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# IMMEDIATE RELEASE CAPSULES OF IRBESARTAN BY USING SOLVENT DEPOSITION TECHNIQUE

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## ABSTRACT

Irbesartan is a non peptide specific competitive antagonist of the angiotensin II receptor (AT1 subtype) used orally for treatment of hypertension. The first approved indication for irbesartan is hypertension. Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water. The drug exhibits low bioavailability related to its poor water solubility. Irbesartan is a class II compound, i.e., water-insoluble, lipophilic, and highly permeable according to Biopharmaceutical Classification System (BCS). The purpose of this study was to prepare and characterize solvent depositions of the irbesartan with carrier to improving its dissolution properties. The formulations were prepared by co-grinding and solvent deposition technique. Evaluation of the formulations was performed using dissolution studies, the results obtained showed that the rate of dissolution of irbesartan was considerably improved when formulated in solvent depositions as compare to pure drug.

**Key words**: irbesartan, solvent depositions, solubility, dissolution enhancement,

## INTRODUCTION:

Some drugs classified as low solubility drugs on the basis of *in vitro* measures of aqueous solubility may have acceptable *in vivo* solubility because of either pH dependence or solubility in GI fluids. If these drugs with acceptable *in vivo* solubility are BCS Class II, they would then be expected to have acceptable oral bioavailability from standard solid oral dosage forms. [1] For BCS Class II drugs that are shown to have low bioavailability owing to their poor solubility and inability to dissolve rapidly, the selection of formulation is often of great importance in developing a successful product for oral administration of Class II drugs. The bioavailability of these drugs can be improved by several formulation approaches.

**Solvent Deposition Technique:**

Reduction of particle size remains the accepted method for increasing dissolution rates. However, upon micronization, hydrophobic drugs have a tendency to clump when exposed to the dissolution medium. [2]

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Sekiguchi and Obi proposed that the incorporation of a microcrystalline or molecular dispersion of a poorly soluble drug in a solid matrix of water-soluble carrier would increase the dissolution rate and absorption of the drug. [3] Since then, modifications of the technique have been suggested under a variety of names, including solid solutions, eutectics, co-precipitates, and fast-release solid dispersions. [4] This new method was investigated for increasing the dissolution rate of drug by depositing drug in "minuscular form" on the surface of an adsorbent. This technique was termed as solvent deposition. The term "minuscular form" implies that the drug has undergone molecular micronization when it is dispersed on the extensive surface of the micro particulate adsorbents. It is an approach used for increasing the dissolution rates of relatively insoluble powders.

**Mechanism of drug release:**

During dissolution, since carriers are insoluble, the minuscular drug system releases only free, absorbable drug into solution. Hydrogen bonding and van der Waals' forces are accounted for desorption of the drug from the adsorbent surface. The minuscular drug delivery system can be regarded as drug in a micro-particulate form molecularly dispersed on the very extensive surface of carrier. The resulting decrease in particle size and the concomitant increase in surface area serve to

increase the thermodynamic activity of the drug in the dispersed state which, in turn, greatly enhances the rate of solution of the drug. [5]

The solvent deposition system is a solid preparation in which a drug is deposited from a solvent on the surface of a matrix. This step is usually done by simple evaporation of the solvent used for distribution of the drug onto the matrix. This is accomplished by equilibration of the drug in an organic solvent on water-insoluble excipients with an extensive surface e.g., fumed silicon dioxide. Till now a wide variety of drugs have been employed in making solvent deposited solid dispersion with different types of water insoluble carriers.

