Comparative In vivo Evaluation of Aripiprazole Coprecipitate, Nanoparticles and Marketed Tablets in Healthy Human Volunteers and In vitro-In vivo Correlation

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Abstract

The aim of this study was to evaluate the bioavailability of two aripiprazole tablets, coprecipitate (CP) and nanoparticles (NP) when compared to the market tablets. A single-dose, randomized, three period crossover design under fasting conditions in healthy human volunteers was studied. The dissolution rate of the CP, NP and market tablets was determined. In order to investigate the feasibility of in vitro data as a tool for predicting in vivo results, two types of in vitro-in vivo correlation (IVIVC), level C and multiple level C, were studied. Almost 75% of aripiprazole was dissolved from the nanoparticles tablets within 10 minutes compared with 20% and 46% for coprecipitate and market tablets, respectively. The mean AUC₀₋₇₂ value of aripiprazole from the NP tablets (6136.35 ± 421.29 ng.hr/mL) was significantly higher than both CP tablets (3216.12 ± 525.02 ng.hr/mL) and market tablets (5215.57 ± 457.28 ng.hr/mL) (p d” 0.05). The relative bioavailability of aripiprazole after oral administration of the CP and NP tablets was 61.66% and 117.65%, respectively. The higher dissolution rate of NP tablets resulted in rapid absorption of aripiprazole and consequently higher bioavailability. Multiple level C IVIVC showed the bioequivalence of NP and bioinequivalence of the CP tablets in comparison to market tablets.

Keywords: Aripiprazole; Coprecipitate; Nanoparticles; Bioequivalence; Volunteers.

Introduction

Solubility of a drug is essential for its effectiveness, independent of the route (1). Dissolution is the rate limiting step in the absorption of BCS class II drugs across the gastrointestinal tract (2). Since poor aqueous solubility is associated with poor dissolution characteristics, solubility has become a challenging problem in drug formulation development (3, 4). Nanomilling and coprecipitation are two particle engineering approaches commonly used for enhancing the dissolution rate of poorly water soluble drugs (5, 6).

The increase in dissolution rate is hypothesized to increase both the rate and extent of absorption resulting in higher bioavailability and faster onset of action (7). The increase in dissolution rate of nanomilled drug powders can be explained using the Noyes Whitney equation as smaller particles result in an increase in surface area and through the Prandtl equation as the particles will have smaller diffusional thickness. In case of coprecipitation, the
dissolution rate was found to increase due to reduction in crystallinity and subsequent lowered energy to break up crystalline lattice of the drug. Moreover, the drug solubility and wettability may be increased by surrounding hydrophilic polymer matrices (8, 9).

The enhancement of the bioavailability of poorly water soluble drugs by nanomilling and coprecipitation has been reported earlier. For example, nanomilling enhanced the AUC and $C_{\text{max}}$ of NVS-102 by a factor of 9 and 5, respectively (10), the AUC of MK-0869 by a factor of 4 (11) and resulted in 86% of the absolute bioavailability of cilostazol (12). Similarly, coprecipitation enhanced the bioavailability of KRN633 7.5 times (13), the $C_{\text{max}}$ and AUC of ER-34122 by 100 times (14), $C_{\text{max}}$ of ritonavir 15 times (15) and resulted in 95% of the absolute bioavailability of albendazole (16).

Aripiprazole is a novel atypical antipsychotic agent with a pharmacological mechanism that is distinct from currently available antipsychotic agents (17). It acts as a potent partial dopamine D$_2$ receptor agonist, a partial serotonin 5-HT$_{1A}$ agonist, and 5-HT$_{2A}$ receptor antagonist (18). Aripiprazole is currently approved for schizophrenia and the acute treatment of manic or mixed manic/depressive episodes of bipolar disorder (19). Aripiprazole has a poor aqueous solubility (10.98 ± 1.39 ng/mL) and is classified as BCS class II (6, 20). Hence, aripiprazole was used as a model drug to compare the effect of nanomilling and coprecipitation on the dissolution rate and in vivo bioavailability of poorly water soluble drugs.

