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# SOLUBILITY ENHANCEMENT OF AMISULPRIDE BY SOLID DISPERSION TECHNIQUE AND PREPARATION OF FAST DISSOLVING TABLETS

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ABSTRACT

Amisulpride exhibits anti-psychotic activities by selectively binding to dopamine D(2) and D(3) receptors in the limbic system. It is used in the treatment of psychoses, paranoid, productive schizophrenias, dysthymia. However, amisulpride (AMP) is poorly water soluble drug, so solubility is the main constraint for oral bioavailability. An attempt has been made to increase the solubility of this drug by formulating solid dispersion (SD) by using β-cyclodextrin (β-CD) employing spray drying method and then formulating fast dissolving tablets(FDT). Among the two different formulation of SD, formulation SD2 containing amisulpride & β-CD in the ratio of 1:2 gives best drug content and dissolution profile and among tablet formulations. FDTs were prepared by direct compression technique using superdisintegrants such as croscarmellose sodium and sodium starch glycolate in different concentrations. SDs were characterized by FT-IR, DSC analysis and evaluated for drug content and *in vitro* dissolution profiles. Tablet formulations were evaluated for pre compressional parameters such as angle of repose, bulk & tap density, Carr's index, Hausner's ratio and post compression parameters such as hardness, friability, weight variations, drug content, wetting time, disintegration time and *in vitro* dissolution profile. Formulation CF2 containing 6.5% croscarmellose sodium gives best disintegration and dissolution profile compared with other formulations. Results showed that β-cyclodextrin is a promising polymer for enhancing the solubility of AMP

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# INTRODUCTION:

Amisulpride a second generation antipsychotic drug used in the treatment of psychoses, paranoid, productive schizophrenias, dysthymia. In humans, AMP rapidly absorbed and showed a biphasic absorption profile, with a first peak plasma concentration at about1.5 h, and a second peak observed between 3 h and 4 h. Its apparent elimination half-life is between 15 h and 20 h. The absolute bioavailability of the 50 mg tablet is48-51%, with little binding to plasma proteins (17%).AMP is mainly excreted unchanged in urine.[1]The property of practical insolubility in water and poor dissolution profile of this molecule, delays its rate of absorption and finally the onset of action. Further it exhibits very bitter taste.[2]

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging task of drug development. Several techniques such as salt formation, solubilization and particle size reduction have been commonly employed to increase dissolution rate. Moreover these techniques suffer with practical limitations. On the other hand, many reports promised that the bioavailability enhancement of poorly water-soluble drugs can be done successfully in the form of solid dispersion.[3, 4]

The taste masking and improving the rate of dissolution become important considerations. Hence, the solid dosage form which can be administered or swallowed where the bitter taste of drug is masked and would be an ideal dosage form. One such approach is fast mouth dissolving tablet. Fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems which aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance.[5]It is difficult for many patients to swallow tablets and gelatin capsules. Hence they do not comply with prescription which results in non-compliance and ineffective therapy.[6] In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult particularly the difficulty is experienced by pediatric and geriatric patients.[7] Such problems can be resolved by means of mouth dissolving tablet. When placed on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.[8]

We have prepared the solid dispersions of AMP with β-CD in two different ratios (1:1 and 1:2) using spray dryer. On performance of dissolution studies for two inclusion complexes, 1:2 ratio has emerged with highest dissolution rate. Further, the optimized 1:2 ratio inclusion complex was subjected to fast dissolving tablet formulation and evaluation.

## Materials and Methods:

Amisulpride hydrochloride was obtained as a gift sample from Intas Pharmaceuticals Ltd., Ahmadabad, India. β-cyclodextrin, microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, sodium saccharine, magnesium stearate, and talc were obtained from S.D. Fine Chem. Ltd, Mumbai, India.

