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Basis to Aid Crisis: Favipiravir Oral Solution for Hospital Compounding During COVID-19 Drug Shortage

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ABSTRACT

The COVID-19 pandemic outbreak has been overwhelming the healthcare system worldwide. A rapidly growing number of younger pediatric patients in Thailand necessitated the formulation of favipiravir, the most locally accessible antiviral agent against COVID-19, into a child-friendly dosage form as a safer alternative to a dispersion of crushed tablets in simple syrup. While striving to quickly develop a liquid formulation that is feasible for any local hospital production units, an oral solution was chosen due to its simplicity. Despite the large dose and poor aqueous solubility of favipiravir, a combination of pH control and use of poloxamer as a solubilizing agent has enabled us to streamline the manufacturing process of a 200 mg/15 mL oral solution for hospital compounding. To ensure its efficacy and safety, a specification for quality control was also established in accordance with the ICH quality guidelines and USP. The finished product stability was subsequently demonstrated under the conditions of 5°C ± 3°C, 25°C ± 2°C/75% RH ± 5% RH, 30°C ± 2°C/75% RH ± 5% RH, and 40°C ± 2°C/75% RH ± 5% RH. The results indicated that our formulation can be stored at 30°C ± 2°C/75% RH for 30 days, which will very well serve the need to allow drug distribution and patient use during the crisis, while the shelf-life can be extended to 60 days when stored at 5°C ± 3°C. Thus, accessibility to an essential medical treatment has been successfully enhanced for pediatric patients in Thailand and neighboring countries during the COVID-19 outbreak.

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Introduction

The pandemic outbreak of COVID-19 caused by SARS-CoV2 virus has been ongoing since early 2020 and continues to overwhelm the healthcare systems of most countries worldwide beyond their capacities. The time constraints imposed by the ultrafast pace of its spread precludes the development of any antiviral medications specifically against SAR-CoV2 infections. Consequently, the idea of re-proposing

a previously approved antiviral agent with SAR-CoV2 replication inhibitory potential could fulfill a pivotal role in COVID-19 treatments.

Favipiravir, 6-Fluoro-3-hydroxypyrazine-2-carboxamide, is a pro-drug of favipiravir-ribofuranosyl-5'-triphosphate that has been discovered through chemical library screening for antiviral agents against influenza viruses by Toyama Chemical Co., Ltd.¹ This drug is effective towards a wide range of influenza viruses, including A (H1N1), A(N5N1), A(H7N9), and Ebola virus, and thus, indicated for the treatments of novel or re-emerging influenza virus infections unresponsive to other anti-influenza agents,² especially in Ebola disease.^{3,4} Its RNA-dependent RNA polymerase inhibitory activity makes favipiravir a very promising candidate in combating COVID-19. To date, favipiravir has been employed in the COVID-19 treatments in several countries.^{5–9} Since March 2020, this molecule has been serving as a drug of choice in Thailand and also incorporated by the Thailand Ministry of Public Health into the Guidelines on Clinical Practice, Diagnosis, Treatment, and Prevention of Healthcare-associated Infection for COVID-19.¹⁰ For patients weighing under 90 kg, the

Abbreviations: %LA, percent label amount; BCS, Biopharmaceutics Classification; COVID-19, coronavirus disease; DMSC, Department of Medical Sciences; EDTA, ethylenediaminetetraacetic acid; HPLC, high-performance liquid chromatography; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; IMWP, International Meeting of World Pharmacopoeias; Lot No, lot number; MP, methylparaben; PP, propylparaben; RH, relative humidity; RNA, ribonucleic acid; RP-HPLC, Reversed-phase high-performance liquid chromatography; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; USP, United States Pharmacopeia; WHO, World Health Organization.

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loading dose is 3600 mg (in two divided doses), followed by 1600 mg per day (in two divided doses) on days 2 to 5. In contrast, the adjusted doses for patients over 90 kg are 4800 and 2000 mg per day, respectively, while pediatric patients are recommended to take 70 mg/kg/day on day 1, and 30 mg/kg/day thereafter. These regimens have been highly efficacious in mild COVID-19 cases in Thailand.

