STUDY ON THE EFFECTS OF VARIOUS DISINTEGRANTS ON AMOXICILLIN TRIHYDRATE DISPERSIBLE TABLETS

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ABSTRACT

The objective of this work was to develop a formulation of amoxicillin trihydrate dispersible tablets of 320mg in a low production value, using cheap amoxicillin trihydrate raw materials available in the market, with direct compression or wet granulation method. Amoxicillin trihydrate is a semisynthetic antibiotic, an analogue of ampicillin with a broad spectrum of bactericidal activity against gram +ve and gram –ve organism. Dispersible tablets are uncoated or film coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion. The WHO prefers dispersible dosage form for the elderly and paediatric patients due to its ease in the administration. Amoxicillin trihydrate dispersible tablet was manufactured with the different disintegrants such as maize starch, crospovidone, croscarmellose, sodium starch glycolate, croscarmellose. The powder blend was evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner’s ratio. After compression the tablets were subjected to weight variation, %drug content, buoyancy studies and in-vitro release studies. The wet granulation was excluded from the formulation due to its high cost if production, direct compression was selected due to its low cost and ease of production. The optimized formulation F10 had showed 99.11% of drug release in 40 min and disintegration of tablet was 25 seconds. The result of FTIR analysis of pure drug alone and drug with excipients there was not showed any physical and chemical interaction. F10 had undergone DTA, which shows the thermal stability of the formulation. The stability studies of optimized formulation F10 at 30°C / 65%RH did not show any change in tested parameters and release.

KEY WORDS: Dispersible tablets (D.T), Dispersibility, Amoxicillin trihydrate

INTRODUCTION

An ideal drug therapy was based on relating pharmacological response to the dose administered. Poor correlation between the dose administered and pharmacological response will resulted because of the decreased absorption rate and poor dose rate. Dispersible tablets which shows high absorption rate and increased therapeutic efficacy. The dispersible tablets are most preferred for elderly patients, paediatric, and patients with swallowing difficulties. Drugs which shows instability and with unacceptable taste can be masked in dispersible tablet. Dispersible tablets are the most famous dosage form in the dosage forms. Dispersible tablets which offers, quicker onset of action, bitter taste of tablet can be masked, improved tablet performance1,2,3.

Dispersible tablets4

Dispersible tablets are uncoated or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion. Hence proper choice of disintegrants and its consistency of performance are of critical importance to the formulation development of such tablets. The administrations of the drugs to the elderly patients have become a major barrier in drug therapy, mainly due to the difficulty in swallowing disability. These tablets are dispersed in the water before administration. Dispersible tablets are well administered for the pediatric, dysphasic patients, mentally ill, unco-operative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing. Amoxicillin trihydrate is likely white or almost white crystalline powder and it is well absorbed when given orally, with a bioavailability that appears to be much higher than excepted based on its physicochemical and biopharmaceutical properties and the pH partition theory. The trihydrate form is slightly soluble in water and its stability in the solid state is possibly related to the effect of the water content and hygroscopic behavior. Because of its poor solubility amoxicillin trihydrate can be considered as a drug candidate may give rise to dissolution related bioavailability problem.

In this formulation an amoxicillin trihydrate dispersible tablet is developed using a cheap raw material available in the market, the development of formulation will help in the production of amoxicillin trihydrate dispersible tablet in a low production cost and high therapeutic efficacy.

MATERIALS AND METHOD

Materials

Amoxicillin trihydrate, Zhuhai Pharmaceutical, was obtained as a gift sample from MICRO LABS LTD, Bangalore. Maize starch, sodium starch glycolate, crospovidone, croscarmellose was gifted from Micro labs, Bangalore. Other reagents and solvents used were of analytical grade.

