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Solubility Enhancement of Iloperidone by Co-Precipation Method Using Anti Solvent Technique

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A B S T R A C T

The current research was to improve the solubility of the poorly soluble drug iloperidone by preparing coprecipitates. Coprecipitation is defined as the simultaneous precipitation of a normally main aim soluble component with a macro-component from the same solution by the formation of mixed crystals, by adsorption, occlusion or mechanical entrapment.The aqueous solubility of the drug was found to be (0.00304mcg/ml). Different coprecipitates were prepared by using different concentrations of Captisol. The coprecipitates were prepared by liquid antisolvent technique. The prepared coprecipitates were characterized for their solubility and in vitro drug release studies. *In vitro* dissolution performance was evaluated using 6.8 pH phosphate buffer as dissolution media and the samples were analyzed using UV-visible spectrophotometer. It was observed from *in vitro* drug release studies that there was a significant improvement in solubility and dissolution of iloperidone from coprecipitates when compared to tablet and pure drug. Thus it can be concluded that the enhancement of solubility and dissolution of iloperidone can be achieved by preparing coprecipitates.

Keywords: Coprecipitation, Antisolvent technique, Solubility enhancement techniques

A R T I C L E I N F O

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1. Introduction

Biopharmaceutical Classification System (BCS):

- Biopharmaceutical classification system classification is a tool for determining intestinal absorption of a drug.
- BCS classification is established by Dr. Gordon Amidon
- This system is related to solubility and intestinal permeability of a drug.
- Solubility classification is based on a United State Pharmacopoeia.
- Intestinal permeability classification is based on a comparison to intravenous injection.
- Drugs are classified by taking solubility, permeability and dissolution into consideration.

Biopharmaceutics Classification System chart:

Class	Solubility	Permeability
I	**High**	**High**
II	**Low**	**High**
III	**High**	**Low**
IV	**Low**	**Low**

Examples:

Class I: High solubility – High permeability (verapamil, metoprolol, diltiazem)

Class II: Low solubility – High permeability (lornoxicam, ketoprofen, mefenamic acid carbamezapine, danazol, nebivolol, iloperidone)

Class III: High solubility – Low permeability (atenolol, acyclovir, ranitidine.)

Class IV: Low solubility – Low permeability (furosemide, taxol)

Some Considerations

- A drug is classified as poorly soluble if the highest dose strength of the immediate release product is not soluble in 250 ml or less aqueous media over the pH range of 1 to 7.5.
- A drug is classified as having low intestinal permeability when the extent of absorption in humans is less than 90% of the administered dose in comparison to an intravenous dose.
- A drug is classified as rapidly dissolving if 85% of immediate release dose dissolves within 30 minutes using either USP dissolution apparatus I at 100 rpm or .dissolution apparatus II at 50 rpm in 900 ml of 0.1 N HCl or stimulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or stimulated intestinal fluid.
- Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration.
- A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption.

Therefore, pharmaceutical researcher's focuses on two areas for improving the oral bioavailability of drugs include: Enhancing solubility and dissolution rate of poorly water-soluble drugs and Enhancing permeability of poorly permeable drugs.

Techniques of Solubility Enhancement:

I. Physical Modifications:

A. Particle size reduction

- Micronization
- Nanosuspension
- Sonocrystalisation
- Supercritical fluidprocess

B. Modification of the crystal habit:

1. Polymorphs 2. Pseudo polymorphs

C. Drug dispersion in carriers:

1. Eutectic mixtures 2. Solid dispersions 3.Solid solutions

D. Complexation: Use of complexing agents

II. Chemical Modifications:

1. Change in the pH
2. Use of buffer
3. Derivatization

III. Other methods:

1. Co-crystallisation
2. Co-precipitation (Anti-solvent technique)
3. Co-solvency
4. Hydrotrophy
5. Solubilizing agents
6. Selective adsorption on insoluble carrier
7. Solvent deposition 8. Use of soluble prodrug
9. Functional polymer technology
10. Microparticle technology
11. Nanotechnology approaches

Precipitation Vs. Coprecipitation

- In analytical chemistry, precipitation is an important technique to separate out a compound/ material out from a solution. Insolubility, purity, easiness to filter, non reactivity with atmospheric substances are some of the significant features of a precipitate, which allows them to be used for analytical purposes.
- Precipitates are solids consisting of particles in a solution. Sometimes solids are a result of a chemical reaction in a solution. These solid particles will eventually settle down due to their density, and it is known as a precipitate.