## Methods:

## Preparation of Solid dispersion

AMP and water soluble carrier β-CD were weighed accurately in two different ratios (1:1 and 1:2). AMP and β-CD solutions were prepared separately in methanol and water respectively. The resultant solutions were mixed in a beaker to get a clear solution. The obtained clear solution was subjected to spray drying using a laboratory-scale spray dryer (Latutima NU222) under the following set of conditions: inlet temperature $60^0$C; outlet temperature $45^0$C; feed rate - 4 to 6 ml/min; atomization air pressure - 2 Kg/cm$^2$ and aspiration - 2300 mm water column, nozzle size - 0.7 mm. The obtained solid dispersions were passed through sieve no. 85 and stored in desiccators till further use.

## Evaluations of solid dispersions

## Drug content[9]

An accurately weighed quantity of solid dispersion equivalent to 50mg of AMP was dissolved in acetone in100ml volumetric flask and suitably diluted with 1.2 pH acid buffer. The dissolved AMP content was determined spectrophotometrically at 280 nm against 1.2 pH acid buffer as blank using UV-visible spectrophotometer (Shimadzu 1800, Kyoto, Japan).

## *In-vitro*dissolution study[9]

**Table 1: percentage of drug content estimation of AMP solid dispersions**

| Formulation cod e | Drug content |
|---|---|
| SD1 | 99.8±1.17 |
| SD2 | 100.2±1.35 |

**Table 2: *in-vitro* dissolution profile data of AMP in pure form and solid dispersion with β-CD**

| Time (min) | Cumulative % drug released | | |
|---|---|---|---|
| | Drug | SD1I | SD2I |
| 0 | 0 | 0 | 0 |
| 3 | 2.82±0.067 | 63.88±0.117 | 71.88±0.067 |
| 6 | 11.89±0.117 | 73.59±0.118 | 83.13±0.067 |
| 12 | 34.51±0.068 | 87.04±0.118 | 97.07±0.067 |
| 15 | 45.60±0.067 | 86.77±0.118 | 96.82±0.117 |
| 20 | 57.41±0.067 | 91.80±0.068 | 95.62±0.069 |
| 25 | 62.65±0.118 | 93.66±0.117 | 96.77±0.068 |
| 30 | 65.30±0.117 | 94.46±0.068 | 96.64±0.136 |
| 45 | 66.54±0.068 | 95.61±0.067 | 96.14±0.068 |

**Table 3: Composition of fast dissolving tablets of AMP inclusion complex (1:2 molar ratio)**

| Ingredients (mg/tablet) | Formulation code | | | |
|---|---|---|---|---|
| | CF1 | CF2 | CF3 | CF4 |
| Inclusion complex | 150 | 150 | 150 | 150 |
| Ac-Di-Sol | 10 | 20 | - | - |
| Sodium starch glycolate | - | - | 10 | 20 |
| Microcrystalline cellulose | 160 | 150 | 160 | 150 |
| Magnesium stearate | 4 | 4 | 4 | 4 |
| Saccharin sodium | 1 | 1 | 1 | 1 |

The solid dispersion equivalent to 50mg of AMP was filled in colorless hard gelatin capsule manually. The dissolution capsules was conducted using dissolution testing apparatus type-1 basket method (Dissolution tester TDT-08L, Electrolab, India) in 900 ml of hydrochloric acid buffer of pH 1.2 at 37±0.5ºC and at a speed of 50

rpm. Aliquots of 5ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 280 nm against suitable blank using UV-visible spectrophotometer(Shimadzu 1800, Kyoto, Japan).

Results of drug content and *in-vitro* drug dissolution studies revealed that among two ratios (1:1 and 1:2) of solid dispersion, 1:2 was emerged as efficient one for further process for compression of tablets.