Methods

Preparation of amoxicillin trihydrate dispersible tablets by Wet granulation method

The amoxicillin trihydrate and other excipients were weighed as per the Table no. 1. Drug and the excipients were dry mixed for 15 mins using a planetary mixer. The mixture was transferred in to a RMG (Rapid mixing granulator), to the mixture in the RMG granulating medium (purified water) was added slowly for a period of 30-180 sec at agitator on slow speed and chopper off till obtain an appropriate
consistency, add additional purified water if required to get the desired consistency. Each experiment was stopped immediately at the end of the liquid addition phase, hence wet massing was not performed, operate RMG for 30-180 sec at agitator and chopper fast speed for additional time to complete the granulation. During the process the mixer impeller and chopper were set at 300 rpm and 1300 rpm respectively. The total amount of the water added was adjusted according to the granule formation.

Granules were dried by using a tray drier. Granules were spread uniformly on the tray and kept inside the tray drier, the temperature and time were set. The drying process is continued until the moisture of the granules reaches a moisture content of 12.4% to 13.4%.

Dried granules were passed through the 22# (ASTM) sieve mesh. Finally magnesium stearate was added to the blend by passing through 22# (ASTM) sieve mesh. This blend is then mixed well and compressed in to tablet using rotary tablet machine.

**Preparation of amoxicillin trihydrate dispersible tablet by Direct compression**

The amoxicillin trihydrate and other excipients were weighed accurately as per the Table no.1, and then all the powders were passed through the 22# (ASTM) sieve mesh, except magnesium stearate which was passed through 22# (ASTM) sieve mesh. The whole blends were mixed in an octagonal blender for 5 min. Then the resulting blend was compressed in to tablets using a rotary tablet machine.

**PREFORMULATION STUDIES OF PURE DRUG AND EXCIPIENTS**

**Drug-excipient compatibility studies**

Drug-Excipient compatibility studies form an important part of Preformulation studies. The interaction between the drug and excipients are determined after a specific time period by using suitable analytical technique like FTIR.

**Evaluation of powder blend**

**Angle of repose**

Flow property of the granules was evaluated by determining the angle of repose and the compressibility index. Static angle of repose was measured according to fixed funnel method. The angle of repose was calculated using the equation,

\[
\tan \theta = \frac{h}{r} \quad \text{……(1)}
\]

**Bulk density**

Loose bulk density (LBD) and Tapped bulk density (TBD) were determined for the prepared granules. LBD and TBD was calculated using the formula,

\[
\text{LBD} = \frac{\text{Wt of Powder}}{\text{Vol. of Powder}} \quad \text{……(2)}
\]

\[
\text{TBD} = \frac{\text{Wt of Powder}}{\text{Tapped Vol. of Powder}} \quad \text{……(3)}
\]

**Compressibility Index**

Car’s Compressibility Index for the prepared granules was determined by the equation,

\[
\text{Car’s Index} (%) = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100 \quad \text{……(4)}
\]

**Hausner’s Ratio**

Tapped density and untapped density were measured and the Hausner’s ratio was calculated using the formula,

\[
\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Untapped density}} \quad \text{……(5)}
\]

**EVALUATION OF TABLETS**

Tablets from all the five formulations were evaluated for its various properties like thickness and diameter using digital vernier calipers (Mitutoyo Measuring Instruments (Suzhou) Co., Ltd. China), hardness by using Monsanto hardness tester (Scientific Engineering Corp, Delhi), friability by using Roche Friabilator, and weight variation by using an electronic balance (Santorious BT 323S, Germany).

**Dispersibility test**

2 tablets were placed in 100 ml of distilled water and stirred until completely dispersed. A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of ASTM # 22.

**Disintegration test**

One tablet was kept in each tube of the disintegration apparatus, suspended the assembly in the beaker containing water and operated with the discs for 4 minutes, unless otherwise stated in the individual monograph. Remove the assembly from the liquid.

Dispersible tablet should complete the disintegration within 3 minutes in water (temperature 15°C to 25°C).

