Development of Gummi Drugs of Aripiprazole as Hospital Formulations

Shinya Uchida,*a Shogo Hiraoka,a,b and Noriyuki Namikia

a Department of Pharmacy Practice and Science, School of Pharmaceutical Sciences, University of Shizuoka; 52–1 Yada, Suruga-ku, Shizuoka 422–8526, Japan; and b Otsuka Pharmaceutical Co., Ltd.; 224–18 Ebisuno, Hiraishi, Kawauuchi-cho, Tokushima 771–0182, Japan.

Received January 14, 2015; accepted March 6, 2015

About half of patients with schizophrenia have poor adherence to taking medication, so many have recurrence, therefore, providing formulations that enable patients to continue their medication without interruption is important. We aimed to develop a gummi drug that contains aripiprazole (which can reduce the symptoms of schizophrenia and manic symptoms in bipolar disorder). We were able to develop gummi drugs (OD-G, PW-G and OS-G) using three commercially available aripiprazole products (Abilify® orally disintegrating tablets, powder formulation, and oral solutions, respectively) as hospital formulations. Furthermore, we developed improved OD-G (iOD-G), which contained high aripiprazole content. Pharmaceutical characteristics of iOD-G were demonstrated to be suitable for hospital formulations, and iOD-G could be stored for ≤1 month. No significant differences in the dissolution and pharmacokinetics of divided portions of iOD-G were observed when compared with commercially available aripiprazole products. This study confirmed that new dosage forms of aripiprazole in gummi drugs can be developed as hospital formulations, which will contribute to improve medication adherence of patients.

Key words gummi drug; aripiprazole; adherence; hospital formulation

About half of patients with schizophrenia have poor adherence to taking medication. Thus, it has been reported that many such patients have recurrence of schizophrenia.1,2) Poor medication adherence occurs if patients forget to take their medicine, or because of a lack of knowledge of their disease. Therefore, providing formulations that enable patients to continue their medication without interruption is important.3,4)

Various pharmaceutical formulations (including those for schizophrenia) are being developed actively with the aim of improving medication adherence. Oral dose formulations are the most common because of their non-invasive administration route. Various formulations have been developed: orally disintegrating tablets (ODTs),5–8) effervescent tablets,9) oral fast-dissolving film formulations,10,11) oral jelly formulations,12) and gummi formulations.13–15)

Among the formulations mentioned above that have been developed to improve adherence, “gummi formulations” have attracted attention because they do not require water for consumption, and can be chewed easily. It has been found that this dose form is better for children and elderly patients, who sometimes have trouble swallowing. “Gummis” are dried jelly sweets. They are created by adding gelatin as a gelling agent to syrup, in which carbohydrates such as sugar and starch syrup have been boiled down, and then cooled and solidified. Formulations to which medicine is added are called “gummi drugs.”

Namiki et al. reported that they developed gummi drugs (including those containing acetaminophen) for use in preparations employed in hospital.13,14) It is easy to take medicine in the form of a gummi drug. Gummi drugs are expected to be effective for patients with psychiatric disorders (including schizophrenia), who tend to have problems such as interruption of taking medications or refusing to take medications.

Aripiprazole is a dopamine D2/D3 receptor partial agonist and aids improvement of schizophrenia and manic symptoms in bipolar disorder.16–20) It is prescribed for depression as well as the symptoms of depression. Uncoated tablets, ODTs, oral solutions (OS), and oral powders (PW) of aripiprazole have been developed and marketed, thereby enabling various choices for oral administration. These four oral-formulation options are available, but adherence of patients who take aripiprazole formulations is not adequate. Furthermore, in addition to schizophrenia, aripiprazole is used for the treatment of irritability associated with autism in children.21) Therefore, development of aripiprazole as a gummi drug could increase the choices of oral formulations and improve medication adherence. By developing a type of aripiprazole gummi drug that children like to take, future development of drugs for other diseases (especially those for children) can be expected.

We aimed to develop a gummi drug that contains aripiprazole. In general, manufacture of gummi drugs does not require special equipment, so they could be prepared in the dispensing chambers of hospitals and pharmacies. In the present study, aripiprazole-containing gummi drugs were prepared by modifying three aripiprazole commercial formulations: ODTs, PW and OS. Then, we carried out pharmaceutical evaluations.

