Solubility Enhancement of Poorly Soluble Drug Carvedilol by Using Complexation and Solid Dispersion Techniques

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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 Carvedilol with an aim to increase hydrophilicity and bioavailability of Carvedilol. Methods: Solid dispersions and inclusion complexes of Carvedilol 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 Carvedilol 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: Carvedilol, Solid dispersion, Inclusion complexes, PEG6000, P188, β-CD, lactose, Solvent Evaporation, Kneading method, Fusion method, Co-precipitation method.

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.[1]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.[2]

Carvedilol (CRV) is a beta-blocker used to treat high blood pressure and heart failure. CRV is partially insoluble in water. The solubility of CRV is limited because of its protonation, resulting in situ hydrochloride saltformation which exhibits less solubility in acidic medium.

Carvedilol, an anti-hypertensive drug. Carvedilol 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 posses 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 superdisintegrants are widely accepted in industry for enhancing the dissolution rate of poorly soluble drugs from the solid dosage forms. 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. [3, 4] The aim of the present work was to enhance aqueous solubility of Carvedilol 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 Carvedilol by adding hydrophilic polymers in different ratios with functional excipients for increasing the solubility and to see an increase in bio-availability.

MATERIALS AND METHODS:

Materials:
Carvedilol was procured as gift sample from Microlabs, 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 CARVEDILOL

Solid dispersions and inclusion complexes of Carvedilol 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
Carvedilol 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 were 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.[6]

Fusion method
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.[7]

Kneading method
Carvedilol 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.[8]

CHARACTERIZATION OS SOLID DISPERSIONS AND INCLUSION COMPLEXES

UV Spectrophotometric methods for determination of Carvedilol[9]
Preparation of standard plot of Carvedilol for quantitative determination in various solubilizers by UV Spectrophotometry: Solvent like 0.1N Hcl was selected to dissolve Carvedilol and the solution (1-40µg/ml) was scanned for λmax.

Preparation of Standard Calibration Curve of Carvedilol : Standard stock solution of Carvedilol: 100 mg of Carvedilol 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 Carvedilol. 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)[10]
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:[11,12]
Solubility studies were carried out according to the method of Higuchi and Connors, 1965. An excess of Carvedilol (10mg) was placed in a 25 ml glass vial containing various concentrations of each carriers 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 Carvedilol in water at the same temperature was also determined following the same procedure.

Drug content[11, 12, and 13]
Drug content of Carvedilol 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 Carvedilol) 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[14,15]**
The *in-vitro* dissolution study was conducted using USP Type I (Basket) Dissolution apparatus (Labindia, Mumbai) at 37±0.2°C using 900 ml of 0.1N Hcl buffer with pH 1.2. The samples equivalent to 100mg of Carvedilol 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)[16,17]: FTIR spectra of Carvedilol 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[18]

All inclusion complexes of Carvedilol 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[19, 20]

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

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

RESULTS

PREFORMULATION STUDIES OF CARVEDILOL

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

Table 1: Absorbance of Carvedilol (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

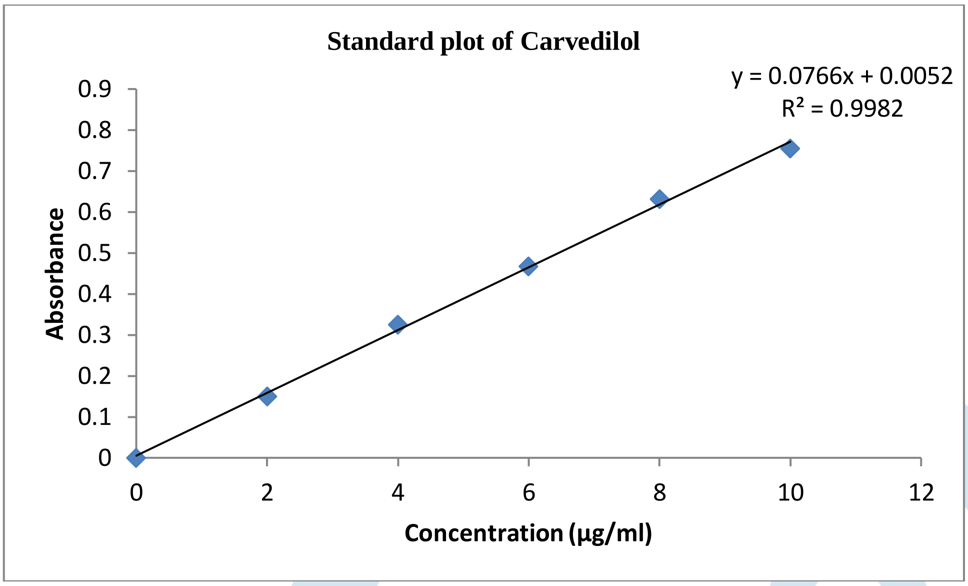


Figure 1: Standard calibration curve of Carvedilol in 0.1 N Hcl buffer.

