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SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE PROTEASE INHIBITOR

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ABSTRACT: There are more than 40% of drugs which are poorly soluble and 90% of the drugs from the pipeline are from BCS class II and IV. Application of techniques like computers, robotics, high-throughput screening, combinatorial chemistry have resulted in database of huge drug-like molecules which are generally derived solely based on the affinity of the molecule with the target physiological bodies viz. enzymes, receptors etc. These new chemical entities or drug-like substances having poor biopharmaceutical properties exhibiting poor pharmacological properties. Poor biopharmaceutical properties like poor solubility poses many difficulties and delay in drug development process as the these molecules show satisfactory performance *in-vitro* or *in-silico* but *in-vivo* they fail to exhibit pharmacological response thereby have low bioavailability. Drug dissolution is rate limiting step in majority of the cases hence increasing solubility leads to increased dissolution rate and thereby likely to increase the bioavailability. By doing so the drug is available in a solubilized form at site of action and is efficacious at lower doses. In the present work dissolution rate of poorly soluble protease inhibitor have been attempted using various methods. Using simple method of preparation formulations were prepared and it was observed that solid dispersion of the given drug exhibited better release than other methods viz. β-Cyclodextrin and adsorption on an inert carrier.

INTRODUCTION: There are more than 40% of drugs which are poorly soluble and 90% of the drugs from the pipeline are from BCS class II and IV. Application of techniques like computers, robotics, high-throughput screening, combinatorial chemistry have resulted in database of huge drug-like molecules. These molecules are generally derived solely based on the affinity between the ligand-receptor binding.

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Thus these new chemical entities or drug-like substances generally suffers from poor biopharmaceutical properties exhibiting poor pharmacological properties or low bioavailability. This may delay the drug development process [1, 2, 3, 4]. Being poorly soluble drug, dissolution becomes the rate limiting step and determining factor for the therapeutic efficacy of the medicament. Higher dose is administered to achieve desired pharmacological effect as undissolved dose is excreted as such. Such high dose exhibits erratic absorption patterns, non linear pharmacokinetics and are highly variable with presence of foods [5, 6].

Darunavir is a second generation bis-tetrahydrofuran based HIV-1 protease inhibitor. It is very slightly soluble in water (0.15 mg/mL) and

undergoes extensive first pass metabolism, yielding absolute bioavailability of barely 37% and administered as Darunavir Ethanolate in high doses to achieve desired therapeutic effect [7].

There have been many methods reported for increasing the solubility viz. solid dispersion, particle size reduction, complexation with Cyclodextrin, lipid based drug delivery systems, polymorphs, salt formation, prodrugs, modification of crystal habit, cosolvency, various nanotechnology approaches, etc.

MATERIALS AND METHODS:

Materials:

Darunavir Ethanolate (DRVE) was provided by Cipla Ltd. (Mumbai, India) as a gift sample. HPMC E50 LV (The Dow Chemicals Company, Mumbai, India); Polyvinylpyrrolidone/Kollidon K30, Poloxamer F407, Soluplus (BASF, Mumbai, India); Aeroperl® 300 Pharma (Evonik Industries, Rheinfelden, Germany); β-Cyclodextrin (Gangwal Chemicals, Mumbai, India) and empty hard gelatin capsules (ACG-Associated Capsules Pvt. Ltd. Mumbai, India) were obtained as gift samples. PEG 6000, Poly vinyl alcohol and isopropyl alcohol were purchased locally (Loba Chemie Pvt. Ltd., Mumbai, India). Fresh double distilled water was used throughout the experiment.

Solid dispersion:

Solid dispersion is one of the widely used method for enhancing solubility of poorly soluble drugs. It is molecular dispersion of solute molecules in hydrophilic polymeric matrix or carrier, which eventually dissolves and increases saturation state of drug molecules and increases exposed surface area, leading to enhanced dissolution rate [8, 9].

Solubility Studies: An excess amount of Darunavir Ethanolate (DRVE) was added to each glass vial containing 1% aqueous polymeric solution. After sealing, the mixture was vortexed using a cyclomixer for 10 min in order to facilitate proper mixing of DRVE with the vehicles and then sonicated for 10 minutes. Mixtures were then kept in orbital shaker for 48 hours maintained at 25°C.