Driven by the rapid increase in pediatric cases in Thailand where only favipiravir tablets are commercially available, an urgency existed to formulate this drug into a more child-friendly dosage form so that both dosing accuracy and patient compliance could be improved over those achieved with a dispersion of crushed tablets in simple syrup. Another important factor to consider was the feasibility of the manufacturing procedure since the developed formulation would ultimately become an extemporaneous preparation for any local hospitals throughout Thailand where production facilities are extremely limited. As a result, a simple oral solution of favipiravir was established.

Experimental

Materials

The following materials were used in the formulation; favipiravir (Raghava Life Sciences Pvt. Ltd., India), poloxamer 188 (BASF Corporation, USA), aspartame (Nantong Changhai, China), propylene glycol (Dow Chemical Thailand Ltd., Thailand), methylparaben (Zhejiang Shengxiao, China), propylparaben (Clariant, Germany), raspberry flavor (Bush Boake Allen, Singapore), vanilla flavor (Sigmadex, Switzerland), edetate disodium (EDTA) (Carlo Erbo, Italy), sodium citrate (Weifang Ensign Industry, China), sodium hydroxide (Carlo Erbo, Italy), sunset yellow dye (Sensient, Mexico), and sodium chloride (Dominion Salt Limited, New Zealand). For quality control work, favipiravir DMSc reference standard (Lot no. 01A63221, potency 994.8 $\mu\text{g}/\text{mg}$) was purchased from the Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Thailand. Methylparaben working standard (Lot no. M030121, potency 100.48%) and propylparaben working standard (Lot no. P140121, potency 99.87%) were provided by Medica Innova Co., Ltd. (Thailand). Acetonitrile (HPLC grade from RCI Labscan, Thailand), methanol (HPLC grade from RCI Labscan, Thailand), triethylamine (AR grade from Merck, Germany), and phosphoric acid (AR grade from Merck, Germany) were used for HPLC analysis.

Formulation Development of Favipiravir Oral Solution

Due to time constraints, our efforts were focused on developing a homogeneous dosage form with a simplified manufacturing process. Favipiravir or 6-fluoro-3-hydroxypyrazine-2-carboxamide is commercially supplied as a white to light yellow powder that is sparingly soluble in acetonitrile and in methanol, while slightly soluble in water and in ethanol. We thus first experimented to obtain a suitable vehicle for a stable favipiravir oral solution. As shown in Fig. 1, favipiravir is a weak acid with a pKa of 5.1 so raising the solution pH to slightly above its pKa might be sufficient to maintain favipiravir in an aqueous medium. Citrate buffer was selected based on the pKa of citric acid at 3.1, 4.7, and 6.4. At an initial 16 mg/mL concentration of favipiravir, we found that 0.01M and 0.02M trisodium citrate could

not completely dissolve this drug substance. Therefore, its solubility was enhanced through both pH adjustment with sodium hydroxide and the use of poloxamer 188 as a solubilizing agent. The best results were obtained with 0.02M trisodium citrate containing 0.07% poloxamer 188 and 0.25 mL of 1M sodium hydroxide, in which favipiravir was completely dissolved at an optimum pH of 5.79 (Table 1). To simplify dose calculations during administration, the concentration was slightly adjusted to 800 mg of favipiravir per 60 mL (13.33 mg/mL), which was confirmed to be completely soluble in 0.02M citrate buffer when pH was greater than 5.8. For the flavoring agents, aspartame was selected as a sweetener while avoiding sucrose to prevent favipiravir from salting out. The unpleasant taste of favipiravir was further masked with sodium chloride, as well as raspberry and vanilla flavors. The commonly used methylparaben and propylparaben served as preservatives. The final formulation of favipiravir oral solution is shown in Table 2.