Experimental

Materials We purchased and used commercial formulations of aripiprazole (ODTs, 24 mg; PW, 1%; OS, 0.1%; all as Abilify®; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). Gelatin (AP-50) and hydrogenated maltose starch syrup (Amalty Syrup) were purchased from Nippi, Inc. (Tokyo, Japan) and Mitsubishi Shoji Foodtech Co., Ltd. (Tokyo, Japan). D-Sorbitol solution (75%), hydrochloric acid (2.9 mol/L), corn starch, and other chemicals were of Japanese Pharmacopoeia (JP) grade.

Preparation of Gummi Drugs Using Orally Disintegrating Tablets, Powder Formulations and Oral Solutions (OD-G, PW-G, and OS-G, Respectively) Table 1 shows...
formula of each of the gummi aripiprazole drugs (OD-G, PW-G, OS-G), which were modified from their commercial aripiprazole formulations (ODT, PW, and OS, respectively). The volume of hydrochloric acid (2.9 mol/L) was adjusted so that the pH of each solution was ≤ 4. Each gummi drug was arranged so that one 7-g gummi contained 6 mg of aripiprazole.

The procedure for the preparation of the gummi drug is a modified version of a procedure described previously (Fig. 1). Amalty Syrup and D-sorbitol solution were weighed and mixed, and then heated (≤ 135°C), to evaporate part of the water. Thus, an Amalty Syrup/sorbitol mixture was created. Separately, water was added to make the gelatin swell, which was dissolved by heating it to 60°C.

For preparation of gummi drugs using aripiprazole ODTs (OD-G, Fig. 1a), a small amount of water was added to Abilify ODTs (24 mg) to obtain the aripiprazole ODT suspension. The gelatin solution, hydrochloric acid (2.9 mol/L), and aripiprazole ODT suspension were added to the Amalty Syrup/sorbitol mixture sequentially, kept at 70°C, stirred and mixed. Finally, 7.0 g of this mixture was dispensed into a plastic plate shaped like a “trapezoidal pocket” (Fig. 2a) using a syringe, and

Table 1. Formulations of Aripiprazole Gummi Drugs (OD-G, PW-G, OS-G and iOD-G)

<table>
<thead>
<tr>
<th></th>
<th>OD-G</th>
<th>PW-G</th>
<th>OS-G</th>
<th>iOD-G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole formulation (Conversion to aripiprazole, mg)</td>
<td>17.8 mg</td>
<td>600 mg</td>
<td>6.0 mL</td>
<td>17.8 mg</td>
</tr>
<tr>
<td>Gelatin (g)</td>
<td>0.518</td>
<td>0.464</td>
<td>0.446</td>
<td>0.245</td>
</tr>
<tr>
<td>Hydrogenated maltose starch syrup (g)</td>
<td>4.736</td>
<td>4.246</td>
<td>4.082</td>
<td>2.239</td>
</tr>
<tr>
<td>ν-Sorbitol solution (g)</td>
<td>3.375</td>
<td>3.025</td>
<td>2.907</td>
<td>1.596</td>
</tr>
<tr>
<td>Dilute hydrochloric acid (mL)</td>
<td>0.014</td>
<td>0.011</td>
<td>0.032</td>
<td>–</td>
</tr>
<tr>
<td>Citric acid (g)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.025</td>
</tr>
<tr>
<td>Water q.s.</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Total (g)</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>

q.s., quantum sufficit (as much as suffices).
cooled to prepare OD-G.

In the case of gummi drugs using aripiprazole powder formulations (PW-G, Fig. 1b), Abilify PW was added to the Amalty Syrup/sorbitol mixture to disperse it, and then hydrochloric acid (2.9 mol/L) and gelatin solution were added sequentially, and stirred and mixed. Finally, 7.0 g of this mixture was dispersed into a plastic plate shaped like a trapezoidal pocket (Fig. 2a) using a syringe to obtain PW-G.