After 48 hours mixtures were centrifuged at 5000 rpm for 5 min, followed by filtration. These filtrates were appropriately diluted and quantified spectrophotometrically using Shimadzu UV-1800 (Shimadzu, Kyoto, Japan) [10].

Preparation of solid dispersion: Drug and polymers viz. HPMC E50 LV; Polyvinylpyrrolidone, Poloxamer F407, PEG 6000, Poly vinyl alcohol, Soluplus were mixed in weight ratio of 1:1 and 1:2 and solid dispersions were prepared by conventional solvent evaporation method. The solid dispersions were kept in desiccators until further experimental tests were carried out.

These solid dispersions were sieved through mesh number 60 then prior to capsule filling sieved mass was diluted with microcrystalline cellulose (Avicel PH 102), lubricated with talc and magnesium stearate. Amongst various polymers attempted in solubility trials, PVP, PEG 6000, Poloxamer and Soluplus were selected for preparing solid dispersions.

Adsorption on a carrier:

Adsorption of drug on mesoporous and inert substance like silica has been studied widely. Doing so increases surface area of drug that being exposed to the dissolution medium [11, 12].

Adsorption using spray drying: DRVE (equivalent to 150 mg DRVE) and Aeroperl 300® Pharma were taken in 1:1 weight ratio and dispersed in isopropyl alcohol. This suspension was spray dried using LabUltima LU-222 Advanced Spray dryer.

Parameters were set for spray drying as Inlet temperature= 55°C, Outlet temperature= 50°C, Aspirator flow rate= 60 Nm^3/hr and Feed flow rate= 1.5 mL/min.

The spray dried product was evaluated for percent drug content. Formulation was filled in capsules and checked for its dissolution performance in discriminating medium.

Complexation with β-Cyclodextrin:

Complexation with Cyclodextrin is one of the most studied solubility enhancement technique. They pose their importance as the drug is dispersed at

molecular level in to hydrophobic cavity of Cyclodextrin. Due to advantages like enhanced solubility, stability, taste masking, prevention of haemolysis, prevention of incompatibilities, conversion of liquids into solids. Darunavir Ethanolate and β-Cyclodextrin complex were prepared using simple kneading technique in specific molar ratios and were subjected for dissolution studies [13].

Preparation of Darunavir Ethanolate-β-Cyclodextrin inclusion complex: Darunavir Ethanolate and β-Cyclodextrin were taken in molar ratios of 1:1 and 1:2, in clean mortar. Complexes were prepared by kneading method using water: acetone (6:4). These complexes were dried at 60°C, and stored in desiccators. These binary mixtures were sieved through mesh number 60 then prior to capsule filling sieved mass was diluted with microcrystalline cellulose (Avicel PH 102), lubricated with talc and magnesium stearate. Finally these formulations were subjected for dissolution studies in discriminating medium.

Optimization of formulae:
Darunavir Ethanolate exhibits pH dependant solubility, and shows increasing solubility at lower pH and vice versa. Phosphate buffer pH 6.8 had least solubility for DRVE; this buffer was selected as discriminating medium to discriminate among various formulations based on their performance. Formulations were filled in hard gelatin capsules and dissolution was performed using parameters as follows in **Table 1**.

TABLE 1: DISSOLUTION TEST IN DISCRIMINATING MEDIUM.

Sr. No.	Dissolution Methodology	Parameters
1	USP apparatus	II (Paddle)
2	Speed (RPMs)	75
3	Medium	Phosphate buffer pH 6.8
4	Volume (mL)	900 mL
5	Sampling Times (minutes)	5, 10, 15, 20, 30, 45 and 60
6	Sample withdrawal volume	10 mL
7	λ_{max}	263.6 nm

RESULTS AND DISCUSSIONS:

Solid dispersion: Solubility studies: Solubility studies were aimed at identifying the suitable polymer which can exhibit maximum solubility and is able to dissolve quickly to release drug from the polymeric formulation. Soluplus aqueous solution exhibited maximum solubility for DRVE and Poloxamer exhibited quick dissolving property. Results are depicted in **Table 2.**

