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DEVELOPMENT OF ORO-DISPERSIBLE TABLETS BASED ON SOLID DISPERSION OF CIPROFLOXACIN

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Abstract

The main objective of this study is to formulate oro dispersible tablets based on solid dispersion of ciprofloxacin. The method used is anti solvent addition method and the green synthesis of solid dispersion is done, thus prepared dosage form is organic solvent free, which is quite safe. Solubility enhancement will be achieved by formulating the drug in the form of solid dispersion and then oro-dispersible tablet provides an added advantage of patient compliance, fast action, increasing bioavailability, reduction in dose and avoiding hepatic metabolism.

1. INTRODUCTION

1.1 SOLID DISPERSION

The term "solid dispersion" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. [(1)]

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid state in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, and enhanced release of drugs from ointment and suppository bases, and improved solubility and stability.[(2)]

The term "solid dispersion" refers to a group of solid products consisting of atleast two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drugs can be dispersed molecularly, either in amorphous particles or crystalline particles.[(3)]

Formulation of water poorly soluble compounds as solid dispersions might lead to particle size reduction, improved wetting, reduced agglomeration, changeability in the physical state of the drug molecules and possibly a dispersion in the molecular level.[(3)]

1.1.1 Types of solid dispersion:

1- Eutectic mixture.
2- Solid solution.
3- Amorphous solid solutions.
4- Glass solutions and glass suspensions. [(2)]

1.1.2 Advantages of solid dispersion:

1- Improve solubility
2- Improve rate of dissolution.
3- Modulates the therapeutic action.
4- Increased bioavailability.
5- Reduced particle size.
6- Improved wettability.
7- Particles with high porosity. [(4)]

1.1.3 Disadvantages of solid dispersion:

Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate. Demerits also include poor scale up for the purposes of manufacturing. [(4)]

1.1.4 Methods of solid dispersion preparation:

1- Kneading method.
2- Solvent melting method.
3- Spray drying method.
4- Supercritical fluid method.
5- Co-precipitation method.
6- Gel entrapment technique.
7- Melting fusion method.
8- Solvent evaporation method.
9- Melt extrusion method.
10- Anti solvent addition method. [(4)]

1.2 ANTI SOLVENT ADDITION

Anti solvent addition, also known as antisolvent precipitation, desolvation, solvent displacement, and solvent shifting and is a method for developing nanoparticles and microparticles.

The basis of this technique involves an organic phase (solvent mix) being added into the aqueous phase. The solvent phase tends to have an effect of diffusion, while the polymer automatically tends to collapse forming nanoparticles or microparticles that can encapsulate an active ingredient that is contained in the organic phase.

This technique has several advantages compared with other methods, among which stand out the facility to develop nanoparticles in one step, not much expense is involved, low electric power is required, and it is fast. On the other hand, emulsion diffusion methods, emulsion evaporation, and precipitation by salting-out need a precursor emulsion; while anti solvent addition does not. The anti solvent addition technique can also usually produce nanoparticles in the range of 50 to300 nm, which is an advantage because the smaller particle size generates greater contact area.

Furthermore, this method should not use an excessive amount or prominent stirring, involve high temperatures, and not to create oil-water interfaces.

It creates an organic phase and an aqueous phase. The organic phase contains a solvent that must be miscible or partially miscible in the aqueous phase; the polymer (synthetic or natural), which will be used to create the polymer matrix of the nanoparticles, must be soluble in the solvent and therefore insoluble in the aqueous phase. The active ingredient used must be soluble in the solvent, and it must have some interaction with the polymeric matrix to be formed, and the aqueous phase will be constituted solely of water and a surfactant (stabilizer). During the process, an organic phase is added dropwise to the aqueous phase under moderate magnetic stirring. [5]