Coprecipitation

"Coprecipitation is a process in which normally soluble compounds are carried out of solution by a precipitate." There are four types of Coprecipitation as surface adsorption, mixed crystal formation, occlusion and mechanical entrapment. Surface adsorption takes place for precipitates with larger surface areas. Specially coagulated colloids contaminate by this method. In mixed crystal formation, one of the ions in the crystal lattice is replaced by another ion. Surface adsorption and mixed crystal formation are equilibrium processes, whereas the other two

are kinetic phenomena. When a crystal is growing rapidly, contaminant can trap inside the growing crystal and this is known as occlusion. Mechanical entrapment is the mechanism where some amount of solution is trapped inside the crystals. This happens when two growing crystals are close together, so that they grow together. In the process of coprecipitation, chemical similarities between a carrier and a solute allow the two to bind in some way. The binding pulls the solute out of the solution as the carrier forms crystals or other structures. These can potentially be skimmed out or remove in other ways, leaving a purified solution behind. In nature, coprecipitationcan occur in waterways, soil, and other environments, and sometimes contributes to the formation of mixed deposits of minerals and other compounds. There are several ways in which a solute can coprecipitate out of a solution. One is through inclusion, where crystals of a carrier form and the solute finds holes in the crystal matrix to occupy. Solutes can also be subject to occlusion. In occlusions, the carrier completely surrounds the solute, trapping it in the middle of a matrix of crystalline material so it cannot return to the solution. Adsorption, where solutes adhere to the surface of a carrier, can occur as well.

Anti-Solvent Technique:

- A Solvent in which the product is insoluble.
- It is added drastically reducing the solubility of the desired product.
- A solid sample is dissolved in a common (organic or inorganic) solvent then injected in to a fluid (held under pressure) resulting in a large decrease in solution density. This effect leads to the reduction in solubility of the solid and precipitation.
- This is anti-solvent technique.

2. Materials and Methods

Table 1: List of Materials

S.N	Materials	Source	Category
1.	Iloperidone	SPI Pharma, Germany	Antipsychotic
2.	Captisol	Cydex Pharmaceuticals, U.S.A	Solubility enhancer
4.	Primellose	DFE Pharma, Germany	Super Disintegrant
5.	Mannogen	SPI Pharma, Germany	Diluent
6.	Lubripharm	SPI Pharma, Germany	Lubricant
7.	Aerosil (R972P)	Evonik Degussa Italy	Anti-adherent

Methodology:

Construction of calibration curve of Iloperidone in 6.8PH Phosphate buffer: Primary stock solution of 1 mg/mL was prepared. Accurately weighed amount of 100mg of iloperidone was transferred into a 100 mL of volumetric flask and was diluted initially with 1ml methanol and finally make up with 6.8 PH phosphate buffer to 100 mL From this primary stock 10 mL was transferred into another volumetric flask and made up to 100 mL with 6.8 PH buffer to obtain 100 µg/mL solution. From this secondary stock, 10 µg/mL working stock solution was prepared by tranfering 10mL of secondary stock into 100 mL and diluting with 6.8 PH buffer up to the mark.2,4,6,8,10 and12 mL solution was taken separately from working stock and made up to the mark with 6.8 PH phosphate buffer to produce 2,4,6,8,10 and 12 µg/mL respectively. The absorbance of samples was measured at 262nm using a double beam UV-visible spectrophotometer. The linear regression equation were obtained to fit the data of unknown concentration into them and to know the drug concentration in the unknown samples and also to know the drug release.