In the case of gummi drugs using aripiprazole oral solution (OS-G, Fig. 1c), Abilify OS was added to Amalty Syrup and D-sorbitol solution. Then it was heated (≤135°C) to evaporate some of the water. Thus, an aripiprazole-containing Amalty Syrup/sorbitol mixture was created. Gelatin solution and hydrochloric acid (2.9 mol/L) were added sequentially and the solution stirred and mixed. OS-G was obtained to disperse 7.0 g of the mixture into a trapezoidal pocket made by pressing corn starch on a plastic plate mold (Fig. 2a). After cooling and solidifying OS-G, excess starch was removed.

**Preparation of Improved Gummi Drugs with High Aripiprazole Content (iOD-G)** We created improved OD-G with high aripiprazole content (iOD-G): we made it with 6 mg of drug in a 3.5-g gummi (Table 1, Fig. 3). A small amount of water was added to Abilify ODTs (24 mg) and citric acid to obtain the aripiprazole ODT suspension and citric acid solution, respectively. Citric acid solution, gelatin solution and aripiprazole ODT suspension were added sequentially to the Amalty Syrup/sorbitol mixture and prepared in the same way as that described for OD-G, being maintained at 70°C, stirred and mixed. Finally, 3.5 g of this mixture was dispersed into a plastic plate shaped like a round pocket using a syringe (Fig. 2b), and cooled to prepare iOD-G.

**Preservation of iOD-G for 1 Month** A 1-month preservation test for iOD-G was conducted. The surface of the plastic plate that formed iOD-G was covered with a film of polyvinylidene chloride, placed in an aluminum laminated bag with a zipper (Lamizip AL-22; Seisannipponsha Ltd., Tokyo, Japan) and maintained at 4°C and 30°C for 1 month.

**Measurement of Aripiprazole Content in Gummi Drugs** Gummi drug (7 g or 3.5 g) was added to 100 mL of JP 1st fluid and heated at ≈40°C until it dissolved. The solution was filtered (Acrodisc GHP Minispike, 0.45 µm; Pall Corp., Port Washington, NY, U.S.A.), and 1 mL of internal standard (10.7 µg/mL of propyl 4-hydroxybenzoate for OD-G and PW-G, and 10.7 µg/mL of 4-hydroxyvalerophenone for OS-G and iOD-G) in high-performance liquid chromatography (HPLC) mobile phase (0.02m sodium sulfate/acetonitrile/methanol/acetic acid=56/33/11/1) was added to the sample solution, and 20 µL of residue was injected into HPLC.

Aripiprazole content of gummi drugs was measured by HPLC using YMC-Pack ODS-AM (5 µm, 4.6 mm i.d.×250 mm; YMC Co., Ltd., Tokyo, Japan) as an analytical column with a flow rate of the mobile phase of 1 mL/min. Column temperature was maintained at 25°C. Measurement of Impurities in the Gummi Drug

**Measurement of Impurities in the Gummi Drug**

A total of 12 mL of HPLC mobile phase was added to a piece of iOD-G to dissolve it by warming it at ≈40°C. Citrate buffer (pH 4.7) containing 0.01 m lauryl sodium sulfate/acetonitrile (55/45) was used as a mobile phase. A filtrate sample solution was made using a membrane filter with a pore size of 0.45 µm (Ekicrodisk 13CR; Pall Corp.) to filter the supernatant. We used an ultraviolet absorption photometer as a detector (wave-length, 254 nm). As an analytical column, YMC-Pack ODS-AM (5 µm, 4.6 mm id×250 mm; YMC Co., Ltd.) were used. Column temperature was set to 25°C. An ultraviolet spectrometer was used for detection at 254 nm.

**Measurement of Penetration** The softness of the gummi drug was measured based on penetration using a penetrometer (Ikenoto Scientific Technology Co., Ltd., Tokyo, Japan). The needle tip of the instrument was in contact with the surface of the gummi drug. Then, a 50-g needle holder was allowed to penetrate the gummi drug for 5 s. The penetrated distance (mm) was defined as the penetration value.