In vitro-in vivo correlations (IVIVC) are generally observed when the dissolution is the rate-limiting step in absorption and appearance of the drug in the circulation (21, 22). Four categories of IVIVC have been described in the literature: level A, B, C and multiple level C (23). A good correlation is a tool for predicting in vivo results based on in vitro data (24). In this respect, dissolution tests may be considered as surrogate markers of availability of a drug in the systemic circulation for drugs with dissolution rate limited absorption (25).

In our previous work, nanomilling resulted in a significant increase in intrinsic dissolution rate of aripiprazole (2 to 9 folds) when compared to coprecipitation (6). This increase in dissolution rate was hypothesized to enhance the in vivo bioavailability in the same rank order. To verify this hypothesis, the pharmacokinetics of 2 aripiprazole tablets containing, coprecipitate (CP) and nanoparticles (NP), respectively were assessed after administration to healthy human volunteers and compared to the market tablets. In addition, two levels of in vitro-in vivo correlation, C and multiple level C were also investigated.

**Materials and Methods**

**Materials**: Aripiprazole was purchased from Hetero Labs Limited, India. Acetonitrile, Formic acid and water (HPLC grade) were purchased from Fisher Scientific Co., Pittsburgh, PA, USA. Pluronic F127 was purchased from BASF, Florham Park, NJ, USA. Escitalopram (internal standard) was provided by Alkan Pharma Co., Egypt. Abilify® 10 mg tablets, used as reference, were purchased from Egypt Otsuka Pharmaceutical Co., and referred to in the manuscript as market tablets.

**Preparation of coprecipitate composition**: The coprecipitate of aripiprazole with Pluronic F127 (1:1) was prepared by solvent evaporation method (26, 27). Briefly, aripiprazole and Pluronic F127 were accurately weighed and each was transferred to a beaker containing dichloromethane:methanol (9:1). The solvent
was evaporated in rotary evaporator (Rotavapor® R-300, Bûchi, Switzerland) at reduced pressure and the resulting coprecipitate composition of aripiprazole was stored in a desiccator until further study.

**Preparation of nanoparticles composition:** The nanosuspension of aripiprazole with Pluronic F127 (1:1) was prepared by media milling using a Dyno®-Mill Multilab (Glenmills, Clifton, NJ) utilizing 200 G zirconia grinding beads at a speed of 4180 rpm for 2 hours. The nanosuspension was lyophilized after preparation. First the nanosuspension was poured into glass flasks and prefrozen using an ultra cold freezer (Thermo Scientific Revco, Waltham, MA, USA) at -80 °C for 12 hours, then the samples were freeze-dried using a Flexi-Dry™ MP Freeze Dryer (SP Scientific, Stone Ridge, NY, USA) at -90 °C and 380 mT of pressure for 48 hours to yield dry nanoparticle powder. Prior to freezing, sucrose (1.67% w/v) was added into the suspension as a cryoprotective agent.

**Particle size analysis of the compositions:** The particle size was determined by introducing an aliquot of the prepared compositions into the water-filled sample cell of a Horiba LA-930 laser light scattering particle size and distribution analyzer (Horiba Instruments, Irvine, CA, USA). The measured particle size distribution values were reported based on volume-weighted analyses (28). For the analysis of particle size of the freeze-dried nanosuspension, the samples were first reconstituted in water. The measurement is based on Mie scattering theory and has a wide range of 0.02–2000 μm (29). All the measurements were made in triplicate.

**Preparation of the tablets:** The coprecipitate and nanoparticles compositions of aripiprazole with Pluronic F127 were mixed with excipients; Ac-Di-Sol, Avicel pH 102 and magnesium stearate (Table 1). The tablets were prepared by direct compression using a single punch tablet machine (Stokes, Pennwalt Chemical Corp., Warminster, PA, USA). The tablets containing coprecipitate and nanoparticles will be referred to in the discussion as CP and NP tablets, respectively.

**Dissolution study of the prepared tablets:** The CP, NP, and market tablets were immersed in a USP II dissolution apparatus (Hanson Research Corp., Los Angeles, CA, USA) containing 900 mL 0.1 N HCl as dissolution medium at 37 °C and stirred at 60 rpm. At predetermined time intervals, aliquots of 5 mL were withdrawn, filtered and replaced by fresh medium. The samples were analyzed by HPLC and the percentage of aripiprazole dissolved was plotted as a function of time.