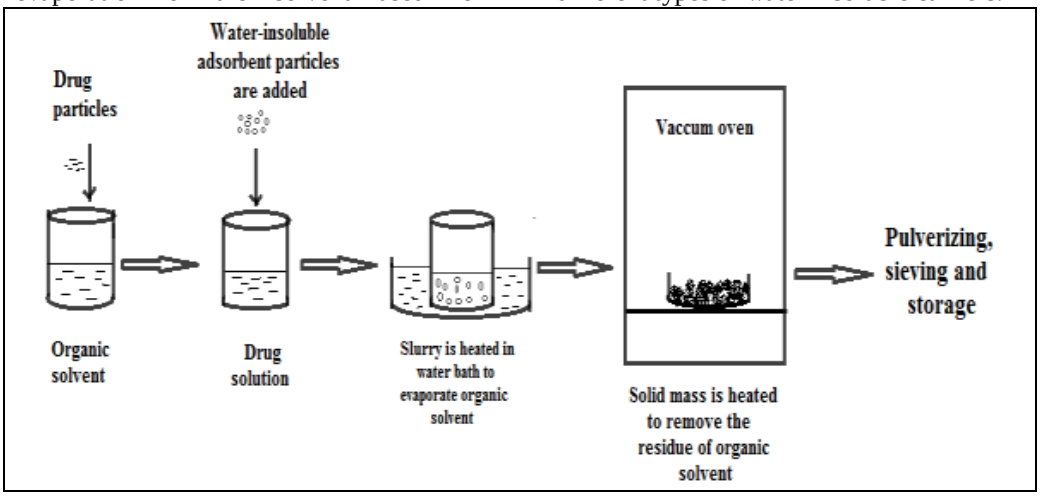



**Fig 1: Schematic diagram of method of preparation**

The drug irbesartan was selected for enhancement of solubility and dissolution rate as it is a poorly water soluble (BCS-II) anti hypertensive drug. One of the major problems in this drug is low solubility in biological fluids, which results into poor bioavailability (26%) after oral administration. Results of literature survey revealed that till date, only 2 techniques have been employed, to improve solubility and dissolution rate of irbesartan, one study reported, an improvement of solubility by complexation with Beta Cyclodextrin's & compared the effect of various complexation methods (co-grinding, kneading, co-evaporation) on drug dissolution profiles. In another study an improved dissolution of a poorly water soluble drug in solid dispersions with carriers like urea, mannitol, PVP, tartaric acid by using quench cooling technique. These solid dispersions of IRB showed an improvement in solubility and dissolution rates. [6, 7] The aim of the present study was to in order to achieve increased dissolution rates. Therefore, in the present study, solvent depositions of irbesartan were prepared by solvent evaporation technique using acetone as solvent for dissolving the drug. Acetone was selected as a solvent of choice since the drug has highest solubility in this solvent and acetone could be easily evaporated and recovered because of its low boiling point. Acetone as per ICH guidelines is categorized under class II solvents thus rendering it to be less toxic than other chlorinated solvents.

## MATERIALS AND METHODS

Irbesartan a gift sample of Hetero drugs, Hyderabad, Acetone (qualigens), Hydrochloric Acid (qualigens), Distilled water. Croscarmellose sodium (CCS) and sodium starch glycolate (SSG) (Qualigens). All other materials used in the study were of analytical or pharmaceutical grade.

**Analytical Methods:**

A number of methods are reported in the literature for the estimation of irbesartan. These methods include spectrophotometrically method derivative spectrophotometry. Spectrophotometric method (US FDA) was used in the present project work for the estimation of irbesartan at 244 nm in 0.1N HCl.

**Preparation of Pure drug Capsules of irbesartan**

50mg of irbesartan was accurately weighed and transferred manually in to hard gelatin capsules. They were coded as gelatin capsules.

**Commercial Tablets of Irbesartan**

Commercial tablets of irbesartan used for comparison. They were purchased from local market.

**Preparation of Solvent Deposited Systems of Irbesartan:**

Required amount of irbesartan was dissolved in 10 ml of acetone. Accurately weighed carrier corresponding to different drug: carrier ratio by weight was dispersed in drug solution. The solvent was allowed to evaporate on water bath under occasional stirring at temperature of 40-42ºC in a protected environmental condition containing an exhaust system. The dried mass was pulverized and was passed through a #100-mesh sieve. The powder was subsequently dried at 40°C for 3 hours in a tray drier. The powder was stored in desiccators for further studies. The dried powder was triturated thoroughly and powder equivalent to 50mg of irbesartan was filled into capsules manually. These capsules were subjected to assay and dissolution studies.

**Preparation of Physical Mixtures**

Physical mixtures (PM) of Irbesartan, CCS and SSG were prepared by geometric dilution method using a mortar and pestle then, powder equivalent to 50mg of irbesartan was filled into capsules manually. These capsules were subjected to assay and dissolution studies. The formulae of the various capsule formulations are given in Table No.1.