## Precompression parameters

**Table 4: Precompression parameters of AMP solid dispersion formulations**

| Formulation code | Bulk density (g/cc) | Tapped density (g/cc) | Angle of repose (υ) | Carr's index (%) | Hausner Ratio |
|---|---|---|---|---|---|
| **CF1** | 0.465±0.006 | 0.540±0.02 | 24.44±0.73 | 13.88 | 1.16 |
| **CF2** | 0..465±0.006 | 0..512±0.03 | 23.50±0.71 | 9.18 | 1.10 |
| **CF3** | 0.455±0.007 | 0.526±0.01 | 25.46±0.68 | 13.50 | 1.15 |
| **CF4** | 0.455±0.006 | 0.512±0.01 | 24.94±0.53 | 11.13 | 1.13 |

## Post compression parameters

**Table 5: Post compression parameters for fast dissolving tablets of AMP solid dispersion formulation**

| Formula-tion code | Wetting time(mm) | Hardness ($Kg/cm^2$) | Friability (%) | Weight variation (mg) | Drug content (%) | Disintega-tion time (sec) |
|---|---|---|---|---|---|---|
| **CF1** | 50±1.17 | 3.7±0.11 | 0.65 | 321.13±0.94 | 99.25±0.67 | 49±1.15 |
| **CF2** | 48±0.15 | 3.8±0.20 | 0.54 | 325.06±0.41 | 99.66±0.33 | 40±0.57 |
| **CF3** | 52±1.09 | 3.7±0.11 | 0.69 | 319.13±0.30 | 99.25±0.33 | 46±0.57 |
| **CF4** | 51±1.07 | 3.6±0.20 | 0.70 | 326.13±0.11 | 97.45±0.89 | 49.3±1.15 |

## Direct compression of inclusion complex

Inclusion complex of AMP: β-CD (1:2 molar ratio) equivalent to 50mg of drug were taken and mixed with directly compressible diluents, super-disintegrants and other excipients in a plastic

container. The powder blends were directly compressed using 10 mm, round-shaped flat punch in eight station tablet compression machine (Ridhi Pharma instrument ltd, Ahmadabad, India).Table 3 presents the composition of tablet formulation.

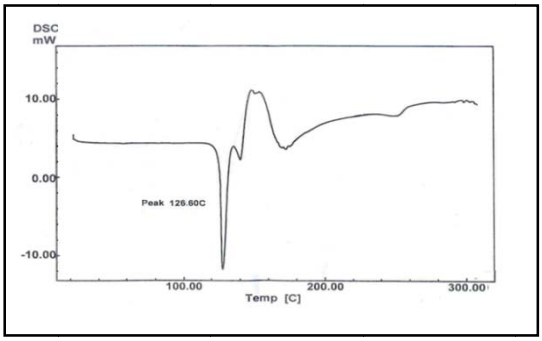


**Figure: 1A.DSC thermogram of pure Amisulpride**.

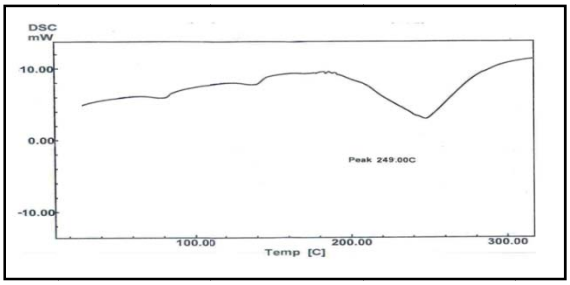


**Figure: 1B.DSC thermogram of pure β-cyclodextrin.**

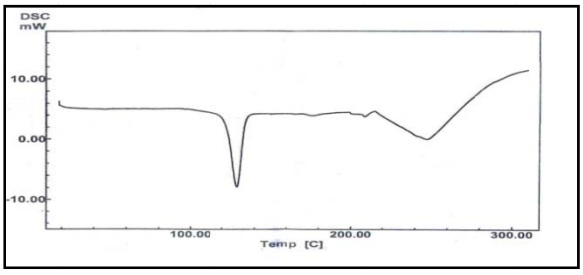


**Figure: 1C. DSC thermogram of solid dispersion of AMP: β-CD (1:2 molar ratio) inclusioncomplex prepared by spray drying method.**