**Measurements of Tensile Strength and Ductility** The tensile strength and ductility of the gummi drug was measured using an autoograph (AG-I, Shimadzu Co., Kyoto, Japan). The gummi drug was pulled upward at a tensile speed of 100 mm/min to measure the tensile strength (i.e., when the test force reached a maximum value). Furthermore, the distance up to the point where the test force became zero again was measured, and was defined to be the ductility.

**Measurement of the Dissolution Rate of Aripiprazole from the Gummi Drug** A dissolution test was conducted in accordance with JP Dissolution Test Method 2 (paddle method) using a JP dissolution tester (VK7010; Varian, Inc., Cary, NC, U.S.A.). The study was conducted in 900 mL of JP 1st fluid and diluted Mcllvaine buffer (pH 1.2 and 5.0, respectively) as the dissolution medium with a paddle speed of 50 rpm at 37±0.5°C for one tablet or iOD-G. Samples of iOD-G were used without division, or were divided into 2–8 pieces. Samples of dissolved solutions were withdrawn at 5, 10, 15, 30, 45 and 60 min.

**Measurement of Impurities in the Gummi Drug**

A total of 12 mL of HPLC mobile phase was added to a piece of iOD-G to dissolve it by warming it at ≈40°C. Citrate buffer (pH 4.7) containing 0.01 m lauryl sodium sulfate/acetonitrile (55/45) was used as a mobile phase. A filtrate sample solution was made using a membrane filter with a pore size of 0.45 µm (Ekicrodisk 13CR; Pall Corp.) to filter the supernatant. We used an ultraviolet absorption photometer as a detector (wave-length, 254 nm). As an analytical column, YMC-Pack ODS-AM (5 µm, 4.6 mm id×250 mm; YMC Co., Ltd.) were used. Column temperature was set to 25°C. The flow rate of the mobile phase was 1 mL/min and the injection volume was 20 µL.

Measurements were undertaken for 40 min (twice as long as the retention time of aripiprazole). We calculated the ratio of the solvent peak and other peaks (excluding the peaks for placebo gummi) to the total peak area detected.

**Determination of Serum Concentrations of Aripiprazole in Beagle Dogs after Oral Administration of iOD-G and Abilify Tablets** Pharmacokinetics of aripiprazole after oral administration of iOD-G and Abilify tablet (6 mg) were studied in fasted male beagle dogs (7.5–9.0 kg, n=4). Animal experiments were approved by the Institutional Animal Care and Use Committee of Otsuka Pharmaceutical Co., Ltd. The iOD-G was divided into eight pieces in consideration of the way it would be chewed. The divided iOD-G and Abilify tablet were inserted into gelatin capsules (n=13, 3 mL; Torpac Inc., Fairfield, NJ, U.S.A.). Gelatin capsules were administered
by gavage with a randomized crossover design with six-day washout. After administration of the iOD-G and tablet, 40 mL of 1 N hydrochloric acid was administered via the oral route. Blood samples (0.5 mL) were taken from the antebrachial vein 0, 0.5, 1, 2, 3, 4, 6, 8 and 24 h after administration. Collected blood was placed in a tube (Separapid tube; Sekisui Chemical Co., Ltd., Tokyo, Japan) for 10 min at room temperature, and centrifuged at 1800×g for 10 min. Collected serum was stored at –20°C until measurement. Aripiprazole concentration in serum was measured using a liquid chromatography–tandem mass spectrometry system with electrospray ionization.

Data Analyses  Pharmacokinetic parameters of the in vivo absorption study were calculated using a non-compartmental analysis method. The maximum concentration of aripiprazole in serum (C_{max}) was used as observed data. The area under the plasma concentration versus time curve from 0 h to 24 h (AUC_{0–24 h}) was obtained using the trapezoidal rule.

Data are the mean±standard deviation (S.D.). Statistical analyses were done by the Student’s t-test or Dunnett’s multiple comparison test using Prism v5.02 (Graphpad Software, San Diego, CA, U.S.A.). A p<0.05 was considered significant.

Results and Discussion

We developed preparations of gummi drugs as hospital formulations using clinically available formulations of aripiprazole. Then, we assessed the pharmaceutical characteristics of gummi drugs to increase drug-treatment options against psychiatric disorders in which improvement of medication adherence is considered to be important.