**Content uniformity**

Determined by liquid chromatography

**Preparation of standard solution**

115mg of amoxicillin trihydrate WS (working standard) was weighed accurately and transfer to 100 ml volumetric flask, 80ml diluent was added and sonicated at room temperature to dissolve the sample and was diluted to the volume with the diluent. The diluent was filtered through 0.45µ nylon membrane filter, discarding first few ml of filtrate.

**Sample preparation**

5 tablets were weighed and noted, then transferred in to 500ml volumetric flask and 350ml of diluent were sonicated for 5 min and diluent was made up to the mark and a magnetic stirring bar was placed and stirred for 30 min. The content was filtered and made up to 25ml.

**IN-VITRO DISOLUTION STUDIES**

Dissolution studies of all tablets were performed using dissolution tester (Paddle type, TDL-08L, Electrolab, India). Tablets were added to the 900 ml of 0.1 N HCl at 37°C ± 0.5°C, which was stirred with a rotating paddle at 75 rpm. At time intervals of 5 minutes, 1ml samples were withdrawn and equal volume of fresh medium prewarmed at the same temperature was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test. Assay carried out using U.V. spectrophotometer (UV 1700 shimadzu /Visible double beam spectrophotometer, Japan) at 272nm.

**DIFFERENTIAL THERMAL ANALYSIS (DTA)**

The DTA analysis was carried out to identify the compatibility between the drug and the excipients. The DSC analysis of the optimized formulation and Pure drug were carried out using ASTM E-537-98, TA instruments Inc. Samples were weighed and heated in a platinum cups with the reference material calcined alumina at rate of 10°C between 30°C to 600°C under the nitrogen atmosphere.

**X-RAY DIFFRACTION STUDIES**

The interaction of the drug and excipients were determined by the X-ray diffractometer under the following condition: target/filter (monochromator) Cu, voltage 40 Kv, current 30mA, receiving slit 0.2 inches. The data were collected in the continue scan mode. The scanned range was 0 to 80°.

**STABILITY STUDIES**

The stability studies were conducted by storing the tablet in a stability chamber at 30°C / 65% RH and 40°C / 75% RH for three months; the tablet physical properties and dissolution were examined once in a month. Each tablet were wrapped in an aluminum foil and packed in black PVC bottle and stored...
for three month. After one month tablets, were analyzed for its physical properties and dissolution properties.

RESULTS AND DISCUSSIONS

DRUG – EXCIPIENTS COMPATIBILITY STUDIES

In this drug-excipient compatibility study, by placing drug-excitient composition in different temperature were investigated. There was no change in physical appearance, color change and spectrum taken showing similar results. From this we concluded that there is no interaction between drug-excipients complex.

EVALUATION OF POWDER BLEND

The formulations showed good flow property and compressibility index. Angle of repose ranged from 29°08’ to 36°11’ and the compressibility index ranged from 12 to 17. The LBD and TBD of the prepared granules ranged from 0.51 to 0.54 and 0.61 to 0.65 respectively. Hausner’s ratio was found to be 1.2 (or) less than 1.2. The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the flow property.

DISINTEGRATION TEST

Disintegration is the most important characteristic test of dispersible tablet, among the formulation F10 formulated with croscarmellose and crospovidone shows an excellent disintegration time of 25 seconds. Fig no 1

IN VITRO DISSOLUTION STUDIES

In formulation F1, F2, F3 were formulated with single superdisintegrants, crospovidone, sodium starch glycolate and croscarmellose respectively were used along with the drug, the release of the drug from the F1 and F2 was below the limits. F3 shows better drug release from the formulation. In F4 was formulated with dispersible cellulose by wet granulation method but the release of the drug from the formulation was not up to the limit. The F5 formulated with maize starch and crospovidone were used in combination with drug, the release was very poor comparing with other formulation.

F6 and F7 which shows comparatively better release of drug from the above formulation, F6 were formulated with maize starch and sodium starch glycolate and F7 with maize starch and croscarmellose.