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TABLE 2: SATURATION SOLUBILITY OF AQUEOUS POLYMERIC SOLUTIONS. (n=3)

Sr. No.	Solution	Solubility (mg/mL) (± SD.)
1	Water	0.28±0.01
2	1% HPMC aq. solution	0.18±0.002
3	1% PVP aq. Solution	0.21±0.01
4	1% PVA aq. Solution	0.22±0.003
5	1% PEG 6000 aq. Solution	0.24±0.003
6	1% Poloxamer F407 aq. Solution	0.33±0.003
7	1% Soluplus aq. Solution	0.42±0.001

Dissolution rate in discriminating medium:
Solid dispersions comprising of Darunavir Ethanolate corresponding to 150 mg of Darunavir were prepared. Prepared solid dispersions were compared for dissolution rate studies in discriminating medium and release obtained are depicted in **Table 3** and **Fig.1**.

Adsorption using spray drying: The spray dried product was evaluated for percent drug content. Formulation was filled in capsules and checked for its dissolution performance in discriminating medium. Percent drug content in the spray dried formulation was found to be 99.23%±0.04% (n=3). Release obtained by this method is depicted in **Table 4** and **Fig.2**.

Complexation with β-Cyclodextrin:
Dissolution rate in discriminating medium was obtained and it is depicted as in **Table 5** and **Fig.3**.

TABLE 3: DISSOLUTION TEST OF SOLID DISPERSIONS IN DISCRIMINATING MEDIUM. (n=3)

Sr. No.	Time (min)	Percent cumulative release (pH 6.8)							
		D:PEG (1:1)	D:PEG (1:2)	D:POL (1:1)	D:POL (1:2)	D:PVP (1:1)	D:PVP (1:2)	D:SOL (1:1)	D:SOL (1:2)
1	0	0	0	0	0	0	0	0	0
2	5	3.23±0.12	5.54± 0.09	39.87±1.83	23.70±1.71	0.74± 0.23	0.96± 0.23	0.90±0.22	0.88±0.27
3	10	5.66±0.12	8.81± 0.03	46.71±0.63	33.64±0.51	1.44± 0.31	1.07± 0.30	0.94±0.21	1.00±0.19
4	15	7.99±0.11	11.68±0.05	49.47±1.13	43.36±0.76	2.28± 0.19	2.47± 0.21	1.31±0.14	1.41±0.12
5	20	9.99±0.08	13.84±0.16	50.88±0.90	51.35±0.89	3.34± 0.12	3.68± 0.13	1.83±0.13	1.96±0.10
6	30	13.04±0.10	14.52±0.88	53.07±0.78	60.39±0.65	5.19± 0.23	5.75± 0.27	2.57±0.17	3.10±0.15
7	45	15.88±0.05	16.39±0.22	55.97±1.16	70.90±0.42	7.38± 0.17	8.55± 0.22	3.55±0.12	4.45±0.20
8	60	17.56±0.50	16.67±0.20	58.55±2.52	77.28±1.03	9.79± 0.26	10.71±0.26	4.42±0.17	5.48±0.22
9	120	18.61±0.26	22.31±0.59	64.01±0.59	83.29±0.80	16.00± 0.20	17.69±0.11	7.27±0.20	8.77±0.16