Hospital Compounding

Favipiravir oral solution was prepared on a scale of 15 L using an overhead stirrer. Favipiravir was first dissolved in a vehicle containing a buffering system (sodium citrate and sodium hydroxide) mixed with poloxamer 188, EDTA, and propylene glycol. The paraben solution was prepared by dissolving methylparaben and propylparaben in propylene glycol, and then added into the favipiravir mix, along with aspartame, sodium chloride, flavors, and colorant. The final product was a clear orange solution with a pH in the range of 5.80–6.20 and filled into 60-mL amber glass bottles. A diagram illustrating the hospital compounding process is shown in Fig. 2.

Specifications and Quality Control Tests

To ensure the product safety and efficacy, various quality attributes of the favipiravir oral solution were established according to The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) quality guidelines: ICH Q6A.¹¹ Despite being uncommonly required for extemporaneous preparations, the specifications of favipiravir oral solution were also justified for subsequent use in quality control tests and stability studies, simply to reflect safety and efficacy of the formulation rather than obtaining full quality data for drug registration. The analytical methods for identification, assay, organic impurities, and antimicrobial preservative contents were developed and validated specifically for use in this study. Procedures for pH determination and microbial limit test were adopted from the USP general chapters (791) pH¹² and (61) Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests,¹³ respectively.

Identification and assay of favipiravir were performed simultaneously with the determination of organic impurities in oral solution by using an LC-20AD HPLC system (Shimadzu, Japan) and a validated reversed phase HPLC (RP-HPLC) method that was developed in our laboratory. The stationary phase was Inertsil ODS-3, 250 mm x 4.6 mm, 5 μm (Shimadzu, Japan) maintained at 45°C in a column oven. The chromatographic conditions involved gradient elution with phosphate buffer pH 3.0 (mobile phase A) and a mixture of methanol and acetonitrile at 1:1 ratio (mobile phase B). The initial mobile phase composition was maintained at 98% mobile phase A for 5 min, then changed linearly to 70% mobile phase A (5–10 min), followed by a change to 5% mobile phase A (10–12 min), and reversed back to 98% mobile phase A (12–15 min), which was maintained for 5 min for column equilibration. The total run time of 20 min per injection (10 μL) at a flow rate of 1.0 mL/min. All analytes were detected at 220 nm. A favipiravir standard stock solution was prepared by accurately weighing 6.6 mg of favipiravir DMSc reference standard using analytical balance XP26DR (Mettler, Switzerland) and

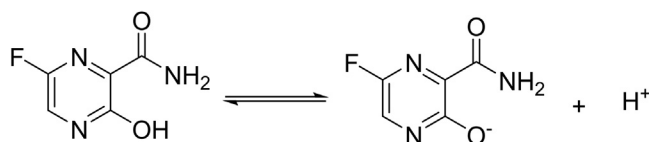


Figure 1. Chemical structure and ionization of favipiravir.

Table 1
Solubility Test of Favipiravir Under Various Conditions.

Trial	Composition	pH	Appearance
1	64 mg of favipiravir was dissolved in 4 mL of 0.01 M trisodium citrate containing 0.1% poloxamer 188 and 0.20 mL of 1 M NaOH was then added.	5.47	Incompletely soluble
2	64 mg of favipiravir was dissolved in 4 mL of 0.02 M trisodium citrate containing 0.14% poloxamer 188 and 0.25 mL of 1 M NaOH was then added.	5.77	Completely soluble
3	64 mg of favipiravir was dissolved in 4 mL of 0.02 M trisodium citrate containing 0.07% poloxamer 188 and 0.25 mL of 1 M NaOH was then added.	5.79	Completely soluble

The concentration of favipiravir in all trials was 16 mg/mL.

dissolving in a 1:1 mixture of acetonitrile and water to a final concentration of 0.66 $\mu\text{g/mL}$. All samples for assay were prepared by 1:50 dilution of the oral solution with acetonitrile and water (1:1), while the samples for impurity determination were prepared by 1:20 dilution of the oral solution with the same diluent.