Comparative *In vivo* evaluation of aripiprazole coprecipitate

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Pluronic F127</th>
<th>Sucrose</th>
<th>Ac-Di-Sol</th>
<th>Avicel pH 102</th>
<th>Magnesium stearate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP tablets</td>
<td>10 mg</td>
<td>-</td>
<td>7.5 mg</td>
<td>121 mg</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>NP tablets</td>
<td>10 mg</td>
<td>83.45 mg</td>
<td>7.5 mg</td>
<td>37.55 mg</td>
<td>1.5 mg</td>
</tr>
</tbody>
</table>

*Total tablet weight: 150 mg, aripiprazole = 10 mg in both tablets.*
expressed as D values. For example, D30 means the mean percentage dissolved after 30 minutes (30).

**HPLC analysis of aripiprazole:** An isocratic HPLC method was employed for the quantification of aripiprazole (31). A Thermo Separation HPLC system (Fremont, CA, USA) equipped with a P4000 pump unit, an AS3000 autosampler including an injection valve with a sample loop of 50 μL volume, and a UV2000 detector was used. A Zorbax Extend-C18 column (4.6 mm x 250 mm) containing 3.5 μm size adsorbent as stationary phase (Agilent technologies, Santa Clara, CA, USA) was used for chromatographic separation. The column was maintained at room temperature (25± 2°C). The mobile phase consisted of a mixture of 10 mM ammonium buffer (adjusted to pH 8.35 with sodium hydroxide 6 mol/L) and acetonitrile (25:75). The flow rate and the UV detector were set at 1.0 mL/min and 254 nm, respectively. Aripiprazole was eluted at 6.6 min under the conditions described above. An external calibration curve was established in the range of 0.1-20 μg/mL.

**Pharmacokinetic study in healthy human volunteers**

**Study design and subjects:** A single-dose, randomized, three period crossover design was adopted to evaluate the pharmacokinetic parameters of CP and NP tablets compared to the market tablets, Abilify® 10 mg tablets (Egypt Otsuka Pharmaceutical Co.). Six healthy adult male volunteers participated in this comparative study. Their mean age was 47.17 ± 5.71 years, mean body weight 77.17 ± 8.45 Kg and mean height 171 ± 9.63 cm. The purpose of the study was fully explained, and volunteers had given their written consent. The volunteers were instructed to abstain from taking any drug, including over-the-counter (OTC), for 2 weeks prior to and during the study period. The study was performed according to the revised Declaration of Helsinki for biomedical research involving human subjects and the rules of Good Clinical Practices (GCP). The study protocol was reviewed and approved by the Cairo University protection of human subjects committee.

**Drug administration and sample collection:** The volunteers were checked-in a hospital at 9:00 P.M. and had a standard dinner at the clinical site. After an overnight fast (at least 10 hr), volunteers were given a single oral dose of the CP tablet, NP tablet and market tablet according to a randomization schedule.

Food and drink (other than water, which was allowed after 2 hr) were not allowed until 4 hr after dosing and then a standard breakfast, lunch and dinner were given to all volunteers according to a time schedule. Beverages and food containing caffeine were not permitted over the entire course of study. The volunteers were under continual medical supervision at the study site. Adverse events including abnormal laboratory values were spontaneously reported or observed either by the volunteers or the resident physician and were recorded, tabulated and evaluated. Approximately 5 mL blood samples for aripiprazole analysis were drawn into evacuated heparinized glass tubes through an indwelling cannula at 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 24.0, 48.0 and 72.0 hours post dose. All the samples were collected and centrifuged at 3500 rpm for 10 min at 4°C and the plasma was transferred directly into 5 mL plastic tubes and stored at -70 °C until the analysis. Plasma samples labeled by protocol number, subject number, study phase and the designated sample number were forwarded to the analysis laboratory. After 21 days washout period, the
study was repeated in the same manner to complete the crossover design.