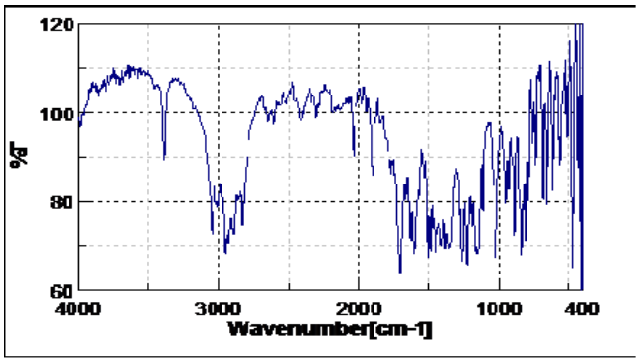


**Figure: 2A.FTIR spectra of pure Amisulpride.**

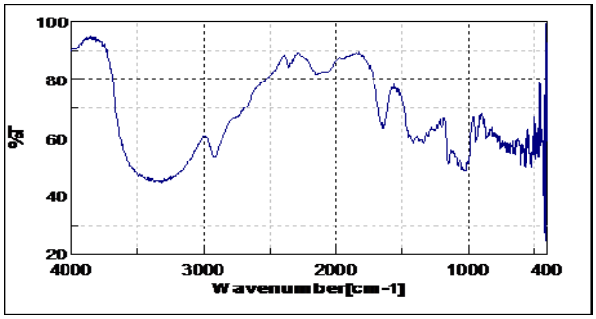


**Figure: 2B.FTIR spectra of β-CD.**

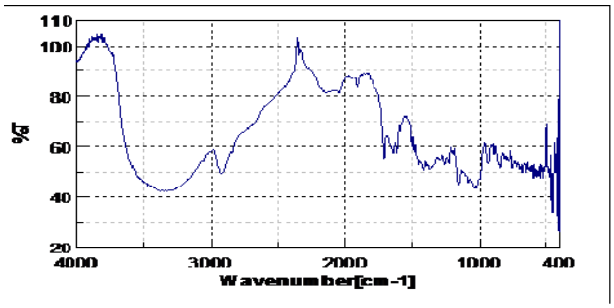


**Figure: 2C. FTIR spectra of solid dispersion of AMP: β-CD (1:2 molar ratio) inclusion complex prepared by spray drying method.**

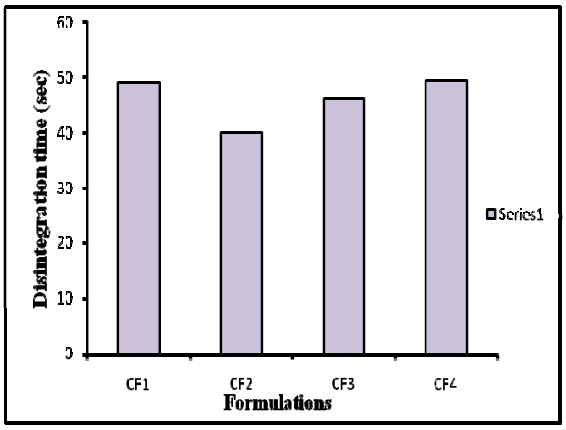


**Figure: 3A.Comparison of disintegration time of fast dissolving tablets of AMP solid dispersion formulations**

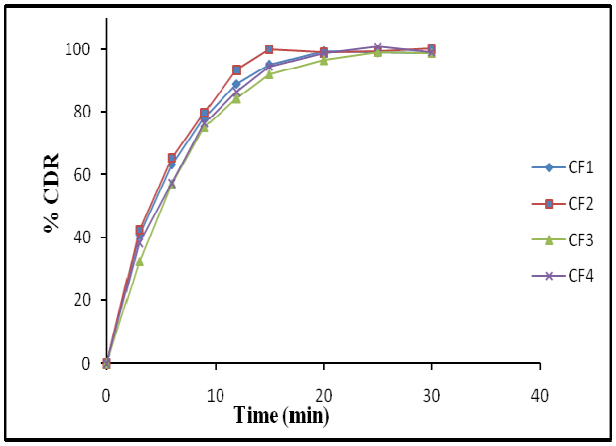


**Figure: 3B.Dissolution profile of CF1, CF2, CF3 and CF4 formulations of fast dissolving tablets of AMP solid dispersion**

