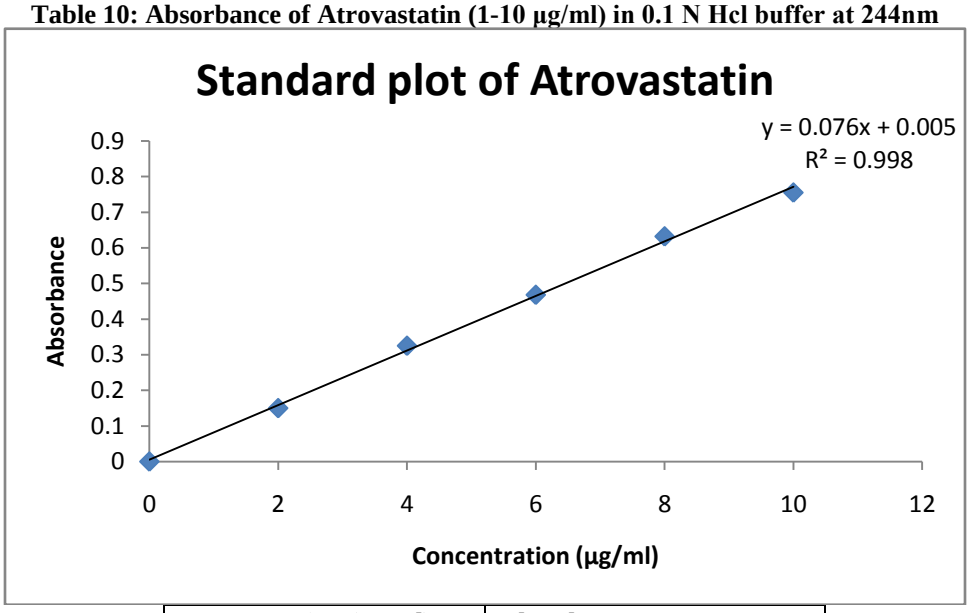
Table 10: Absorbance of Atrovastatin (1-10 µg/ml) in 0.1 N Hcl buffer at 244nm



Concentration (µg/ml)	Absorbance
0	0
2	0.15±0.002
4	0.328±0.0032
6	0.460±0.0094
8	0.630±0.0015
10	0.752±0.0025

Figure 5: Standard calibration curve of Atrovastatin in 0.1 N Hcl buffer.

Drug-Excipients and Drug-Polymer Compatibility Studies:

Drug and polymers used to prepare solid dispersions and inclusion complexes were checked for compatibility by carrying out FTIR spectroscopy. FTIR spectra obtained for pure drug and drug-polymer mixtures from 4000 to 400 cm-1 are given as follows:

Functional groups	IR range cm^{-1}	Drug	Drug + PEG6000	Drug + P188	Drug + PEG6000 + Lactose	Drug + P188 + Lactose	Drug+ β –CD	Drug + β –CD + Lactose
N-H stretching	3200-3500	3345	3342	3344	3342.75	3342.75	3344.68	3344.68
C-N Stretching	1285.41 -1347.95	1325.14	1346.43	1344	1344.43	1342.5	1340.57	1342.50
C-H Stretching	2800-3000	2924.18	2883.6	2887	2887.53	2914.54	2922.25	2924.18
C-C	1202-1402	1236	1215.19	1215.1	1398.44	1394.58	1215.19	1251.84

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stretching				9				
C=C stretching	1502-1607	1602.90	1595.18	1595	1595.18	1595.18	1595.18	1595.18
C-H deformations	1600-2000	1602.9	1664.62	1662.69	1666.55	1664.62	1595.18	1666.65

Percent yield, Solubility, Drug content of prepared solid dispersion using PEG6000, Poloxamer 188 and lactose with different methods.

Sl.no	Formulation	Percent yield (%)	Solubility (mg/ml)	Drug content (%)
01	PURE DRUG	95%	0.003	95.31±0.18
02	SDF1	99%	0.015	95.78±0.39
03	SDF2	98.85%	0.020	96.32±0.18
04	SDF3	96.66%	0.026	96.99±0.38
05	SDF4	99%	0.030	97.57±0.41
06	SDF5	98.5%	0.037	98.10±0.20
07	SDF6	96.66%	0.042	97.76±0.22
08	SDE1	99.6%	0.049	98.14±0.25
09	SDE2	98.5%	0.055	98.97±0.21
10	SDE3	98%	0.061	99.02±0.34
11	SDE4	97%	0.066	99.18±0.32
12	SDE5	99%	0.070	99.57±0.37
13	SDE6	98.5%	0.074	99.27±0.44
14	SDE7	99%	0.079	99.47±0.34
15	SDE8	99.7%	0.086	99.77±0.48
16	SDE9	99.9%	0.092	99.9±0.52

Percent yield, Solubility, Drug content of prepared Inclusion complexes using β-Cyclodextrin and lactose using different methods.