**Sample preparation:** All frozen plasma samples were thawed at ambient temperature. A solvent extraction procedure was used. 1 mL of human plasma samples and 100 μL of escitalopram (internal standard) solution were placed in 10 mL glass tubes, and vortexed for 1 min using a vortex mixer (Julabo Para Mix II, Munich, Germany). Four mL Ethyl Acetate was added and samples were vortexed for 2 min. The tubes were centrifuged for 10 min at 4000 rpm using a Centrifuge R32 A (Remi Laboratory Equipment, Bombay, India). The upper organic phases were then transferred to clean glass tubes and evaporated to dryness using centrifugal vacuum concentrator Vacufuge® 5301 (Eppendorf AG, Hamburg, Germany) at 40 °C. Dry residues were reconstituted by dissolving in 200 μL of (50% acetonitrile + 50% water) and vortexing for 1 min.

**Liquid chromatography/tandem mass spectrometry (LC-MS/MS) method for the determination of aripiprazole in human plasma:** Plasma samples were analyzed using a sensitive, reproducible and accurate LC-MS/MS method, developed and validated before the study (32). Escitalopram (internal standard) stock solution was prepared by dissolving 40 mg of escitalopram in 100 mL (50% acetonitrile + 50% water) and serially diluted to give a final working concentration of 40 ng/mL. A shimadzu Prominence (Shimadzu, Japan) series LC system equipped with degasser (DGU-20A3), solvent delivery unit (LC-20AB) along with autosampler (SIL-20 AC) was used to inject 30 μL aliquots of the processed samples on a Luna C18 column (4.6 x 50 mm) containing 5 μm size adsorbent as stationary phase (Phenomenex, Inc., Torrance, CA, USA). The Guard column used was Phenomenex C18 (4.0 x 5 mm), 5 μm particle size. Analysis was carried out at room temperature (25 ±2 °C). The isocratic mobile phase consisted of acetonitrile and water (70:30) and 0.1% formic acid, which was delivered at a flow rate of 1.0 mL/min into the mass spectrometer’s electrospray ionization chamber. Quantitation was achieved by LC-MS/MS detection in positive ion mode for both aripiprazole and escitalopram, using an API-3200 mass spectrometer (MDS Sciex, Foster City, CA, USA) equipped with a Turbo ionspray™ interface at 400°C. The ion spray voltage was set at 5500 V. The common parameters: nebulizer gas, curtain gas, auxiliary gas, and collision gas were set at 60, 23, 50, and 12 PSI, respectively. The compound parameters: declustering potential, collision energy, entrance potential, and collision exit potential were 51, 19, 9, and 4 V, respectively, for aripiprazole and 72, 28, 18, and 4 V for escitalopram. Detection of the ions was performed in the multiple reaction monitoring (MRM) mode, analyzing the transition of the m/z 447.89 precursor ion to m/z 285.20 for aripiprazole and the m/z 324.98 precursor ion to m/z 109.10 for escitalopram. Quadrupoles Q1 and Q3 were set on unit resolution. The analytical data were processed using Analyst software version 1.4.2 (Applied Biosystems Inc., Foster City, CA, USA).

**Pharmacokinetic and statistical analysis:** Plasma concentration-time data of aripiprazole was analyzed for each subject by non-compartmental pharmacokinetic models using kinetica® software version 4.4.1 (Thermo Fisher Scientific Inc., Waltham, MA, USA). The peak plasma concentrations (C_max) and the time of their occurrence (T_max) were directly obtained from the concentration-time data. The area under the plasma concentration-time curve (AUC) from time zero to last measured concentration (AUC_0–72) was calculated according to the linear trapezoidal method. Two-way analysis of
variance (ANOVA GLM procedure; Kinetica™ 2000 Computer program for a crossover design) was used to assess the effect of formulation, period, and subjects on $C_{\text{max}}$ and AUC$_{0\text{-}t}$. Differences between two related parameters were considered statistically significant for $p$-value equal to or less than 0.05.