## Evaluations of fast dissolving tablets

## Precompressional parameters:

### Angle of repose[10]

It was determined according to the free standing cone funnel method for drug-excipient blend. The accurately weighed blend was allowed to flow through the funnel freely onto the graph paper, until its apex and the funnel tip touches each other, till a maximum heap height h was obtained. The diameter D, of the powder heap was measured and angle of repose was computed using the following equation:

$$\tan \theta = h/r \qquad (1)$$

Where h and r are the height and radius of the powder cone.

### Bulk Density[11]

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined for powder blend individually using Tap Density Tester (Electro lab ETD-1020). A quantity of 50 g of powder from formula, previously gentle shaken to break any lumps formed, was introduced into a 100 ml measuring cylinder. After the initial volume was noted, the cylinder was allowed up and down movement from a height of 2.5 cm at 2-second intervals, until no further change in volume was observed. LBD and TBD were calculated using the following formulae:

LBD = weight of the powder/volume of the packing (2)

TBD = weight of the powder/tapped volume of the packing (3)

### % Compressibility or Carr's index[12]

Based on the poured density and tapped density, the % compressibility of the powder blend was computed using the Carr's compressibility index:

Carr's index (%) = [(TBD – LBD) × 100]/TBD.. (4)

**Table 6: *In vitro* dissolution profile data of CF1, CF2, CF3 and CF4 formulations of fast dissolving tablets of AMP solid dispersion**

| Time (min) | Cumulative % drug released | | | |
|---|---|---|---|---|
| | CF1 | CF2 | CF3 | CF4 |
| 0 | 0 | 0 | 0 | 0 |
| 3 | 40.82±0.31 | 42.47±0.17 | 32.35±0.36 | 38.35±0.24 |
| 6 | 63.33±0.18 | 65.45±0.30 | 57.21±0.18 | 57.33±0.12 |
| 9 | 78.34±0.44 | 79.87±0.24 | 75.15±0.34 | 76.45±0.11 |
| 12 | 89.01±0.24 | 93.45±0.13 | 84.28±0.14 | 86.41±0.07 |
| 15 | 94.94±0.23 | 99.99±0.13 | 91.99±0.23 | 94.49±0.23 |
| 20 | 99.31±0.29 | 99.00±0.67 | 96.46±0.24 | 98.80±0.47 |
| 25 | 98.94±0.24 | 99.27±0.18 | 99.07±0.37 | 100.80±0.11 |
| 30 | 98.80±0.24 | 100.17±0.29 | 98.89±0.23 | 99.15±0.27 |

## STABILITY STUDIES

**Table 7: Stability study data of formulation CF2**

| Time | Hardness ($kg/cm^2$) | Friability (%) | Drug content (%) | Disintega-tion time (Sec) | Cumulative % drug released at the end of 15 min |
|---|---|---|---|---|---|
| Zero month | 3.8±0.20 | 0.54 | 99.66±0.33 | 40±0.57 | 99.99±0.13 |
| First Month | 3.9±0.11 | 0.52 | 98.63±0.67 | 41±1.15 | 99.94±0.52 |
| Second Month | 3.9±0.05 | 0.51 | 98.59±0.29 | 40±0.36 | 99.72±0.26 |

## Hausner ratio[12]

Hausner ratio was calculated using the formula:

Hausner's ratio = TBD/ LBD (5)

## Post compression parameters[13, 14]

## Tablet Hardness

The hardness of ten tablets was found using Monsanto Hardness tester. Mean and standard deviation were computed and reported in $Kg/cm^2$.