**Table 1: Coding Data of Irbesartan Formulations**

| DRUG | CARRIER& METHOD | CODE | RATIO |
|---|---|---|---|
| IRBESARTAN | Nil | A | pure |
| | Cross caramellose sodium<br>Solvent deposition | B<br>C | 1:1<br>1:2 |
| | Sodium starch glycolate<br>Solvent deposition | D<br>E | 1:1<br>1:2 |
| | Cross caramellose sodium<br>Physical mixture | F | 1:1 |
| | Sodium starch glycolate<br>Physical mixture | G | 1:1 |
| | Marketed | H | - |

## CHARACTERIZATION:

**1. Percent yield:**

Percent yield was determined by following formula:

$$Yield = \left(\frac{a}{b+c}\right) \times 100$$

Where, a is the weight of solid dispersion sifted through a # 60 sieve,

b is the weight of irbesartan taken for solid dispersion preparation, and

C is the weight of polymer taken for solid dispersion preparation.

**2. Assay of Capsules**

The contents and the shells of one capsule were taken in a 100 ml volumetric flask, 20 ml ethanol and 20 ml of 0.1N HCL was added and the contents were sonicated for 10 min. Later it was made up to the mark with 0.1N HCL. This solution was filtered and suitably diluted with 0.1N HCL and was assayed at 244nm for irbesartan.

**3. Dissolution Rate Studies**

The dissolution rate testing of different irbesartan capsule formulations was studied using USP XX1 dissolution rate testing apparatus, (basket type) (LAB INDIA DISSO 2000). The basket was rotated at a speed of 50rpm and the dissolution fluid (1000 ml 0.1NHCl) was maintained at a temperature of $37.5^0 \pm 0.5\ ^0C$. At specific time intervals, a 5 ml aliquot of dissolved medium was withdrawn and was replaced with fresh quantity of dissolution medium. The samples were suitably diluted with dissolution medium and assayed for irbesartan content by measuring the absorbance at 244 nm using U.V Spectrophotometer (ELICO SL 159).

**4. Mechanism of drug release:**

Mechanism of drug release was obtained by applying the release data to various models like zero order, first order, Higuchi.

**Table 2: Mechanism of drug release**

| MODEL | EQUATION | PLOT OF GRAPH | PARAMETER |
|---|---|---|---|
| Zero order | F= Ko t | % drug release Vs time | Ko- release rate constant |
| First order | Log (100-F)=Kt | log % drug remaining Vs time | K- release rate constant |
| Higuchi release | F= $K_1$ t1/2 | % drug release Vs square root of time | K1- release rate constant |

## RESULTS AND DISCUSSION

**Percentage yield:**

Percentage yield was calculated according to the formula and results are given in Table 3

**2. *In vitro* dissolution studies:**

Dissolution data of solvent depositions on excipients were reported in Fig 2, all the prepared surface solid dispersion showed an enhancement in the dissolution rate of the drug compared to plain drug. Solvent depositions prepared by using sodium starch glycolate showed enhanced dissolution rate when compared to other carriers. Solvent depositions of irbesartan were prepared with various carrier concentrations and the effect of increasing carrier concentration on dissolution rate was determined.

**3. Mechanism of drug release:**

To determine the kinetics of release, the drug release data was treated and rate constants for zero order, first order and Higuchi model was obtained and reported in Table 5. The release of drug from solvent depositions followed first order kinetics as seen from R2 value.

**Table 3: % Yield & Assay of various formulations of irbesartan solvent depositions**

| CODE | D:C RATIO | % YIELD | ASSAY |
|---|---|---|---|
| B | 1:1 | 94.25 | 97.89±0.5 |
| C | 1:2 | 97.65 | 98.25±0.2 |
| D | 1:1 | 91.58 | 95.88±0.6 |
| E | 1:2 | 93.55 | 97.54±0.5 |
| F | 1:1 | 95.64 | 96.99±0.4 |
| G | 1:1 | 96.57 | 98.62±0.8 |

**Table 4: Comparison studies of Dissolution profiles of formulations in 0.1 N HCL (n=3)**

| CODE | D:C RATIO | T5 | T20 | T30 | T45 | T60 | T90 |
|---|---|---|---|---|---|---|---|
| A | PURE | 4.52 | 10.21 | 14.62 | 19.95 | 25.82 | 32.22 |
| B | 1:1 | 10.22 | 16.46 | 25.29 | 32.54 | 45.95 | 65.89 |
| C | 1:2 | 25.21 | 35.48 | 45.21 | 58.55 | 62.84 | 82.78 |
| D | 1:1 | 19.87 | 42.22 | 54.35 | 69.86 | 72.54 | 89.95 |
| E | 1:2 | 29.89 | 52.62 | 65.98 | 74.86 | 84.52 | 92.54 |
| F | 1:1 | 7.52 | 14.56 | 26.31 | 31.57 | 39.78 | 52.55 |
| G | 1:1 | 12.24 | 38.47 | 41.53 | 52.21 | 59.67 | 75.68 |
| H | MARKETED | 10.58 | 24.85 | 36.86 | 54.22 | 65.14 | 79.96 |