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 stretching	1202-1402	1236	1215.19	1215.19	1398.44	1394.58	1215.19	1251.84
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 Carvedilol from various formulations:

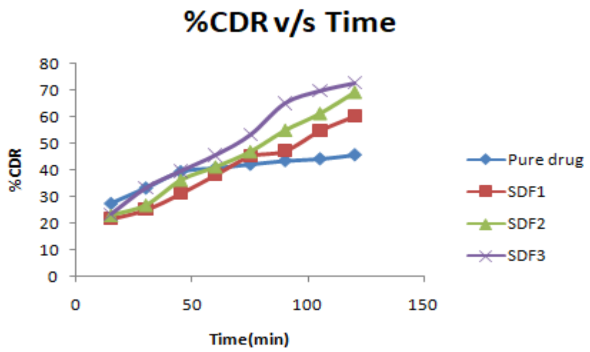
Time	Pure drug	SDF1	SDF2	SDF3	SDF4	SDF5	SDF6
15	27.34	21.75	23.07	23.62	29.07	31.14	33.66
30	33.18	25.15	26.92	33.36	36.16	35.63	39.00
45	39.32	31.23	36.27	39.65	45.63	46.36	52.96
60	40.72	38.16	41.24	45.61	49.03	49.22	57.30
75	42.11	45.16	46.96	53.16	57.58	57.59	62.48
90	43.46	47.14	54.95	64.98	59.51	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

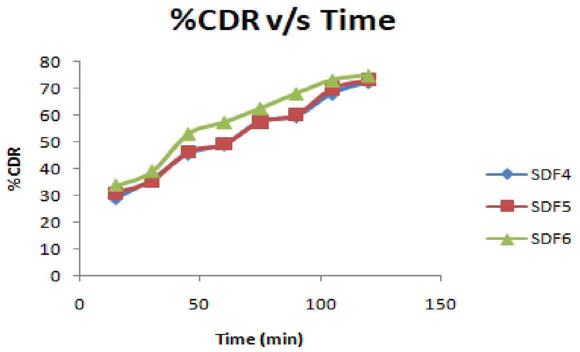
Percentage cumulative drug release of Carvedilol from various formulations:

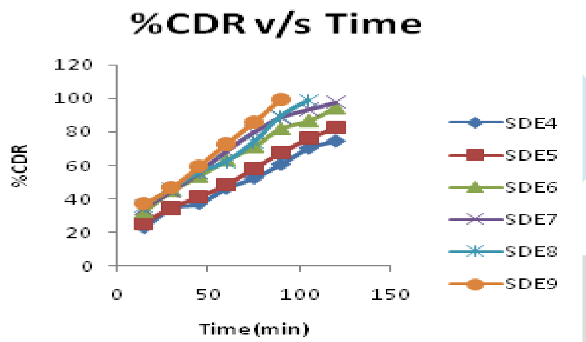
Time	SDE1	SDE2	SDE3	SDE4	SDE5	SDE6	SDE7	SDE8	SDE9
15	20.42	25.03	28.73	22.84	25.26	32.19	34.5	35.7	37.15
30	24.11	34.51	36.65	34.62	34.4	44.82	44.69	45.99	46.58
45	37.04	39.79	45.47	37.23	40.83	53.29	55.63	55.60	59.53
60	46.45	46.69	54.61	46.32	48.05	62.90	68.4	62.13	72.55
75	49.50	55.95	61.81	52.43	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	-	-

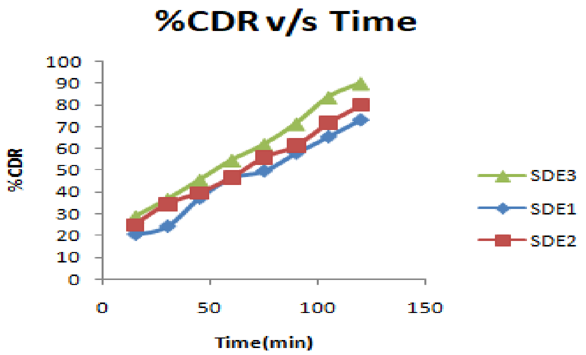
Percentage cumulative drug release of Carvedilol from various formulations:

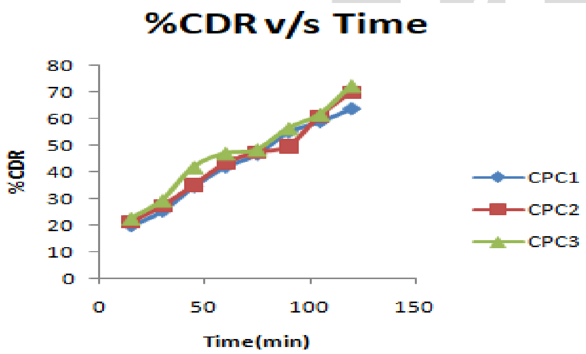
Time	CBK1	CBK2	CBK3	CBK4	CBK5	CBK6	CPC1	CPC2	CPC3
15	22.77	23.07	26.76	27.9	28.84	28.8	19.8	21.33	22.59
30	26.08	30.69	37.29	40.76	41.92	43	25.31	27.40	29.37
45	35.97	38.94	46.73	51.32	52.31	56.43	34.45	35.08	41.77
60	46.38	47.24	58.07	58.53	64.25	69.73	41.84	43.13	46.95
75	54.37	57.81	64.16	68.7	71.87	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

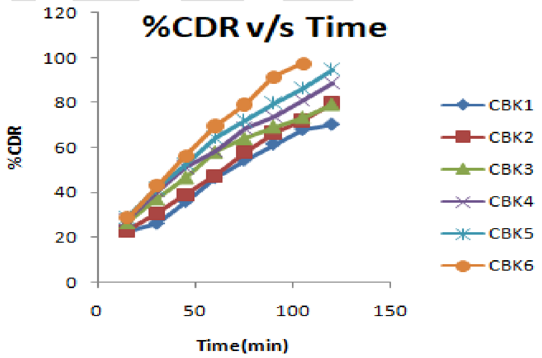












Graph no 1: *In-vitro* drug release of pure drug and solid dispersions of drug with PEG 6000 (SDF1 to SDF3) by Fusion method

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 amount 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.

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

Sl.no	Parameters	Observation						
		Initial	1 month		2 month		3 month	
			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 Carvedilol in water was found to be 0.003 mg/ml. In case of solid dispersion an enhanced solubility were 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 Carvedilol 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 Carvedilol: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 Carvedilol: β-CD in 1:6 ratio prepared by kneading method. Formulation SDE9 (solid dispersions containing Carvedilol: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 Carvedilol: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

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.

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 Carvedilol 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 Carvedilol: 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 Carvedilol: 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.

REFERENCES

[1] Wadher SJ, Gattani SG, Jadhav YA, Kalyankar TM. Recent approaches in solubility enhancement of poorly water soluble drug-Simvastatin: review. *World J of Pharm Pharm Sci* 2014;3(4):366-84.

[2] Vidyadhara S, Babu RJ, Sasidhar RLC, Ramu Prasad SS, Tejasree M. Formulation and evaluation of glimepiride solid dispersions and their tablet formulations for enhanced bioavailability. *Int J Adv Pharm Sci* 2011;2(1):2231-541.

[3] Kaldepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. *Acta Pharm Sinica B* 2015;5(5):442-53.

[4] Balvinder D, Narendra Kr. Goyal, Rishabha Malviya and Pramod K. Sharma. Poorly Water Soluble Drugs: Change in Solubility for Improved Dissolution Characteristics a Review. *Global J Pharmacology* 2014;8(1): 26-35.

[5] Patil MS, Godse SZ, Saudagar RB. Solubility enhancement by various techniques: an overview. *World J Pharm Pharm Sci* 2013;2(6):4558-72.

[6] Singh J, Walia M, Harikumar SL. Solubility enhancement by solid dispersion method: a review. *J Drug Deliv Therapeutics*, 2013;3(5):148-55.

[7] Bhowmik D, G Harish, S Duraivel, BK Pragathi, et al, Solid Dispersion – A Approach To Enhance The Dissolution Rate of Poorly Water Soluble Drugs. *The Pharma Inn-J* 2013;12(1):2277-95.

[8] Chowdary KPR, Ravi SK, Chowdary CS. Recent Research on solid dispersions employing super disintegrants and surfactants as carriers. *Int J Chem Sci Tech* 2015;5(1):378-86.