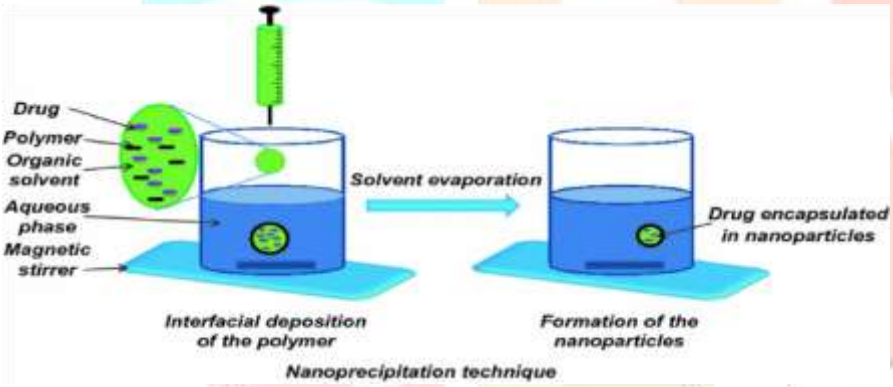

Figure 1- Anti solvent addition method

. MATERIALS AND METHODS

Table 1- Chemicals used in experiment

CHEMICAL NAME
SODIUM HYDROXIDE
HYDROCHLORIC ACID
EUDRAGIT S 100
CIPROFLOXACIN
METHANOL
WATER
PHOSPHORIC ACID
POTTASIUM DIHYDROGEN PHOSPHATE

5.3 METHODS

• **Preformulation study**

A- Solubility study by Shake flask method.

This study is done by using UV spectrophotometric analysis. Excess of pure drug (100 mg) is dissolved in 0.5 ml of 0.1 N NAOH and 6.8 PBS in eppendorf tubes. Now placed both the eppendorf tubes in shaker incubator for 30 min. Centrifuged the tubes at 10000 rpm in research centrifuge for 10 min and took 0.1 ml supernatant, diluted it up to suitable volume and took absorbance in UV spectrophotometer. Calculated the solubility by using caliberation curve.

B- Determination of melting point.

The melting point is a parameter to judge the purity of crude drugs. In this case of pure chemicals or photochemical, melting point is very sharp and constant. Since the crude drugs contain the mixed chemicals, they are description with certain range of melting point. A small quantity of Ciprofloxacin powder was placed in a capillary tube. The tube is placed in the melting point (VEGUS) apparatus. The temperature in apparatus was increased automatically and noted the temperature at which powder started to melt.

• SYNTHESIS OF CIPROFLOXACIN SOLID DISPERSION

The method used in synthesis is **ANTI SOLVENT ADDITION method.**

Table 2 _ F ormula for anti solvent addition method

C hemical	Quantity
0.1 N HCL	12 ml
0.1 N NAOH	3 ml
EUDRAGIT S 100	110 mg
CIPROFLOXACIN	55 mg

Procedure:-

1- Dissolve 110mg of Eudragit S 100 polymer and 55 mg Ciprofloxacin in 0.1N NAOH by stirring at low speed.
2- Then, add this above polymer solution in 12 ml of 0.1N HCL dropwise while stirring. A turbid solution is formed.
3- The above solution is centrifuged at a specific speed.
4- Pellet is formed at the base and supernatant is discarded.
5- Washed the pellet 3 times by suitable solvent to remove unwanted residual solvent.
6- Collected the pellet.
7- Dried it in oven at appropriate temperature.
8- Crushed and powdered by mortar pestle.
Collected the powder.

• **Determination of Percentage % Yield :**

The percentage yield of all of the solid dispersion was determined by calculating the initial

Weight of the solid raw materials and the final weight of the obtained solid dispersion then Calculated according to the equation below: [30]

Practical weight

Percentage yield = ---------- X 100 Theoretical weight (polymer + drug)

• Entrapment efficiency

The encapsulation efficiency (EE %) is defined by the concentration of the incorporated material (such as active ingredients) detected in the formulation over the initial concentration used to make the formulation. [30]

Encapsulation efficiency (EE %) was calculated using below formula:

EE %= entrapped drug/ total drug taken * 100

Procedure

- Firstly, injected the solid dispersion sample in HPLC, then peak area is taken.
- Put the value in calibration curve.
- Calculated the entrapped drug.
- Put the values in formula above.

• Drug content

Drug content is determined by finding out the amount of entrapped drug in the formulation and dividing it by the total amount of formulation. [30]

Formula:-

Practical amount/ total amount * 100

• Solubility enhancement determination by Shake Flask Method

- Took excess of ciprofloxacin drug in 1 ml of solvent in eppendorf tubes.
- Place the tube in shaker incubator for 30 min.
- Centrifuged the tube in research centrifuge for 10 min at 10000 rpm.
- Collected 0.1 ml supernatant and make up to 10 ml by solvent.
- Did the further dilutions if necessary. 6. Injected and observed peak in HPLC.
- Put the values in calibration curve and calculated the solubility.