Gummi Drugs Prepared by Modifying Three Commercially Available Aripiprazole Formulations

We were able to form each of OD-G, PW-G and OS-G as gummi drugs, which were prepared by commercially available formulations, Abilify ODT, PW and OS, respectively. In terms of appearance, OD-G was transparent white, PW-G was shiny opaque white, and OS-G was chalky white with a rough surface (Fig. 4). OD-G and PW-G could be molded using a plastic plate. However, we were unable to mold OS-G even though we had changed the composition of the gummi. Therefore, we created a trapezoidal pocket and pressed the plastic plate to the surface of corn starch, and then poured the sol gummi drug. Thus, we were able to mold the gummi drug with the OS. We thought this was possible because, on the gummi surface where the sol was formed, water was absorbed by the layer of starch powder and the surface became solidified.

Pharmaceutical Evaluation of Gummi Drugs

Table 2 shows the average drug content, penetration, tensile strength, and ductility of OD-G, PW-G and OS-G. Target drug content of the gummi formulation was 6 mg. All formulations exceeded 95% of the target, which is the standard value of quality management of factories producing formulations for pharmaceutical companies. Furthermore, the penetration, tensile strength and ductility of OD-G, PW-G and OS-G were different among gummi drugs. These results showed that the physical properties of the gummi drug were dependent upon differences in commercial formulations (i.e., ODTs, PW and OS) used during preparation. Penetration for PW-G was large, whereas tensile strength and ductility were small. These results suggested that PW-G was soft and easily broken if pulled, and that elasticity (a specific characteristic in gummi drugs) might be weak in PW-G. Conversely, because tensile strength and ductility in OS-G was the greatest, this formulation of gummi drug was considered to be soft. In case of PW-G preparation, PW contains much more solids additives than the other formulations, and these additives would have gelatin-gelatin bond (e.g. hydrogen bond) weaken. As the result, PW-G was easily broken. As to OS-G, OS contains liquid additives (e.g. glycerin), and the physical properties of OS-G could be influenced by these additives. For OD-G, the tensile strength and ductility was intermediate between PW-G.
and OS-G, and its lower penetration showed OD-G to be soft. Thus, OD-G was considered to have the most suitable hardness and elasticity as a gummi drug. To date, the standard or suitable values of physical properties (penetration, tensile strength and ductility) of gummi drugs are not clear. Thus, it may be useful to estimate these values of gummi drugs in both settings of industrial development and clinical use.

**Improved Gummi Drugs with High Aripiprazole Content (iOD-G)** Comparing the three gummi drugs in terms of appearance, moldability, and ease of preparation at hospitals or community pharmacies, OD-G was considered to be the most suitable. Next, we prepared gummi drugs with high aripiprazole content by making the gummi weight smaller (from 7 g to 3.5 g) without changing the content per gummi drug (6 mg). Thus, we improved the formulation of OD-G (iOD-G).

Furthermore, as a pH-adjusting agent of gummi drugs, we changed to citric acid (used widely as a food additive) from hydrochloric acid. As a result, it became possible to prepare improved gummi drug with high aripiprazole content. The appearance exhibited a semi-translucent white (just like OD-G) (Fig. 4b).

**Pharmaceutical Evaluation of iOD-G** Average content of iOD-G was 100% (Table 3). Furthermore, we conducted a content uniformity test of the JP using the three lots that had been prepared separately. All three lots met the standard (data not shown). Thus, we showed that uniform formulations could be employed as hospital preparations.

We conducted a dissolution test for Abilify tablets (6 mg), Abilify ODTs (6 mg) and iOD-G. Figure 5 shows the dissolution rate of Abilify ODT and iOD-G. In the test solutions, gummi drugs were gradually getting small, and then dissolved completely between 15 and 30 min. Average dissolution rate of tablets, ODTs and iOD-G in 15 min was 95.7%, 98.5% and 72.4% at pH 1.2, and 46.7%, 91.3% and 58.9% at pH 5.0, respectively. The dissolution property of iOD-G without division showed a value between the commercially available tablets and ODTs at pH 5.0. At pH 1.2, however, dissolution in iOD-G without division was slower than that observed in tablets.

