The present study is aimed to formulate and evaluate various formulations to enhance the solubility of poorly aqueous soluble drug Clopidogrel. For this we have selected different techniques like solid dispersion, Nanosuspension and cyclodextrin complexes. As a part of it we prepared solid dispersions of drug employing PVPK30 and PEG 4000. Beta cyclodextrin complexes are prepared by various solubility enhancement techniques such as liquisolid, in which drug is in the solution state or the dissolved drug is absorbed over the insoluble carriers. To improve the wettability and solubility of the poorly soluble drugs methods such as Micronization, Nanonization, complex formation, permeation enhancer and solid dispersion can be utilized to improve the bioavailability of the poorly water soluble drugs. Oral route of drug administration is said to be most convenient and easy way of administration. For many drugs it is problematic to deliver the drug through oral route, because of many reasons due to limited drug absorption because of poor bioavailability and ultimately upon the drug solubility. So solubility is an important parameter to achieve the desired concentration of drug in systemic circulation for the pharmacological response.

**INTRODUCTION**

The aim of this study is to formulate and evaluate the Comparison of different solubility enhancement techniques for Clopidogrel.

Clopidogrel is an anti-platelet drug, used to reduce the risk of myocardial infarction, peripheral vascular disease and stroke, it belongs to class Thienopyridine. Clopidogrel is a prodrug; it should be activated for the pharmacological action. So, it is metabolized to active form by carboxylesterase-1 and the active form is the platelet inhibitor, which binds to P2Y12 adenosine diphosphate receptor of the platelets and it results in reduced ADP-Mediated activation of the glycoprotein IIb/IIa complex. Due to poor solubility and high permeability of the drug clopidogrel, it belongs to BCS Class II, so we need to improve the solubility and bioavailability of poorly soluble drug clopidogrel by various solubility enhancement techniques such as solid dispersions, Nanosuspensions, Complex formations and Microspheres etc. Solubility is a physiochemical factor affecting the drug absorption and therapeutic effectiveness. So based on the solubility parameter the formulation development would lead to failure if it’s poorly aqueous soluble. The low dissolution rate and low aqueous solubility of drug in the aqueous GI fluids leads to inadequate bioavailability. Several methods have been introduced to overcome the problem. For the enhancement of solubility and dissolution rate of the poorly soluble drugs, various commercial methods are available such as liquisolid, in which drug is in the solution state or the dissolved drug is absorbed over the insoluble carriers. To improve the wettability and solubility of the poorly soluble drugs methods such as Micronization, Nanonization, complex formation, permeation enhancer and solid dispersion can be utilized to improve the bioavailability of the poorly water soluble drugs. Oral route of drug administration is said to be most convenient and easy way of administration. For many drugs it is problematic to deliver the drug through oral route, because of many reasons due to limited drug absorption because of poor bioavailability and ultimately upon the drug solubility. So solubility is an important parameter to achieve the desired concentration of drug in systemic circulation for the pharmacological response.

**MATERIALS AND METHODOLOGY**

**Materials**

The following materials were used: Clopidogrel – API (Aurobindo Pharma LTD), PVPk30, PVA, PEG4000, acetone, methanol, β-Cyclodextrin (Evonik), Poloxamer (BASF),

**METHODS**

**Formulation of solid dispersion by solvent evaporation method**

Clopidogrel, PVP and PEG 4000 were made in different ratios of drug and polymer. Clopidogrel was taken in a china dish and methanol was added to it, when the drug is completely dissolved, the polymer is added to the drug solution. Then the solution was triturated or stirred till the entire solvent is evaporated. Then the drug powder was sieved through 60mesh sieve.

**Formulation of Cyclodextrin complexes by solvent evaporation method**

Complex forming agents are prepared by different ratios using β-cyclodextrin as complexing agent. Clopidogrel was taken in a china dish and methanol was added to it, when...
the drug is completely dissolved, β-CD is added to the drug solution. Then the solution was triturated or stirred till the entire solvent is evaporated. Then the drug powder was sieved through 60mesh sieve and sample was analyzed by UV apparatus.

Formulation β-CD complexes by Kneading method
Complex forming agents are prepared by different ratios using β-cyclodextrin as complexing agent. In this method the drug and β-CD are dissolved with little amount of methanol till form into a paste. The kneaded mass is then triturated and sieved9,10.

Formulation of Nanosuspension
Nanosuspensions are prepared by anti-solvent precipitation method. The drug was dissolved in methanol to form organic solution. The stabilizers (PVP, PVA and Poloxamer) were separately dissolved in distilled water to form aqueous solution. After that organic solution containing drug added by means of syringe drop by drop to the aqueous solution with stirring for about 2hours maintained at temperature of 30-40°C to get aqueous suspension10.

Evaluations of Solid Dispersions, Nano Suspensions and β-Cyclodextrin Complexes

Drug content
10mg product was taken to this 10 ml of methanol was added. The dispersion was stirred thoroughly. Then the dispersion was filtered through whatman filter paper, the clear filtrate is further diluted and concentration of drug was measured U.V spectrophotometrically11-13.