**In vitro-in vivo correlation (IVIVC):** Two levels of in vitro-in vivo correlation, C and multiple level C, were studied (23). Level C IVIVC was investigated for each of the in vitro dissolution D values (D10, D20 and D30) versus $C_{\text{max}}$ (30). Multiple level C IVIVC was studied by correlating partial AUCs (AUC$_{0\text{-}1\text{hr}}$, AUC$_{0\text{-}2\text{hr}}$, and AUC$_{0\text{-}3\text{hr}}$) versus D10, D20 and D30 (33). The partial AUCs were also calculated according to the linear trapezoidal method. In vitro and in vivo results were taken as independent ($x$) and dependent ($y$) variables, respectively. The correlation coefficient and the slope were calculated and interpreted using linear regression analysis (Microsoft Excel software).

**Results and Discussion**

**Dissolution study of the tablets:** The particle size of the freshly prepared nanosuspension (0.41 ±13.70 μm), resuspended nanoparticles (0.39 ±16.45 μm) was comparable and significantly lower than the coprecipitate composition (11.08 ±0.31 μm) ($p$ d” 0.05). The nanoparticles compressed tablets (NP) showed a significant increase in the rate and extent of dissolution and the dissolution rate was maintained at higher level throughout all time intervals compared to coprecipitate (CP) and market tablets. The rank order increase in dissolution rate was as follows: NP tablets > Market tablets > CP tablets (Fig. 1). Within 10 minutes, almost 75% of aripiprazole was dissolved from the NP tablets compared with 20% and 46% for CP tablets and market tablets, respectively. After 45 minutes, the dissolution was almost complete (99.5%) for NP tablets compared to only 72% and 82% for CP and market tablets, respectively.

The increase in dissolution rate from NP tablets was similar to the intrinsic dissolution rate of aripiprazole nanoparticles based on the disruption of the crystalline structure of aripiprazole and conversion into amorphous (6). In addition, after the disintegration of NP tablets, the increased surface area described by Noyes Whitney equation (34, 35, 36, 37, 38) and higher surface to volume ratio enabled hydration over larger surface area and consequently resulted in increased drug dissolution (39). Moreover, the increase in dissolution rate caused due to particle size reduction can be explained by the decrease in diffusional thickness $h$ leads to an increase in the concentration gradient $(Cs-Ct)/h$ which consequently increases the dissolution rate.

**Pharmacokinetic study in healthy human volunteers:** All volunteers fully completed the study. No adverse reactions were reported by any of the subjects.

The LC-MS/MS assay has been validated and a good linearity from 1-500 ng/mL with acceptable within and between day
reproducibility was observed. The lower limit of aripiprazole quantification in plasma was 1 ng/mL.

The aripiprazole mean plasma concentration-time profiles following single oral administration of CP tablets, NP tablets, and market tablets to six healthy human volunteers are shown in Fig. 2. Corresponding pharmacokinetic parameters are summarized in Table 2.

The mean $C_{\text{max}}$ value of aripiprazole from the NP tablets was numerically higher than both the CP tablets and the market tablets. However, statistical analysis showed that the mean $C_{\text{max}}$ value of NP tablets was significantly higher than the CP tablets but not significant between the NP and the market tablets (p $d^*$ 0.05). The mean $AUC_{0-72}$ value of aripiprazole from the NP tablets was significantly higher than both the CP tablets and market tablets (p $d^*$ 0.05). This indicated that the extent of absorption of aripiprazole from the NP tablets is significantly higher than that of the other tablets. The rate of absorption of aripiprazole from the CP tablets ($T_{\text{max}} = 2.42 \pm 0.38 \text{ hr}$) and NP tablets ($T_{\text{max}} = 2.25 \pm 1.08 \text{ hr}$) was comparable and significantly higher than the market tablets ($T_{\text{max}} = 3.83 \pm 1.03 \text{ hr}$) (p $d^*$ 0.05). The calculated relative bioavailability of aripiprazole after oral administration of the CP and NP tablets was 61.66% and 117.65%, respectively compared to the market tablets. This shows that NP tablet was bioequivalent with the market tablet while the CP tablet was bioinequivalent.
The higher C\text{max} and AUC_{0-72} following the oral administration of the NP tablets compared to CP tablets are due to the higher dissolution rate and consequently rapid absorption of aripiprazole from the gastrointestinal tract. This resulted in higher bioavailability (117.65%) (1, 3, 12, 41, 42).