For antimicrobial preservative contents, a methylparaben (MP) and propylparaben (PP) standard stock solution was prepared in acetonitrile and water (1:1) at a concentration of 45 $\mu\text{g/mL}$ and 5 $\mu\text{g/mL}$ respectively. Samples were prepared by 1:50 dilution of the oral solution with the same diluent. MP and PP in the oral solution were quantified by RP-HPLC with an LC-20AD HPLC system (Shimadzu, Japan). The stationary phase was Inertsil ODS-3, 4.6 \times 150 mm with 5 μm particle size and maintained at 45°C in a column oven. The mobile phase for isocratic chromatographic conditions was composed of acetonitrile and phosphate buffer (pH 3.0) at a ratio of 40:60 and a flow rate of 1.0 mL/min. The injection volume was 10 μL , and both parabens were detected with a UV detector at 220 nm. The amounts of MP and PP in each sample were calculated using a standard comparison. pH measurement was performed by using a pH meter (Model 827 from Metrohm, Switzerland).

Stability Study of Favipiravir Oral Solution

The chemical stability of favipiravir in aqueous solutions was expected to be low due to the sensitivity of amide functional groups to hydrolysis. However, even a month-long shelf-life would be sufficient for an extemporaneous formulation considering its usage during a crisis. Thus, the stability of our favipiravir oral solution was investigated to identify optimum storage conditions that can provide an acceptable shelf-life according to ICH Q1A.¹⁴ Two hospital production batches, CRAFV018 and CRAFV019, were also evaluated in this stability study. The test solutions were exposed to four conditions, i.e., 5°C \pm 3°C, 25°C \pm 2°C/75% RH \pm 5% RH, 30°C \pm 2°C/75% RH \pm 5% RH, and 40°C \pm 2°C/75% RH \pm 5% RH. Stability-indicating parameters, including appearance, assay, organic impurities, and pH, were then

determined on days 0, 7, 14, 30, 45, and 60, while the tests for antimicrobial preservative contents and microbial limits were performed only on days 0 and 60.

Results and Discussion

Formulation Development and Hospital Compounding of Favipiravir Oral Solution

Favipiravir tablets are rapidly dissolving such that 85% or more of the labeled amount of the drug substance dissolves within 30 minutes at pH 1.2 (0.1 N HCl), pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer), hence, no potential lag time in absorption is observed. In addition, favipiravir is considered as a highly permeable drug substance with a bioavailability of 97.6%.¹⁵ Based on the Biopharmaceutics Classification System (BCS), the safety and efficacy of favipiravir administered as a solution should therefore be comparable to those of tablet dosage form. On the other hand, a suspension formulation would require not only additional studies on dosage form performance, including dissolution profiles, but also a rather demanding preparation process, especially for hospital compounding. Considering these fundamentals, a favipiravir oral solution would be the most promising candidate to fulfill an unmet need of pediatric patients who prefer an easy-to-take dosage form. However, the challenges of oral solution formulation are to achieve sufficient quality and a suitable shelf-life that is long enough for distribution and patient usage.

Based on the chemical structure of favipiravir, amide hydrolysis and oxidation are potential major degradation pathways (Fig. 3). Mechanistically, hydrolysis of this compound is expected to increase at higher pH, where specific base catalysis can play an important role in amide hydrolysis. Moreover, the increased favipiravir anions can deprotonate water molecules, which further facilitate hydrolysis of amide functional groups. Therefore, solubility enhancement solely by adjusting pH could be problematic, while a combined use of

Table 2
Formulation of Favipiravir Oral Solution for Hospital Compounding.

Ingredient	Quantity per 60 mL	Quantity per 15 L	Function
Favipiravir	800 mg	200 g	Active ingredient
Poloxamer 188	42 mg	10.5 g	Solubilizing agent
Aspartame	84 mg	21 g	Sweetening agent
Propylene glycol	2400 mg	600 g	Solubilizing agent
Propylparaben	6 mg	1.5 g	Preservative
Methylparaben	54 mg	13.5 g	Preservative
Raspberry flavor	120 μL	30 mL	Flavoring agent
Vanilla flavor	60 μL	15 mL	Flavoring agent
EDTA	60 mg	15 g	Chelating agent
Sodium citrate	324.8 mg	81.2 g	Buffering agent
Sodium hydroxide	165.6 mg	41.4 g	pH adjustment
Sunset yellow dye	0.8 mg	0.2 g	Coloring agent
Sodium chloride	48 mg	12 g	Flavoring agent
Purified water	q.s. to 60 mL	q.s. to 15 L	Solvent