In vitro Drug Release Studies
The in vitro drug release of clopidogrel formulations was determined by dissolution apparatus using USP II. Accurately weighed clopidogrel formulations of 100mg equivalent weight particles are placed in capsules and kept in 900ml buffer in each basket and rpm is set to 50. The dissolution studies were carried out by withdrawing 5ml of sample at equal intervals of time intervals of time and maintain sink conditions with equal volume of buffer. The samples were analyzed by UV apparatus. Whereas for Nanosuspensions the drug equivalent to 1ml was taken into the dialysis bag and sealed. This sealed dialysis bag was then suspended into the dissolution basket containing 900ml of phosphate buffer solution of 0.1NHCL the temperature of 37± 2°C, and stirred at a constant speed of 100rpm. Aliquots were collected at each hour upto6 hours and the same was replaced with the fresh buffer. The drug content was determined spectrophotometrically by measuring the absorbance at 210nm using the same buffer solution as the blank14-17.

RESULTS AND DISCUSSION
Characterization and Evaluations of Different Solubility Enhancement Techniques

Table 1: Solid dispersion by Solvent Evaporation method by using PVP k30and PEG4000 as carriers

| Formulation code | Drug:polymer ratio | Drug (clopidogrel) in mg | Polymer in mg |
|------------------|--------------------|-------------------------|--------------|
| K1               | 1:1                | 100                     | 100          |
| K2               | 1:2                | 100                     | 200          |
| K3               | 1:3                | 100                     | 300          |
| K4               | 2:1                | 200                     | 100          |
| K5               | 3:1                | 300                     | 100          |
| P1               | 1:1                | 100                     | 100          |
| P2               | 1:2                | 100                     | 200          |
| P3               | 1:3                | 100                     | 300          |
| P4               | 1:4                | 100                     | 400          |
| P5               | 1:5                | 100                     | 500          |
| P6               | 2:1                | 100                     | 100          |

Table 1.1: Percentage of Drug content for Solid Dispersion

| Formulation code | K1 | K2 | K3 | K4 | K5 | P1 | P2 | P3 | P4 | P5 | P6 |
|------------------|----|----|----|----|----|----|----|----|----|----|----|
| %DC              | 48 | 59 | 65 | 56 | 53 | 51 | 59 | 67 | 70 | 82 | 60 |

Table 2: β-CD by Solvent Evaporation method and kneading method

| Formulation code | Drug : polymer ratio | Drug (clopidogrel) in mg | β-CD in mg |
|------------------|----------------------|--------------------------|------------|
| C1               | 1:1                  | 100                      | 100        |
| C2               | 1:2                  | 100                      | 200        |
| C3               | 1:3                  | 100                      | 300        |
| C4               | 1:4                  | 100                      | 400        |
| C5               | 2:1                  | 200                      | 100        |
| Ck1              | 1:1                  | 100                      | 100        |
| Ck2              | 1:2                  | 100                      | 200        |
| Ck3              | 1:3                  | 100                      | 300        |
| Ck4              | 1:4                  | 100                      | 400        |
| Ck5              | 2:1                  | 200                      | 100        |
Table 2.1: Percentage of Drug content for β-CD

| Formulation code | C1  | C2  | C3  | C4  | C5  | Ck1 | Ck2 | Ck3 | Ck4 | Ck5 |
|------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| %DC              | 82  | 88  | 94  | 99  | 78  | 83  | 89  | 97  | 98  | 80  |

Table 3: Nanosuspension by Polymer precipitation method

| Formulation code | Drug : polymer ratio | Drug (clopidogrel) in mg | β-CD in mg |
|------------------|----------------------|-------------------------|------------|
| N1               | 1:1                  | 100                     | 100        |
| N2               | 1:2                  | 100                     | 200        |
| N3               | 1:3                  | 100                     | 300        |
| N4               | 2:1                  | 200                     | 100        |

Table 3.1: Percentage of Drug content for Nanosuspension

| Formulation code | N1  | N2  | N3  | N4  |
|------------------|-----|-----|-----|-----|
| %DC              | 71  | 76  | 80  | 68  |

Drug Content: The percentage of Drug Content of each of the formulations is given in the table. It can be seen that percentage of drug content was found to be in the range of 48 to 99% of drug content, from all the formulations, it shows that, higher ratios of all formulations gave good %DC.

In vitro drug release studies

Figure 1: %Drug Release for solid dispersion with PVP k30

Figure 2: %Drug Release for solid dispersion with PEG 4000

Figure 3: % Drug release for β-Cyclodextrin by solvent evaporation method

Figure 4: % Drug release for β-Cyclodextrin by kneading method
Nanosuspensions the %DR was found to be 67 to 99% within 60 mins, drug content was found to be 71 to 80%. All of these techniques are said to be the promising techniques which enhances the dissolution rate of the drug so all these techniques can be easily employed for poorly soluble drugs to enhance the solubility of the drug.

CONCLUSION
Various techniques like solid dispersion, cyclodextrins and Nanosuspension were tried to enhance the solubility of clopidogrel. All the techniques employed in the present study were promising to enhance the solubility of the drug, when compared to all techniques employed in the present study β-Cyclodextrin technique is showing the better results that is 100% drug release within 15 mins.

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