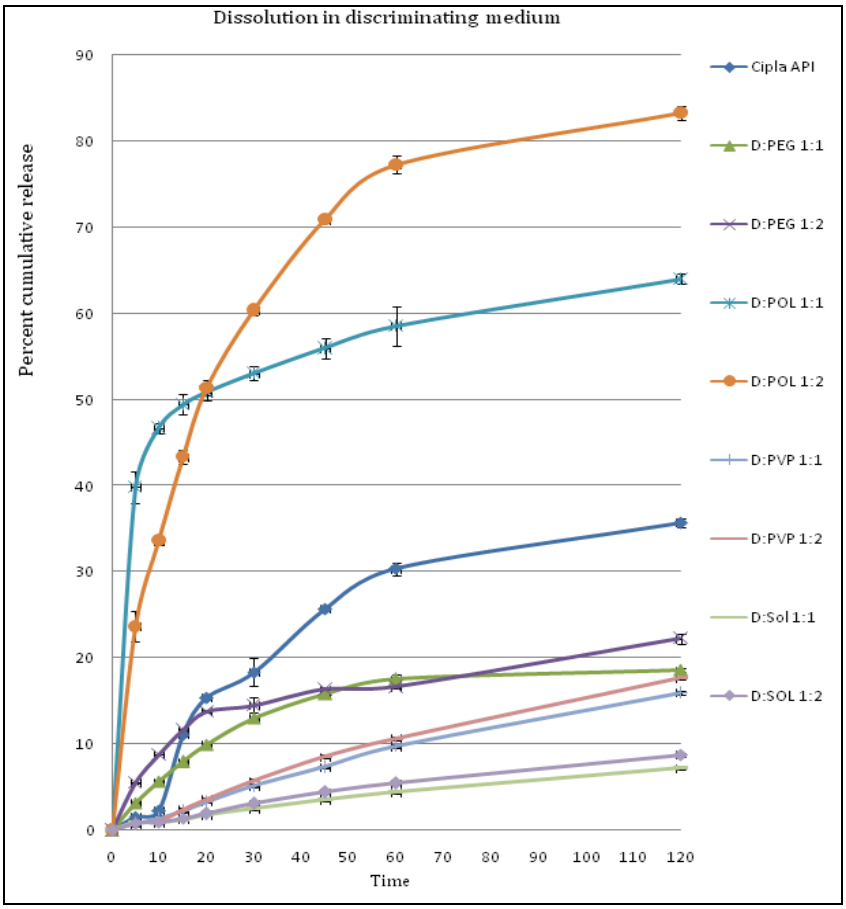

FIG.1: DISSOLUTION OF SOLID DISPERSIONS IN DISCRIMINATING MEDIUM. (n=3)

TABLE 4: DISSOLUTION OF DRUG ADSORBED ON AEROPERL. (n=3)

Sr. No.	Time(min.)	Percent cumulative release (pH 6.8)	
		API	D:Aeroperl (1:1)
1	0	0	0
2	5	1.59±0.12	1.55±0.18
3	10	2.32±0.02	10.95±0.30
4	15	11.18±0.24	20.81±0.62
5	20	15.40±0.22	27.61±0.62
6	30	18.39±1.61	35.95±1.73
7	45	25.70±0.14	41.10±1.38
8	60	30.39±0.75	43.71±2.01
9	120	35.74±0.51	51.96±1.15

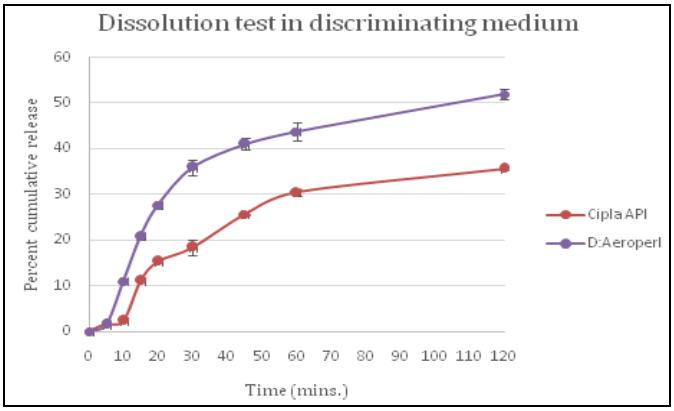

FIG.2: DISSOLUTION OF DRUG ADSORBED ON AEROPERL 300 IN DISCRIMINATING MEDIUM. (n=3)

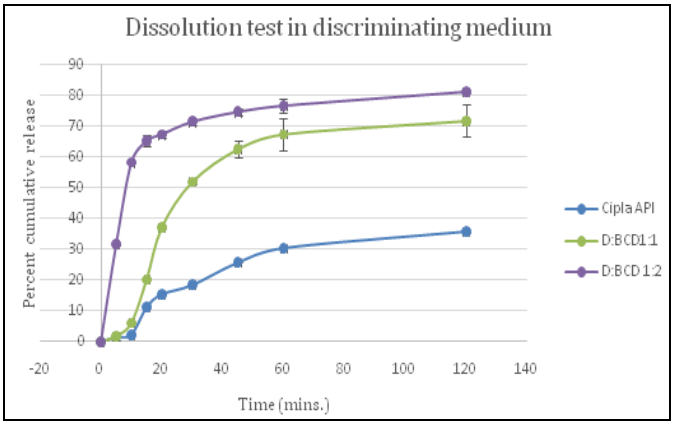

FIG. 3: DISSOLUTION OF CYCLODEXTRIN INCLUSION COMPLEX IN DISCRIMINATING MEDIUM. (n=3)