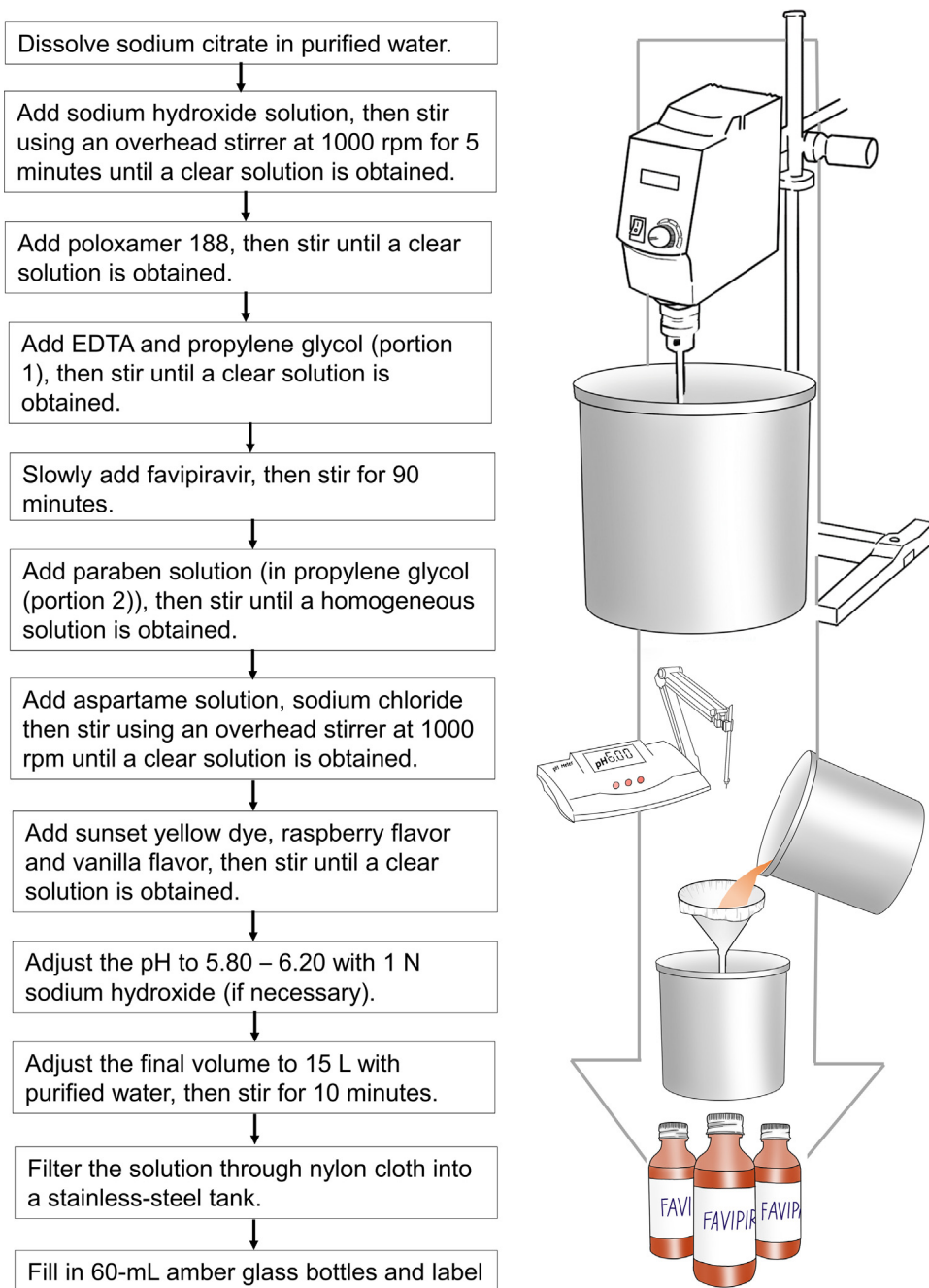


Figure 2. Hospital compounding process for favipiravir oral solution.