## Friability

The friability of the tablets was determined using Roche's friabilator. 10 tablets were initially weighed and transferred into the friabilator. The instrument was operated at 25 rpm for four minutes. After four minutes the tablets were taken out and weighed again. Result is expressed in percentage.

## Weight Variation Test

Twenty tablets were individually weighed using an electronic balance (Shimadzu, AUX-220, Japan) and average weight was calculated. The individual weight of tablets was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit.

## Wetting Time

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 6 ml of water, a tablet was put on the paper and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was determined.

## Disintegration test

The disintegration test was carried out using USP disintegration test apparatus type II (Electrolab ED-22, India). Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed over each tablet. Distilled water was used as the medium maintained at 37°C ±0.5°C and the time taken for each tablet to disintegrate completely was recorded.

## Content Uniformity

Ten tablets were randomly selected and allowed to equilibrate with hydrochloric acid buffer of pH 1.2 overnight in volumetric flask and the solution was filtered (0.22 µ, Millipore) after 24 hours. Suitable dilutions were made with the hydrochloric acid buffer of pH 1.2 to get the concentration in Beer's range. The drug content was analyzed spectrophotometrically at 280nm against suitable blank using UV-visible spectrophotometer (Shimadzu 1800, Kyoto, Japan).

## *In-vitro* dissolution study

Dissolution study was carried out using USP dissolution test apparatus type II (Dissolution tester TDT-08L, Electrolab, India). The hydrochloric acid buffer (900 ml) of pH 1.2 at 37±0.5ºwas used as dissolution medium. The paddle speed was kept at 50 rpm throughout the study. Three tablets were placed in each basket of apparatus. Aliquot of 3 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain the sink condition. The aliquot was suitably diluted with 1.2 pH hydrochloric acid buffer. The amount of drug released was analyzed spectrophotometrically at 280nm against suitable blank using UV-visible spectrophotometer (Shimadzu, 1800, Kyoto, Japan).

# RESULTS

## Characterization of AMP inclusion complexes

## Differential scanning calorimetric analysis

The DSC thermogram of AMP exhibited sharp endothermic peak at 126.60°C (Fig 1A), which corresponds to its melting point. The DSC thermogram of β-CD showed endothermic peak at 249.03° C (Fig 1B) corresponding to its melting point. The peak of drug was absent in AMP:β-CD inclusion complexes (Fig 1C) indicates the complete complex formation.

## Fourier transform infrared spectroscopy

The FTIR spectra of AMP presented in Fig 2A. Important vibrations detected in the spectrum of AMP are -NH stretching lies in 3337 $cm^{-1}$. Other characteristic bands are attributed to the stretching of different group vibration:1628 $cm^{-1}$ stretching of amide carbonyl, 1529 $cm^{-1}$ stretching of the second amide band, 1640 $cm^{-1}$ stretching of primary amide and 1050 $cm^{-1}$ stretching of –SO group. The IR spectra of β-CD showed prominent absorption bands at 2879 $cm^{-1}$ (for C-H stretching vibrations); and 1164 $cm^{-1}$, 1083 $cm^{-1}$(C-H, C-O stretching vibration). The FTIR spectra of inclusion complexes seemed to be only summation of drug and β-CD spectra. This result suggested that there was no chemical interaction between drug and β-CD in their combination.

## Evaluation of fast dissolving tablets

## Pre-compression parameters

Tablets of various formulations were subjected for pre-compression parameters such as angle of repose, bulk density &tap density, Carr's index and Hausner'sratio.The results of pre-compression data were shown in Table 4.

## Angle of repose[10]

The results of angle of repose were found in the range of 23°-26°indicated good flow properties of the powdered blend.