[9] Jadhav YL, Parashar B, Ostwal PP, Jain MS. Solid dispersion: solubility enhancement for poorly water soluble drug. *Res J Pharm Tech* 2012;5(2):190-97.

[10] Bhusnure OG, Kazi PA, Gholve SB, Ansari MMAW, Kazi SN. Solid dispersion: an evergreen method for solubility enhancement of poorly water soluble drugs. *Int J Res Pharm Chem* 2014;4(4):906-18.

[11] Manisha Karpe, Nikhil Mali and Vilasrao Kadam. Formulation and Evaluation Of Acyclovir Orally Disintegrating Tablets. *J App Pharm Sci* 2012;02(03):101-05.

[12] Kadam VB, Bamane GS, Raut GS. Solubility enhancement of Nebivolol hydrochloride using β-CD complexation technique. *Int J Cur Pharm Sci* 2014;1(1):6-12.

[13] Anjana MN, Sreeja CAN, Jipnomon J. An updated review of cyclodextrins-an enabling technology for challenging pharmaceutical formulations. *Int J Pharm Pharm Sci* 2013;5(3):54-8.

[14] Magnusdottir A, Masson M, Loftsson T. Cyclodextrins. *J Incl Phenom Macroc Chem* 2002;44:21-38.

[15] Tiwari G, Tiwari R, Rai AK. Cyclodextrins in delivery systems: applications. *J Pharm Bioallied Sci* 2010;2(2):72-9.

[16] Sachan NK, Pushkar S, Solanki SS, Bhatere DS. Enhancement of solubility of Acyclovir by solid dispersion and inclusion complexation methods. *World App Sci J* 2010;11(7):857-64.

[17] Kane RN, Kuchekar BS preparation, physiochemical characterization, dissolution and formulation studies of Telmisartan cyclodextrin inclusion complexes. *Asian J Pharm* 2010;11(7):857-64 .

[18] Janamala RS, Valluru R, Anusha T, Devisetty J, Sridhar KA. Solubility enhancement of indomethacin by solid dispersion technique and development of fast dissolving tables. *Int Res J Pharm* 2012;3(12):145-50.

[19] Raj RA, Nair SS, Harindran J. Formulation and evaluation of Cyclodextrin inclusion complex tablets of Carvedilol. *Asian J Pharm* 2016;10(2):84-94.

[20] Sharma MC, Sharma S. Preparation, physicochemical characterization, dissolution, formulation and spectroscopic studies of β-cyclodextrin inclusion complex. *Int J Chemical Techno Res* 2011;3(1):104-11.

[21] Srinivasa Rao Y, Vijaya L,Varalakshmi TSNS, Chandana R and Chowdary KPR . Formulation and Evaluation of Carvedilol by solid dispersion for solubility enhancement and dissolution rate enhancement. *Int J Adv Pharm, Bio and Chem, 2012;1(4):2277-88.*

[22] AbdelmouminZoghbi, Bo Wang Carvedilol solubility Enhancement by inclusion Complexation and Solid dispersion. *J Drug Deliv Therapeutics, 2015;5(2):1-8*

[23] YarraguntlaSrinivasa Rao, Veeraiah Enturi, Vyadana Ramakrishna, Moturi Srinivasa Rao, Chandrasekhar K.B. Enhancement of Solubility and dissolution rate of poorly soluble Antihypertensive drug using solid dispersion technique. *Asian J Pharm, 2016;10(4):676-81.*

[24] Kavitha Bhamani, Inclusion Complexation of antihypertensive drug for solubility enhancement to increase its bioavailability, *Asian J Adv Res Reports, 2018;2(2):1-15.*

[25] Rajbanshi K, Bajracharya R, Shrestha A, Thapa P. Dissolution enhancement of Aceclofenac tablet by solid dispersion technique. *Int J Pharm Sci Res* 2014;5(4):127-39.

[26] A.Sharma and C.P. Jain, Preparation and characterization of Solid dispersions of Carvedilol with PVPK (30), *Res in PharmSci, 2010;5(1):49-56.*

[27] ThorsteinnLoftsson, Stine Byskov Vogensen, And Phatsawee Jansook Solubilization and Cyclodextrin Complexation AAPS, *Pharm Sci Tech, 2008;9(2):425-30.*

[28] Alam AA, Masum MAA, Islam RB, Sharmin SMF, Islam A.Formulation of solid dispersion and surface solid dispersion of nifedipine: a comparative study. *Afr J Pharm Pharmaco*. 2013;7(25):1707-18.