Preparation of Physical Mixtures:

Physical mixtures of coprecipitate with other excipients, were prepared by taking them as per formula and mixing the mixture to form a homogeneous mixture was obtained. The resulting mixture was sieved through a mesh size # 60. The powder was stored in desiccators until it was used.

Preparation and Evaluation of iloperidone oral dispersible tablets (ODT):

The blended mixture was compressed to tablet by direct compression method using 16 stage cadmach rotary press using suitable punches.

Evaluation of prepared tablets:

The tablets exhibited uniform thickness and hardness.

- The friability and drug content were also within the acceptable limits.
- Disintegration time was found to be 80 seconds.

Preparation of Coprecipitates:

Iloperidone coprecipitates were prepared using an anti-solvent precipitation process [37]. Iloperidone was completely dissolved in 1 mL of acetone. The prepared drug solution was added drop wise into 20 mL water containing Captisol i.e. Drug: carrier in 1:1, 1:3 and 1:5 ratio without any stirring. Coprecipitation of drug particles with carrier occurred immediately upon mixing. The obtained coprecipitates were oven dried at 30°C for few minutes.

Preparation of coprecipitates with Captisol:

Coprecipitates of Iloperidone were prepared in various ratios of drug and carrier. The method adopted for preparation was liquid antisolvent precipitation method. An appropriate amount of Iloperidone was dissolved in 1ml of acetone. The prepared drug solution was added drop wise into 20mL water containing captisol without any stirring. The obtained coprecipitates were oven dried at 30°C for few min.

Table 2: Formulation of Coprecipitates using Captisol as a carrier

Formulation	API (mg)	Captisol (mg)	Ratio	Formation of coprecipitates
CP1	50	50	1:1	✔
CP2	50	100	1:3	✔
CP3	50	150	1:5	✔

Figure 1: Formation of coprecipitates with different organic solvents using Captisol as carrier: (Acetone is used in this research)

3. Results and discussions

Analytical method development for drug estimation:

The standard graph of iloperidone in 6.8 PH phosphate buffer showed good linearity with r^2 value of 0.989, which suggest that it obeys the "Beer-lambert" law. The equation was y=0.047x. This was utilized in estimation of iloperidone samples.

Table 3: Absorbance Values

Concentration (µg/mL)	Absorbance
2	0.080
4	0.109
6	0.160
8	0.191
10	0.255
12	0.297

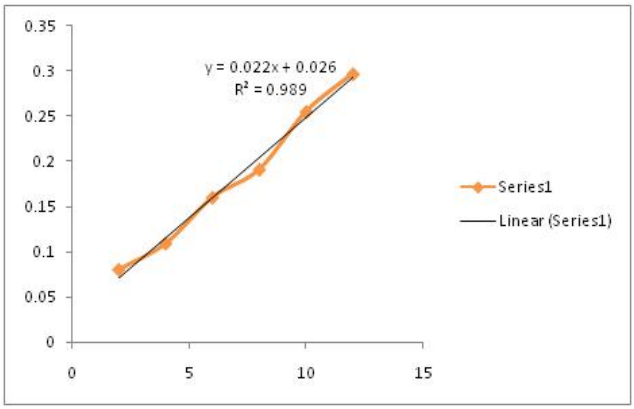

Figure 3

Table 4: *In-vitro* dissolution studies parameters

Parameters	PH Phosphate Buffer
Dissolution apparatus	USP type II (paddle method)
Volume	900 Ml
Rotation for minute (rpm)	50 rpm
Temperature	37±0.5°C
Dissolution medium	6.8 PH Phosphate buffer
Sample volume withdrawn	5 Ml
Time periods	5,15,30,45,60,75 min.
Analytical method	UV-VIS spectrophotometer.
λ_{max}	262 nm