## Bulk density & Tap density[11]

The results of bulk density and tapped density of various formulations were found to be in the range of 0.455±0.007 to 0.465±0.006 (g/cc) and 0.512±0.03 to 0.540±0.02 (g/cc) respectively.

## Carr's Index[12]

Carr's index of the prepared blends fall in the range of 9.18to 13.88%.

## Hausner's ratio[12]

Hausner's ratio of the prepared blends fall in the range of 1.10 to 1.16% which is less than 1.21%.

## Post compression parameters[13, 14]

## Wetting time

Wetting is closely related to inner structure of tablets and the hydrophilicity of excipients. The record of the wetting time was shown in Table 5.The wetting time in all the formulation was very fast found in between 48±0.15 to 52±1.09. This is attributed due to ability of swelling and also capacity of absorption of water by MCC, starch glycolate and croscarmellose sodium. This parameter also duplicates disintegration time in oral cavity as tablet is kept motionless on tongue; hence correlation between wetting time and disintegration time in oral cavity can also be made.

## Hardness test

The values for hardness test have shown in Table 5. The results showed that the hardness of the tablets was in range of 3.6±0.20 to 3.8±0.20 Kg/cm$^2$.

## Weight variation test

The results of weight variation test are presented in the Table 5. The results showed that the weight variation of the tablets was found to be 319.13±0.30 to 326.13±0.11 mg. The results were within specified limit.

## Drug content uniformity

Drug content uniformity study was carried out on the tablets of every batch and the data were shown in the Table 5. The value of content uniformity was found to be 97.45±0.89 % to 99.66±0.33 % which showed that there was uniform distribution of the drug throughout the batch.

## Friability

The data of friability shown in Table 5. The average friability of all the formulations lies in the range of 0.54 % to 0.70 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

## *In-vitro* disintegration time

Tablets of each batch were evaluated for *in vitro* disintegration time and the data's were shown in the Table 5. The results of disintegration time were in the range of 40±0.57 to 49.3±1.15 seconds. The tablets of batch CF2 prepared using 6.5% of Ac-Di-Sol showed faster disintegration time of 40±0.57 seconds. It indicates that amongst the disintegrants used Ac-Di-Sol was better disintegrant it exhibits shortest time for wetting time test with highest values for water uptake study. This is due to the fiber like structure of CCS, act as a hydrophilic microcapillary to impart rapid water uptake into the tablet deeper levels.

## *In- vitro* dissolution studies

Finally, the tablets were evaluated for *in vitro* dissolution studies in simulated gastric fluid and the results were shown in the Table 6.Formulation CF2 which contain Ac-Di-Sol super-disintegrant showed more than 95% of drug release within 12 min, whereas in formulation CF3 and CF4 containing SSG super-disintegrant, more than 95% of drug release within 20 min. From the results it is observed that, the concentration of super-disintegrant of formulation CF1 was reduced to 3.0%, more than 95% of drug release within 20 min. This result exhibit a direct relationship between selection & concentration of super-disintegrants and drug release. Among the various formulations tablets of batch CF2 prepared with 6.5% Ac-Di-Sol showed complete release of drug within 15 min.

## Stability studies[15]

Stability studies were carried out for the selected formulation CF2 and the results were shown in Table 7.The result showed that there was no significant difference in the drug content, disintegration time, hardness and friability at various sampling intervals. The *in vitro* dissolution profiles were super imposable which confirms the stability of the product.

## Conclusion

The present study suggests that the solubility of AMP can be enhanced by solid dispersion using β-cyclodextrin as a carrier employing spray drying method. The obtained best solid dispersion formulated in to fast dissolving tablets of AMP using super-disintegrants such as Ac-Di-Sol, sodium starch glycolate by direct compression technique. It can be concluded that the solid dispersion technique useful to improve solubility, dissolution rate and may be subsequently bioavailability of poorly soluble drug. This concept offers a suitable and practical approach in serving desired objectives of faster disintegration and dissolution characteristics.

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