Sl.no	Formulation	Percent yield (%)	Solubility (mg/ml)	Drug content (%)	% Inclusion efficiency
01	CBK1	98.9%	0.045	96.96±0.502	75.36±2.31
02	CBK2	94%	0.059	97.17±0.41	82.96±1.87
03	CBK3	96%	0.064	98.91±0.46	87.6±1.53
04	CBK4	97.7%	0.072	98.37±0.30	93.73±1.6
05	CBK5	94%	0.079	98.57±0.40	95.6±1.23
06	CBK6	97%	0.08	99.19±0.45	97.45±1.76
07	CPC1	96.6%	0.025	96.97±0.48	76.3±2.12
08	CPC2	99%	0.036	97.27±0.45	84±2.23
09	CPC3	99%	0.048	97.99±0.49	96.53±1.50

In-vitro Drug Release Studies:

Percentage cumulative drug release of Atrovastatin from various formulations:

Time	Pure drug	SDF1	SDF2	SDF3	SDF4	SDF5	SDF6
15	27.34	21.75	23.07	23.62	29.07	31.14	33.66
30	33.18	25.15	26.92	33.36	36.16	35.63	39.00

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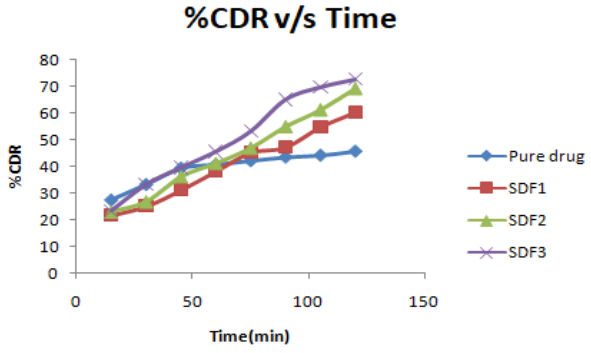
45	39.32	31.23	36.27	39.65	45.63	46.36	52.96
60	40.72	38.16	41.24	45.61	49.03	49.22	57.30
75	42.11	45.16	46.96	53.16	57.58	57.59	62.48
90	43.46	47.14	54.95	64.98	59.51	60.21	67.95
105	44.16	54.67	61.25	69.60	67.94	69.94	73.00
120	45.67	60.09	69.19	72.48	72.26	73.02	74.80

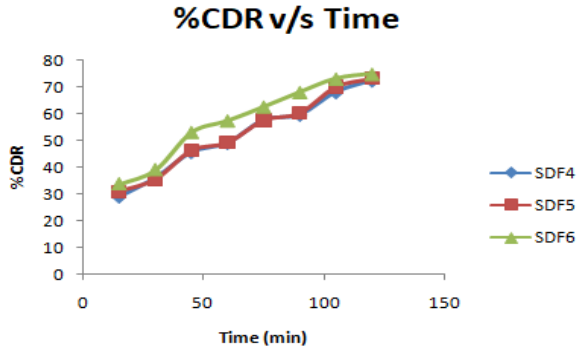
Percentage cumulative drug release of Atrovastatin from various formulations:

Time	SDE1	SDE2	SDE3	SDE4	SDE5	SDE6	SDE7	SDE8	SDE9
15	20.42	25.03	28.73	22.84	25.26	32.19	34.5	35.7	37.15
30	24.11	34.51	36.65	34.62	34.4	44.82	44.69	45.99	46.58
45	37.04	39.79	45.47	37.23	40.83	53.29	55.63	55.60	59.53
60	46.45	46.69	54.61	46.32	48.05	62.90	68.4	62.13	72.55
75	49.50	55.95	61.81	52.43	58.11	71.02	79.74	73.78	85.64
90	57.62	61.34	71.4	60.56	67.24	81.64	88.43	89.19	99.1
105	65.21	71.82	83.55	70.27	76.05	86.36	93.23	98.78	-
120	72.94	80.06	90.02	74.46	82.45	94.10	97.34	-	-

Percentage cumulative drug release of Atrovastatin from various formulations:

Time	CBK1	CBK2	CBK3	CBK4	CBK5	CBK6	CPC1	CPC2	CPC3
15	22.77	23.07	26.76	27.9	28.84	28.8	19.8	21.33	22.59
30	26.08	30.69	37.29	40.76	41.92	43	25.31	27.40	29.37
45	35.97	38.94	46.73	51.32	52.31	56.43	34.45	35.08	41.77
60	46.38	47.24	58.07	58.53	64.25	69.73	41.84	43.13	46.95
75	54.37	57.81	64.16	68.7	71.87	79.29	46.57	47.37	48.29
90	61.51	66.62	69.32	74.23	79.65	91.49	54.92	49.6	56.29
105	67.94	71.83	73.41	81.21	86.31	97.39	58.82	60.92	61.55
120	70.14	79.76	79.24	88.92	94.51	-	63.64	69.77	72.29