TABLE 5: DISSOLUTION OF DRUG β-CYCLODEXTRIN COMPLEX IN DISCRIMINATING MEDIUM. (n=3)

Sr. No.	Time (min)	Percent cumulative API	D: βCD (1:1)	D: βCD (1:2)
1	0	0	0	0
2	5	1.59±0.12	1.86±0.23	31.57±1.10
3	10	2.32±0.02	6.22±0.20	58.12±0.75
4	15	11.18±0.24	20.23±1.84	65.16±0.51
5	20	15.40±0.22	37.14±1.00	67.26±0.76
6	30	18.39±1.61	51.91±1.01	71.36±0.40
7	45	25.70±0.14	62.51±1.03	74.55±0.65
8	60	30.39±0.75	67.34±2.26	76.55±0.66
9	120	35.74±0.51	71.70±0.41	81.07±0.30

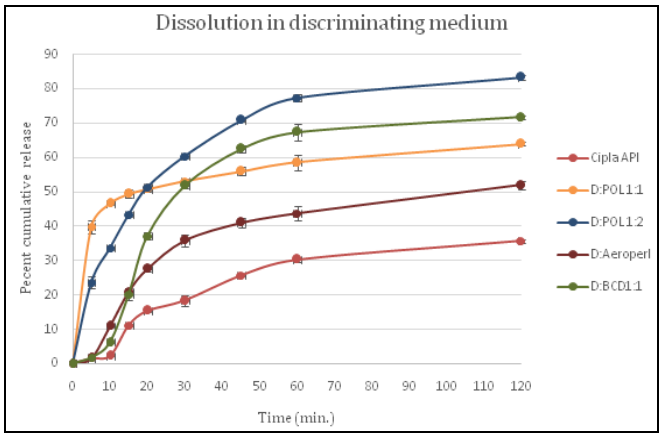

FIG. 4: COMPARATIVE DISSOLUTION OF VARIOUS FORMULATIONS IN DISCRIMINATING MEDIUM. (n=3)

DISCUSSION: Various methods were attempted to increase dissolution rate of Darunavir Ethanolate. Formulations prepared using various approaches were screened on the basis of their dissolution performance in discriminating medium. Solid dispersion of Darunavir Ethanolate in Poloxamer yielded promising results followed by β-Cyclodextrin and adsorption on inert carrier, as mentioned in the following:

Solid dispersions were prepared which exhibited slightly fair release with Poloxamer formulation containing drug: Poloxamer ratio 1:1 showed 58.55% and that with ratio 1:2 showed 77.28% release at the end of one hour.

Adsorption of drug on an inert carrier like Aeroperl can be used to increase its effective surface area for dissolution leading to increase rate of dissolution. However, It showed merely 43.71% release at end of one hour. β-Cyclodextrin inclusion complexes were prepared in equimolar ratio of 1:1 using kneading method which showed 67.34% and further incorporation of molar ratio 1:2 gave results of 76.55% at the end of one hour. This method can also be one of the choice; more enhancements can be achieved upon spray drying the β-CD and Drug complex mixture. **Fig.4** shows comparative dissolution release performance of various formulations formulated using different techniques.

CONCLUSION: Attempts were made to enhance the solubility of Darunavir Ethanolate by increasing dissolution rate using various approaches. The study shown increased dissolution rate than the API, hence solubility of Darunavir Ethanolate was increased. The methods used are simple and easy to scale up.

Among formulation methods attempted Darunavir Ethanolate-Poloxamer solid dispersion shown promising results hence this formulation is most convenient, easy and cost-effective dosage form that can be prepared. Here methods attempted are simple, industrially feasible and easy to scale up.

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