[29] Rao S.K, Priscilla G.M, Bhargava P, Rao B. Enhancement of dissolution rate of Fenofibrate by using various Solid dispersion techniques, *J Pharm Res,* 2014;3(7):126-34.

[30] Singh N and Sarangi M.K, Solid dispersion for Enhancement of solubility and bioavailability of Poorly soluble drugs in oral drug delivery system , *Global J Pharm Pharm Sci, 2017;3(2):001-8.*

[31] Varun Raj Vemula, Venkateshwarlu Lagishetty, Srikanth Lingala , Solubility enhancement techniques , *Int J Pharm Sci Rev Res, 2010;5(1):41-51.*

[32] MargritAyoub, AzzaHasan, Hanan El Nahas, Fakhir- EldinGhazy,Enhancement of oral bioavailability of Carvedilol by using solid dispersion technique , *Int J Pharm Sci, 2016;8(7):193-9.*

[33] Iyer SR, Sivakumar R, Siva P, Sajeeth CI. Formulation and evaluation of fast dissolving tablets of risperidone solid dispersion. *Int J PharmBio chemsci* 2013;3(2):388-97.

[34] Asif Mahmood, Mahmood Ahmad, Rai Muhammad Sarfraz, Muhammad Usman Minhas, Ayesha Yaqoob. Formulation and *In-vitro* Evaluation of Acyclovir Loaded Polymeric Microparticles: A solubility Enhancement Study. *Acta Poloniae Pharm Drug Res* 2016;73:1311-24.

[35] Kushwaha Anjali, Prajapati Sunil K, Sharma Bhawna .Comparative study of acyclovir solid dispersion for bioavailability enhancement. *Americian J Pharmtech res* 2011;1(3):2249-57.

[36] Balvinder dhillon, Narendra Kr. Goyal and Pramod K Sharma. Formulation and Evaluation of Glibenclamide Solid Dispersion Using Different Methods. *Global J Pharmaco* 2014;8 (4): 551-6.

[37] Enose AA, Dasan P, Sivaramakrishanan H, Kakkar V. Formulation, characterization and pharmacokinetic evaluation of Telmisartan solid dispersions. *J Mol Pharm Org Process Res* 2016;4(1):1-8.

[38] Kavita D. Patel, Sunila T. Patil, Sunil P. Pawar, Bhushan R. Rane. Solubility Enhancement of Poorly Water Soluble Drug by Solid Dispersion Technique. *Int J Pharm Res scholars* 2016;5(3): 2277- 7873.

[39] Shinkar Dattatraya Manohar, Dhake Avinash Shrichar, Setty Chitral Mallikarjuna. Solubility and Dissolution Enhancement of Carvedilol by Solid dispersion technique using Gelucire 50/13. *Int J Pharm Sci Rev Res* 2014;29(1): 161-65.

[40] Jamakandi G Vilas, Kerur S Shashidhar, Patil S Umesh. Formulation and Evaluation of Immediate Release tablet of Carvedilol using Liquisolid Compacts technique for Solubility Enhancement. *Asian j pharm 2016;10(3)*:S324-32.

[41] Ankit Gupta1, Mahesh Kumar Kataria, Ajay Bilandi. Formulation and evaluation of solid dispersion of glipizide for solubility and dissolution rate enhancement. *Int J Pharm Drug Analysis* 2014;2(2):74-87.

[42] Bhanudas S. Kuchekar, Varsha B. Divekar, Swati C. Jagdale, Gonjari. Solubility enhancement and formulation of rapid disintegrating tablet of Febuxostat Cyclodextrin complex. *J pharm Res* 2013;1(2):168-75

[43] Anroop B. Nair, Mahesh Attimarad, Bandar E. et al Enhanced oral bioavailability of acyclovir by inclusion complex using hydroxypropyl-b-cyclodextrin. *Informa Healthcare USA* 2013;1071-7544.

[44] Wagh Supriya R, Arsul Vilas A, Gadade Deepak D,Rathi Pavan B. Solubility enhancement of antiviral drug acyclovir by solid dispersion-a research article Technique. *Indo American J Pharm Sci* 2015;2(10):1352-65

[45] Patil J. S , Kadam D.V, Marapur S.C, Kamalapur M.V , Includion complex system to improve the solubility and bioavailability of poorly soluble drug:Review , *Int J Pharm Sci Rev Res, 2010;2(2):29-34.*

[46] Raj R. Arun , Harindran Jyothi Enhancement of bioavailability of Carvedilol using Solvent deposition technique, *Int J Pharm sci Res,* 2017;8(8):3391-401.