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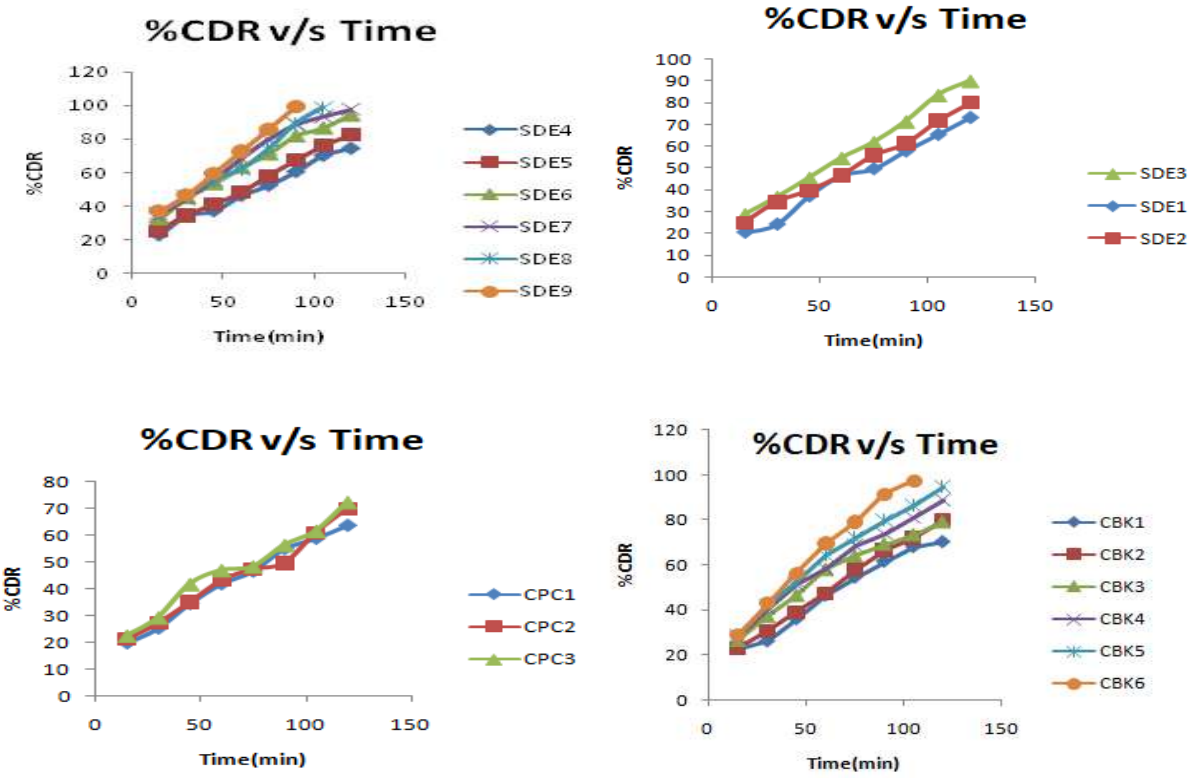

Graph no 1: In-vitro drug release of pure drug and solid dispersions of drug with PEG 6000 (SDF1 to SDF3) by Fusion method
Graph no 2: In-vitro drug release of solid dispersion of drug with P188 (SDF4 to SDF6) by Fusion method
Graph no 3: In-vitro drug release of solid dispersion of drug with P188 (SDE4 to SDE9) by Solvent evaporation method
Graph no 4: In-vitro drug release of solid dispersion of drug with PEG 6000 (SDE1 to SDE3) by Solvent evaporation method
Graph no 5: In-vitro drug release of Inclusion complex of drug with β-cyclodextrin (CPC1 to CPC3) by co-precipitation method
Graph no 6: In-vitro drug release of Inclusion complex of drug with β-cyclodextrin (CBK1 to CBK6) by Kneading method

Stability studies:

The selected formulation was tested for its stability studies. Short-term stability studies were performed at 40±2°C over a period of 3 months. Sample number of granules were packed in amber colored screw capped bottle and kept in stability chamber maintained at 40±2°C. Samples were taken at 1 month interval for their drug content estimation. At the end of 3 months period, dissolution test were performed to determine the drug release profile.

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Stability study of formulation SDE9 and CBK6 of solid dispersion and inclusion complex.