**Fig 2: Dissolution profiles of different formulation in 0.1 N HCL**

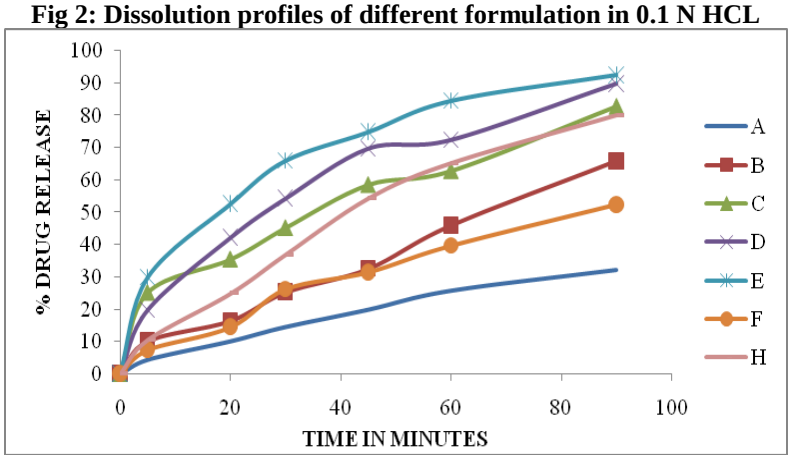



**Fig 3: Formulation E Zero Order Plot**

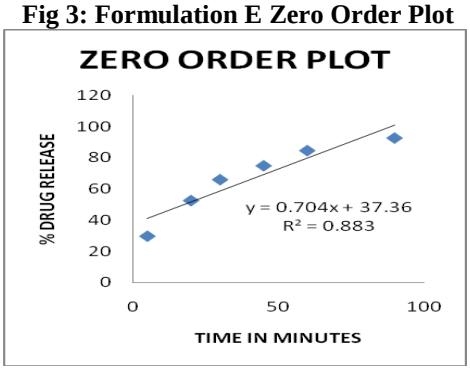



**Fig 4: Formulation E First Order Plot**

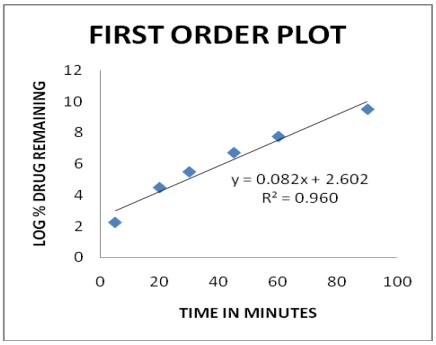
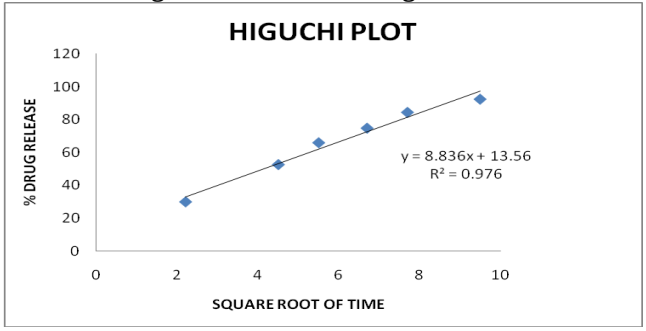



**Fig 5: Formulation E Higuchi Plot**



| CODE | PARAMETER | ZERO ORDER | FIRST ORDER | HIGUCHI |
|---|---|---|---|---|
| E | K | 0.704 | -0.082 | 8.836 |
| | $r^2$ | 0.883 | 0.960 | 0.976 |

## CONCLUSION:

The solubility and dissolution profile of Irbesartan which is a poorly water soluble drug was significantly improved by preparing solvent depositions by using Croscarmellose sodium and sodium starch glycolate as carriers. Compatibility studies revealed that there is no interaction between the drug and carrier. The mode of drug release is following first order kinetics, the release of drug is expected as erosion of polymer from the solid dispersions.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