If patients take gummi drugs, they are assumed to be chewed and divided into several pieces. Thus, the dissolution test was conducted with iOD-G divided into 2–8 pieces (Fig. 5). It was found that, as the number of divisions increased, the speed of dissolution also increased. Average dissolution rate when iOD-G was divided into eight pieces in 15 min was >90% at pH values of 1.2 and 5.0. Therefore, it was suggested the dissolution of iOD-G was close to those of commercially available aripiprazole tablets and ODTs, and that bioequivalence would be obtained if patients chewed iOD-G.

**Preservation of Improved Gummi Drug That Contains High Aripiprazole Content (iOD-G)** We considered storage conditions in clinical settings (e.g., pharmacies, patients’ homes) and assessed the storage stability of iOD-G for 1 month at 4°C and 30°C (Table 3). Drug content of aripiprazole in iOD-G was not changed significantly at 4°C and 30°C, and retained ≥95% of loaded content (6 mg). With regard to the dissolution of aripiprazole from gummi drugs, as well as the tensile strength and ductility of gummi drugs, obvious changes were not observed (Table 3). Thus, these results confirm excellent preservation of iOD-G in terms of content and pharmaceutical properties as hospital formulations.

We also examined the impact on the amount of impurities in the drugs upon 1-month storage of gummi drugs (Table 4).
After storage at 4°C for 1 month, none of the peaks appeared to exceed the threshold (0.1%), which had to be reported according to International Conference on Harmonization (ICH) guidelines. However, after 1-month storage at 30°C, the total amount of the impurity increased significantly compared with the amount of the impurity at the time of starting storage. One impurity (peak number 5 in Table 4) that exceeded the threshold required on the ICH guideline was confirmed. Thus, it was determined that the storage condition at 30°C was not desirable from the aspect of impurity. It was assumed that gummi drugs should preferably be stored at a low temperature.

Pharmacokinetics of Aripiprazole after Oral Administration of iOD-G in Beagle Dogs

To assess the pharmacokinetics of aripiprazole after oral administration of iOD-G, the time course of serum drug concentrations were determined in beagle dogs, and compared with that of Abilify tablets (6 mg) (Fig. 6). The Cmax of Abilify tablets and iOD-G was 37.3±30.4 and 47.3±34.0 ng/mL, and the AUC0-24h was 312±289 and 377±421 h·ng/mL respectively. Cmax and AUC0-24h of iOD-G were 1.3- and 1.2-times, respectively, higher than those of Abilify tablets, though significant differences in these pharmacokinetic parameters were not observed. However, there are inter-species differences in the bioavailability of aripiprazole between humans and dogs (unpublished data). Bioavailability of aripiprazole (5 mg) in humans has been reported to be 86.6%, which is high compared with that in dogs. Therefore, it was assumed that similar differences would not be shown if iOD-G was administered in humans, though it would be necessary to conduct a pharmacokinetic study in humans in the future.

Conclusion

We were able to develop gummi drugs using commercially available aripiprazole products as hospital formulations. Furthermore, we prepared the improved OD-G and iOD-G (which contained high aripiprazole content). Pharmaceutical characteristics of iOD-G were demonstrated to be suitable for a hospital formulation, and iOD-G could be stored for ≤1 month. Significant differences in the dissolution and pharmacokinetics of divided iOD-G were not observed compared with commercially available aripiprazole products. Because of this study, a new dose form of aripiprazole in a gummi formulation can be developed as a hospital formulation. Gummi drug, which is a confectionary shaped dosage forms, is easily taken by chewing, and swallowed without water. Thus, it is considered that schizophrenia patients who have poor adherence to
taking medication, could naturally take this formulation in their daily life, and that the gummi drug will contribute to the improvement of the adherence.

Acknowledgments Authors are grateful to Ms. Tomoka Maeda, Ms. Miki Ozawa, Ms. Sayuri Nakajima, and Ms. Wakana Shibakiri for their excellent technical assistance.

Conflict of Interest The authors declare no conflict of interest.

References