8. Formula-1

V_1/ standard 1 * 100, where V_1 = pure drug peak in 6.8 PBS.

Standard 1 = pure drug standard peak in 0.1 N HCL.

9. Forumla-2

V_2/ standard 2 * 100, where V_2 = sample peak in 6.8 PBS.

Standard 2= sample peak in 0.1 N HCL.

Powder preformulation studies

1. Bulk density

The **bulk density** of a material is the ratio of the mass to the volume (including the interparticulate void volume) of an untapped powder sample. A quantity of 2 gm of powder blend was introduced in to 10 ml measuring cylinder. After that the initial volume was noted.

Bulk density = weight of powder / bulk volume

2. Tapped density

The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change is observed. In this method powder is filled in measuring cylinder. After that it is mechanically tapped on device. After 500 taps the volume is measured. [27]

Tapped density = weight of powder / tapped volume

3. Compressibility index

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Tapped (td) and apparent bulk density (bd) measurements can be used to estimate the compressibility of a material. [28]

4. Hausner's ratio:-

It is the ratio of bulk volume to tapped volume or tapped density to bulk density. [28]

Hausner ratio = td / bd

5. Carr's index (%)

Formula = [(tapped density-bulk density) x100] / tapped density [28]

6. Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder surface. The diameter of the powder cone was measured and angle of repose was calculated. [28]

Tan □ = h/r

θ = angle of repose,

1. **h = height of the powder cone, r = radius of the powder cone Caliberation curve of Ciprofloxacin in 0.1 N HCL by UV Spectrophotometry**

Table 7- Caliberation curve table

S.no.	Concentration (microgram/ml)	Absorbance
1	2	0.055
2	4	0.091
3	6	0.122
4	8	0.166
5	10	0.200
6	12	0.240
7	14	0.281

EQUATION: - $y = mx + c$

$y = 0.0188x + 0.0144$

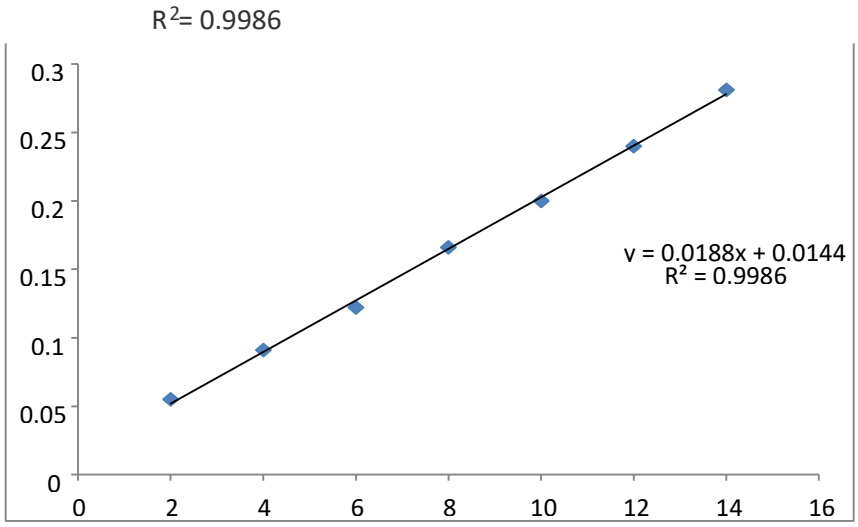

Figure 4 Caliberation curve by Uv-Vis spectroscopy

2. **Solubility study by UV spectroscopy: -**

After taking absorbance of sample in UV spectrophotometer, solubility is calculated by putting value of absorbance in caliberation curve.

Table 8- Solubility study result

SOLVENT	**SOLUBILITY**
In 0.1 N NAOH	**9.89 mg/ml.**
In 6.8 PBS	**5.30 mg/ml.**

3. **Melting point determination**

Table 9- Melting point result

Reported melting point of Ciprofloxacin	**253-225°C**
Practically obtained melting point of Ciprofloxacin	**251°C**

4. **% Entrapment efficiency: -**

Theoretical drug weight (amount) = 1.66mg in 10 mg of powdered formulation.

Practical weight (amount) = 0.853mg in 10 mg of powdered formulation.