Sl.no	Parameters	Observation					
		Initial	1 month		2 months		3 months	
			RT	40°C	RT	40°C	RT	40°C
01 02 03	Nature Colour Flow properties	Compact solid White Good	Compact solid White Good	Compact solid White Good	Compact solid White Good	Compact solid White Good	Compact solid White Good	Compact solid White Good

EVALUATION OF SOLID DISPERSIONS AND INCLUSION COMPLEXES

Percentage yield

Percentage yield of different formulations were found to be in the range of 95% to 99.9% indicating good percentage yield and suitability of the formulation methods.

Drug content

Drug content was found to be in the range of 95.31%±0.18 to 99.9%±0.52 indicating good uniformity in drug content in all formulations.

Solubility studies

The solubility study of Atrovastatin in water was found to be 0.003 mg/ml. In case of solid dispersion an enhanced solubility was obtained by solvent evaporation method when combined with functional excipients and inclusion complex also showed high solubility when compared to pure drug solubility i.e., 0.092 mg/ml for solvent evaporation method and 0.08 mg/ml by Kneading method.

In-vitro dissolution studies

The In-vitro dissolution studies showed that percentage drug release from all formulations was found to be 99.1% within 90 minutes which is highly greater than 43.46% of pure drug in 90 minutes. Dissolution rate of Atrovastatin increased with the increase in the concentration of carrier. This might be due to increased wettability of drug and decreased interfacial tension between drug and dissolution medium. From the in-vitro release profile, formulations prepared by Solvent Evaporation method and kneading method were found to show higher dissolution rate than those prepared by Fusion method and co-precipitation method. Inclusion complexes prepared by kneading method were found to give better dissolution rate than inclusion complex prepared by co-precipitation method. Formulation CBK6 (inclusion complex containing Atrovastatin: β-CD: lactose in 1:6:1.5 ratio prepared by kneading method) showed the highest dissolution rate than the other formulations i.e., 97.39% in 105 minutes than the formulation CBK3 which showed 73.41% in 105 minutes (containing Atrovastatin: β-CD in 1:6 ratio prepared by kneading method. Formulation SDE9 (solid dispersions containing Atorvastatin: P188: lactose in 1:6:1.5 ratio prepared by solvent evaporation method) showed higher dissolution rate of 99.1% at 90 minutes than the other formulation (containing Atorvastatin: P188 in ratio 1:6 prepared by solvent evaporation method) SDE6 which showed 81.64% in 90 minutes. Therefore, solvent evaporation and kneading method showed higher dissolution than fusion and co-precipitation method.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of drug and drug-polymer mixture did not show any major shifts of the characteristic peaks indicating drug and polymers (PEG 6000, P188, β-Cyclodextrin and Lactose) are compatible. FTIR spectra of sample drug showed that the functional group frequencies were in the reported range indicating that the obtained sample of drug was pure.

Drug content

Drug content was also found to be uniform in all formulations ranging from 95.31±0.18 to 99.9%±0.52 % which is required for the therapeutic action of drug.

Stability studies

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The stability studies of the optimized formulation SDE9, SDE6, CBK3, CBK6 showed negligible changes in the properties of the granules which indicated the stability of the formulation.

IV. CONCLUSION

Solid dispersions and inclusion complexes were prepared by kneading method, fusion method, co-precipitation and solvent evaporation methods in different ratio of drug and carrier.

From the research work carried out, following conclusions can be drawn:

- FTIR spectra led to the conclusion that there was no interaction between drug and polymers; hence they are compatible.
- The percentage yield of different formulations was found to be in the range of 95% to 99.9%.
- The In-vitro release study showed that all the formulations gave better drug release than pure drug.
- It was concluded that while we use functional excipients with the drug and hydrophilic carrier it increases the double the times of the dissolution rate of drug.
- It also showed the four-fold increase in the solubility of drug Atrovastatin by the addition of functional excipients with drug and polymer.
- The entrapment of drug in β-cyclodextrin was found higher in the kneading method than co-precipitation method.
- The formulations prepared by Solvent evaporation method gave higher release than those Prepared by Kneading method.
- Inclusion complexes by Kneading method were found to show better release than Co-precipitation method.
- Inclusion complex (CBK6) containing 1:6:1.5 ratio of Atrovastatin: β-Cyclodextrin: lactose showed highest drug release i.e., 97.39% in 105 minutes than the inclusion complex CBK3 containing 1:6 ratio without functional excipients showed the drug release i.e., 73.41 % at 105 minutes.

The solid dispersion i.e., SDE9 containing 1:6:1.5 ratio of Atrovastatin: P188: Lactose showed higher drug release i.e., 99.1% in 90 minutes than the solid dispersion SDE6 containing 1:6 without functional excipients showed the drug release i.e., 81.64% at 90 minutes.

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