[47] Bhavsar R. Malavi, Savkare D. Anand, Enhancement of aqueous solubility of Carvedilol by liquisolid technique, *Indo Ame J Pharm Res, 2017;7(8):537-49.*

[48] Irin Dewan, Md. Ayub Hossain, SM. Asharful Islam. Formulation and evaluation of Solid dispersions of Carvedilol, a poorly water soluble drug by using different polymers, *Int J Res Pharm Chem, 2012;2(3):585-93.*

[49] Kadam D. Vinayak, Gattani G. Surendra. Dissolution enhancement of Carvedilol by using Surfactant as coating material, *Asian J Pharm Cli Res, 2009;2(3):39-43.*

[50] Shewta U. Kannao et al. Solid dispersion –A Technique For Solubility Enchancement Of Weakly Water Soluble Drug-A Review. INDO American J of Pharmaceutical Research 2014;4(06):2839-48.

[51] Mogal SA, Gurjar PN, Yamgar DS, Kamod AC. Solid dispersion technique for improving solubility of some poorly soluble drugs. Der Pharmacia Lettre 2012;4(5):1574-86.
[52] Khakeshan KF, Nikghalb LA, Singh G. Solid dispersion: methods and polymers to increase the solubility of poorly soluble drugs. J App Pharm Sci 2012;2(10):170-75.
[53] Rowe RC, Sheskey PJ, Quinn ME. Handbook of pharmaceutical excipients.
[54] Shrivastava P, Sethi V. A review article on: superdisintegrants. *Int J Drug Res Tech* 2013;3(4):76-87.
[55] Shihora H, Panda S. Superdisintegrants, utility in dosage forms: a quick review. *J Pharm Sci Biosci Res* 2011;1(3):148-53.
[56] Li J, Wu Y. Lubricants in pharmaceutical solid dosage forms. Lubricants 2014;2:21- 43.
[57] Yuksel N, Turkmen B, Kurdoglu AH, Basaran B, Erkin J, Baykara T. Lubricant efficiency of magnesium stearate in direct compressible powder mixtures comprising cellactose 80 and pyridoxine hydrochloride. *J Pharm Sci* 2007;32:173-83.
[58] Wagh Supriya R, Arsul Vilas A, Gadade Deepak D,Rathi Pavan B. Solubility enhancement of antiviral drug acyclovir by solid dispersion-a research article Technique. Indo Americian J of Pharmaceutical Sci 2015;2(10):1352-65
[59] Morin G, Briens L. The effect of lubricants on powder flowability for pharmaceutical application. *Pharm Sci Tech* 2013;14(3):1158-68.
[60] Jadhav NR, Paradkar AR, Salunkhe NH, Karade RS, Mane GG. Talc: a versatile pharmaceutical excipients. *World J Pharm Pharm Sci* 2013;2(6):4639-60.
[61] Subrahmanyam CVS. Textbook of Physical Pharmaceutics. Third edition. Delhi.
[62] Vallabh Prakashan; Kumar KV, Kumar NA, Verma PRP, Rani C. Preparation and *invitro*characterization of Valsartan solid dispersions using skimmed milk powder ascarrier. *Int J PharmTech Res* 2009;1(3):431-7.
[63] Bhise S, Mathure D, Patil MVK, Patankar RD. Solubility enhancement of antihypertensive agent by solid dispersion technique. *Int J Pharm Life Sci* 2011;2(8):970-5.
[64] Singhvi G, Singh M. Review: *In-vitro* drug release characterization models. *Int J Pharm Sci Res* 2011;2(1): 77-84.
[65] Suvankata D, Padala N. Murthy, Lilakanta Nath, Prasanta Chowdhury. Kinetic Modeling on Drug Release from Controlled Drug Delivery Systems. *Acta Poloniae Pharm Drug Res* 2010; 67(3):217-23.
[66] ICH Guideline Available at: www.tga.health.gov.au/docs/pdf/euguide/ich/273699r2en.pdf.
[67] ICH Harmonized Tripartite Guideline. Stability testing of new drug substance and product Q1 A (R2) 2003; 1-24.
[68] Indian Pharmacopeia 2014: vol (II)
[69] IDR-Triple 2018 issue :page no 41