F8 formulated with maize starch, crospovidone and croscarmellose shows increased drug release when comparing to the above formulation. F9 with sodium starch glycolate and croscarmellose with good release of the drug. F10 were formulated with crospovidone and croscarmellose shows an excellent release of the drug from the formulation. It was considered as an optimized formulation in this work.

EVALUATION OF TABLETS

The thickness and average weight were found in the range of 3.41±0.06 to 3.68±0.007 and 319±1.22 to 322± 1.20 respectively. In each formulation, weight variation was within the IP limit and the variation was within ±5%. The hardness of the different formulations ranged from 5-7 kg /cm². All the formulations exhibited less than 1% friability. The results were found to be within the limits (98 to 99.5%). It shows that the drug was uniformly distributed throughout the tablets. The disintegration test for the F10 shows 25 seconds which is the optimized formulation. All the formulation passed the dispersibility test.

DIFFERENTIAL THERMAL ANALYSIS (DTA)

The DTA thermogram studies were carried out to determine the thermal compactability of the excipients with the drug in the optimized formulation.

The Tg values of the Amoxicillin trihydrate (pure drug) was 196.22°C

When DTA thermogram for Amoxicillin trihydrate and optimized formulation of amoxicillin trihydrate dispersible tablet were compared, the Tg value of the pure drug was situated within the Tg values of dispersible tablet revealed that there was no interaction between pure drug and excipients used in the formulation.

CONCLUSION

The aim of the present work was to study the effects of different disintegrants on Amoxicillin trihydrate dispersible tablet and to develop a formulation in a low production value, using cheaper raw material. But this raw material shows problems in the release of the drug from the formulation. The Amoxicillin trihydrate is formulated with different disintegrants at various amounts in single and in combination. Ten formulations were developed with four disintegrants using direct compression method and wet granulation method. Each formulation composed of drug and disintegrants at various amount. The disintegrants used in this study are maize starch, crospovidone, croscarmellose, sodium starch glycolate etc.

The Preformulation studies and the evaluation studies of the tablet were done and found to be within the limits of the IP. The In-vitro drug release studies are conducted and compared with a standard formulation.

The formulation F10 formulated with the combination of Crospovidone and Croscarmellose as disintegrating agents was found to be the optimized formulation. The formulation F10 also exhibited better disintegration time (25 sec) which according to the IP limits is below 2 min. Formulation also shows passes the dispersibility test.

The results of dissolution studies indicated that the formulations F3, F8, F9and F10, were successful and exhibited drug release pattern very close to innovator drug release profile. But the drug release of F10 was found to be better than other formulation i.e. (99.11). Also the key factor of a dispersible tablet i.e. disintegration time was found to be much better than any other formulation i.e. (25 seconds). Hence F10 was selected as the optimized formulation. The above formulation was found to be more economical.

REFERENCES


**PREPARATION OF AMOXICILLIN TRIHYDRATE DISPERSIBLE TABLETS**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Amoxicillin trihydrate (mg)</th>
<th>Dispersible Cellulose (mg)</th>
<th>Maize starch (mg)</th>
<th>Crospovidone (mg)</th>
<th>SSG (mg)</th>
<th>Croscarmellose (mg)</th>
<th>Mg Stearate (mg)</th>
<th>Colloidal Silicon (mg)</th>
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<td>-</td>
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<td>4</td>
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<td>320</td>
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</table>

Table 1: 287 mg of amoxicillin trihydrate = 250 mg amoxicillin

**DISINTEGRATION TEST**

Figure 1, Disintegration time of the ten formulation, the F10 formulation is more than other formulation.
INVITRO DISSOLUTION STUDIES

Figure 2, Dissolution profile of F1-F4.

Figure 3, Dissolution profile of F5 – F9.

Figure 4, Dissolution profile F 10.

DIFFERENTIAL THERMAL ANALYSIS (DTA)
Figure 5, DTA thermogram of pure drug

Figure 6 DTA thermogram of F 10

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