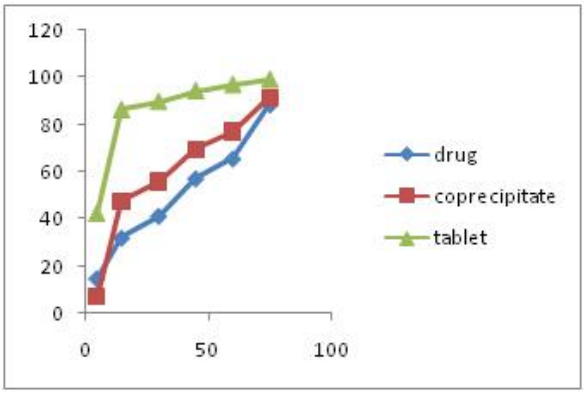

Figure 4: Overall Drug Release Graphical Representation

Discussion

The coprecipitates of iloperidone were prepared by maintaining constant drug concentration and increasing carrier (Captisol) concentrations by liquid antisolvent technique. The aqueous solubility of iloperidone increased from 3.04mcg/ml to 4.234, 4.27mcg/ml .The formulated coprecipitates were compared with tablet and pure drug prepared by liquid anti-solvent technique. The coprecipitates were formed with the carrier Captisol alone. *In vi*tro dissolution rate of drug from coprecipitates and formulated tablet was higher compared to pure iloperidone. The pure drug showed a release of 65.63% at the end of 60 min, while coprecipitates showed 77.22 % drug release in 60 min and Tablet showed 99.35% drug release in 60 min . The dissolution parameters studied indicated increased solubility and dissolution rate of iloperidone in 1:5 ratio of captisol.

4. Conclusion

The solubility and dissolution rate of iloperidone can be enhanced by formulating as coprecipitates using Captisol. The dissolution parameters indicated increased dissolution of iloperidone in coprecipitates when compared with pure drug. The drug release from dosage form i.e. tablet was improvised when compared to pure drug and thus the enhancement of solubility and dissolution rate of iloperidone was achieved with release of 39.58% at 15 minutes and 65% at 1 hour and 47% from coprecipitate at 15 minutes and 77% at 1 hour time and this was drastically improvised to 86.5% and 97.2% in case of tablet. This process can be used in a cost effective manner for improving the solubility and dissolution rate and immediate release formulations.

Table 5: Drug release from pure drug

Time	Absorbance	Dilution factor	Conc. (microgm./ml)	Amount	Cumulative amount	%drug release
5	0.029	1	1.306	1.175	1.175	14.68
15	0.063	1	2.837	2.553	2.559	31.98
30	0.081	1	3.648	3.283	3.303	41.28
45	0.112	1	5.045	4.540	4.578	57.22
60	0.128	1	5.765	5.18	5.25	65.63
75	0.172	1	7.747	6.97	7.08	88.58

Table 6: Drug release profile of Co-precipitates

Time	Absorbance	Dilution factor	Conc. (micro gm/ml)	Amount	Cumulative amount	%drug release
5	0.007	1	0.315	0.283	0.283	7.075
15	0.047	1	2.117	1.905	1.906	47.65
30	0.055	1	2.477	2.229	2.24	56.0
45	0.068	1	3.063	2.756	2.77	69.47
60	0.075	1	3.378	3.040	3.08	77.22
75	0.088	1	3.963	3.560	3.66	91.52

Table 7: Drug release profile of Tablet

Time	Absorbance	Dilution factor	Conc. (micro.gm/ml)	Amount	Cumulative amount	%drug release
5	0.042	1	1.891	1.701	1.701	42.52
15	0.085	1	3.828	3.445	3.46	86.5
30	0.088	1	3.963	3.566	3.6	90.0
45	0.092	1	4.144	3.729	3.78	94.55
60	0.094	1	4.234	3.810	3.88	97.2
75	0.095	1	4.27	3.851	3.97	99.35

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