Thus, % entrapment efficiency is,

% EE = practical amount / theoretical amount * 100

% EE = 0.853 mg/ 1.66 mg* 100 **% EE = 51.43%.**

7. % Drug content: -

%Drug content: -Practical amount/ theoretical amount of formulation taken * 100

%Drug content: - 0.853mg / 10 mg * 100

%Drug content: - 8.5 %

8. % Yield: -

According to formula of anti solvent addition method, polymer used in this method is 55 mg and drug used is 10 mg. Thus total theoretical yield is 65 mg.

After preparation, the practical field found to be: - 35 mg.

Thus,

% Yield = practical yield / theoretical yield * 100

% Yield = 35 mg / 65 mg * 100

% Yield = 53.84 %

9. Solubility enhancement determination by Shake flask method

- Pure drug (2 mcg/ml) peak in 0.1 N HCL - 1905(drug standard 1 in 0.1 N HCL)
- Sample (2 mcg/ml) peak in 0.1 N HCL - 1090 (V_1)
- Pure drug (2 mcg/ml) peak in 6.8 PBS - 1143(drug standard 2 in 6.8 PBS)
- Sample (2mcg/ml) peak in 6.8 PBS - 1012 (V_2)

The main motive of this study is to check the enhancement in solubility of Ciprofloxacin in less soluble solvent i.e. PBS 6.8. By these results, we can predict that in PBS 6.8, the peak of pure drug is less as compared to solid dispersion sample peak in PBS 6.8. This states that, the prepared solid dispersion enhanced the solubility of ciprofloxacin.

10. Solubility studies enhancement determination result

1. Formula-1

V_1/ standard 1 * 100,

Where, V_1 = pure drug peak in 6.8 PBS.

Standard 1 = pure drug standard in 0.1 N HCL.

= 1143/ 1905 * 100 = **60%**

2. Forumla-2

V_2/ standard 2 * 100,

Where, V_2 = sample peak in 6.8 PBS.

Standard 2= sample peak in 0.1 N HCL.

= 1012/ 1090 * 100 = **92.844%.**

The results stated that the solubility of pure Ciprofloxacin in 6.8 PBS **(60 %)** is less as compared to solubility of solid dispersion containing drug **(92.844 %)**. thus, it is evident that after the incorporation of drug into solid dispersion, **the solubility is enhanced 1.54 times.**

11. Preformulation study

Table 11- Powder preformulation study data

Parameters	Range	Remarks
Bulk density	0.4±0.015	**Within limits**
Tapped density	0.63±0.017	**Within limits**
Carr's index	19.20	**Fair**
Hausner ratio	1.45	**Fair**
Angle of repose	28.43 ±1.21	**Good flow**
Compressibility index	19± 1	**Fair**

Result for post compression parameter

Parameters	Range	Remarks
Friability (%)	0.10 ± 0.03	Within limits
Hardness(kg/cm^2)	2.7 – 2.9	Sufficient hard
Thickness (mm)	2±4	
Wetting time (sec)	27 ± 1	Acceptable
Dispersion Time (sec)	31 ± 2	Acceptable

Table 12- Post compression study data

7. CONCLUSION

ODT concept evolved to overcome some of the problems that existed in conventional solid dosage form i.e. difficulty in swallowing of tablet in pediatric and geriatric patients who constitute a large proportion of world's population. ODT may lead to improve efficacy, bioavailability, rapid onset of action, better patient compliance due to its quick absorption from mouth to GIT as the saliva passes.

In future ODT may be most acceptable and prescribed dosage form due to its fast action (within minute). Because of increased patient demand, popularity of these dosage forms will surely expand in future.

Ciprofloxacin, an antiulcer and an antacid agent, is selected in this study because its dose is very high and the main route of administration is by oral route. The preformulation studies of the given drug are performed like melting point determination, solubility studies etc.

There is bioavailability problem associated with oral drug delivery and also the drawbacks of high dosing of drugs, which leads to toxicity. Thus, an attempt is made in this work to decrease the dose of ciprofloxacin by enhancing solubility by formulating the solid dispersion using Anti solvent addition method. Anti solvent addition method is a fast method to prepare solid dispersion of desired size range, and another advantage is the low cost during preparation.

There are many harmful health effects of using organic solvents in pharmaceutical preparations. So, in this work, we tried to develop the solid dispersion without using any organic solvent i.e. Green synthesis is done, which successfully prepared the desired formulation.

After the preparation of solid dispersion, determination of solubility enhancement is performed by HPLC analysis. It was found that the solubility of the drug in pH 6.8 PBS is enhanced as compared to pure drug solubility in 6.8 PBS.

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