**Evaluation of the in vitro- in vivo correlation (IVIVC):** In level C correlation, one single in vitro dissolution time point is related to one single pharmacokinetic parameter (23, 43). It is most applicable to immediate release tablets (30). Multiple level C correlation relates one or several pharmacokinetic parameters of interest to the amount of drug dissolved at several time points of the dissolution profile (23, 33). Multiple level C correlation can be as useful as level A correlation from a regulatory point of view, although the later is the most desirable (33, 44).

C\text{max} is one of the pharmacokinetic parameters primarily related to the absorption phase and has been selected as the pharmacokinetic parameter of choice in bioequivalence testing (30, 45). D values as in vitro data were shown to be good estimates of the rate of dissolution (30, 46, 47, 48). Hence, D values were correlated with C\text{max}.

**Table 2.** Pharmacokinetic parameters of aripiprazole after single oral dose administration of 10 mg tablets (CP, NP, and Market tablets) to six healthy adult male volunteers.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>CP tablets</th>
<th>NP tablets</th>
<th>Market tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (ng/ml) ± SD</td>
<td>159.97 ± 55.59</td>
<td>223.50 ± 71.78</td>
<td>186.17 ± 18.36</td>
</tr>
<tr>
<td>T\text{max} (hr) ± SD</td>
<td>2.42 ± 0.38</td>
<td>2.25 ± 1.08</td>
<td>3.83 ± 1.03</td>
</tr>
<tr>
<td>AUC 0-72 (ng.hr/ml) ± SD</td>
<td>3216.12 ± 525.02</td>
<td>6136.35 ± 421.29</td>
<td>5215.57 ± 457.28</td>
</tr>
<tr>
<td>Relative bioavailability (%)</td>
<td>61.66%</td>
<td>117.65%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Market tablets are used as reference standard.

*Relative bioavailability for CP and NP tablets was calculated as follows: \( \frac{AUC_{\text{test}} \times Dose_{\text{reference}}}{AUC_{\text{reference}} \times Dose_{\text{test}}} \)

The relationships between each of the in vitro dissolution D values (D10, D20 and D30) versus C\text{max} are shown in Figs. 3-5. A high correlation
was observed. This indicates that $C_{\text{max}}$ can be well predicted at D10, D20 and D30 as evident from the high in vitro-in vivo correlation (30). In addition, the rank order increase in $C_{\text{max}}$ was similar to the in vitro dissolution curves, NP tablets > Market tablets > CP tablets (Fig. 3).

In immediate release dosage forms, the in vitro and in vivo sampling time points are different. Therefore, in order to establish a multiple level C correlation between the in vitro and in vivo data that were collected at different time periods, a time scale factor is needed (33, 43, 49). Hence, the partial AUC obtained in the first three hours (60, 120, and 180 min) were compared with the amount dissolved at in vitro times six-fold lower (10, 20, and 30 min) (33). The correlation between partial AUC ($\text{AUC}_{0-1\text{hr}}$, $\text{AUC}_{0-2\text{hr}}$, and $\text{AUC}_{0-3\text{hr}}$) and percentage of aripiprazole dissolved at different time intervals (D10, D20 and D30) is shown in Fig. 4. The intercepts and slopes were calculated for the three tablets and the correlation coefficients were higher than 0.94 (Fig. 5). The similarity between the intercept and slope of NP tablet and market tablet supported that the two tablets were bioequivalent (33). On the other hand, the slope and intercept of the CP tablet were different than that of market tablet supporting bioinequivalence.

Conclusion

A significant increase in the in vivo bioavailability of aripiprazole (~2 folds) due to nanomilling was achieved when compared to coprecipitation. This higher bioavailability of the NP tablets (117.65%) was due to the higher dissolution rate and consequently rapid absorption of aripiprazole from the gastrointestinal tract. A high level C IVIVC was found between each of the in vitro dissolution D values and $C_{\text{max}}$. Furthermore, multiple level C IVIVC supported the bioequivalence and bioinequivalence of the NP and CP tablets, respectively compared to the market tablets.

References


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