solubilizing agent(s) and optimum pH might help balance solubility and stability of the formulation. In the pH range of 5.80–6.20 generated by a citrate buffer system in the presence of favipiravir itself, more than half of drug molecules would be in the more soluble ionized form. Moreover, propylene glycol was used to lower the dielectric constant of the vehicle, while poloxamer188 served as a surfactant that enhances the solubility of favipiravir. As a result, a 200 mg/15 mL favipiravir solution was finally obtained with the excipients commonly used in oral formulations as listed in Table 2. The actual hospital preparation appeared as a clear orange solution filled in 60-mL amber glass bottles, as shown in Fig. 4.

In terms of the manufacturing process, only laboratory-scale glassware, a 20-liter stainless steel mixing tank, and a 1000-rpm overhead stirrer were required for hospital compounding on a 15L scale. The in-process control was also simple and involved

monitoring of appearance and pH. Thus, our primary goal was successfully achieved by developing a favipiravir oral solution with a simplified production process that would provide both product homogeneity and batch-to-batch consistency. More importantly, a recent pharmacokinetic comparison study has demonstrated that our 200 mg/15 mL oral solution exhibited similar pharmacokinetic profiles to those of the commercially available 200-mg favipiravir tablets.¹⁶ The strategies reported herein could also be modified for other nucleoside analogs, such as molnupiravir.

Specifications and Quality Control Analyses

The specifications of favipiravir oral solution were established and justified for use in the quality control of hospital preparation, as shown in Table 3. The quality attributes in the specifications were based on a

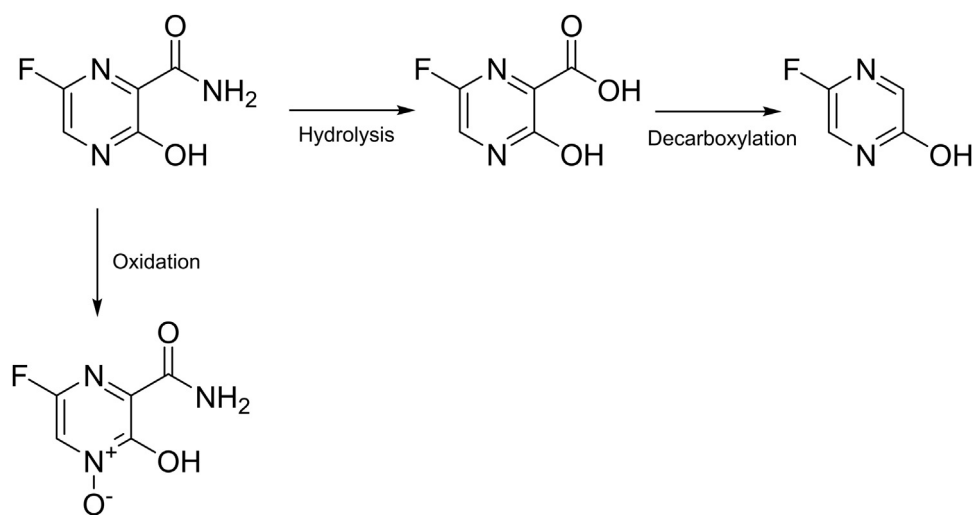


Figure 3. Potential degradation pathways of favipiravir.

set of universal tests and included appearance, identification, assay, and impurities, according to ICH Q6A. Specific tests required for favipiravir oral solution comprised of pH measurement, antimicrobial preservative contents, and microbial limit test. The acceptance criteria or limits for each test were justified based on available data of the reference favipiravir tablet, the general chapters of pharmacopeial monographs, and the ICH quality guidelines. Urgency of the crisis and a risk-based approach were also taken in consideration while justifying the specifications and acceptance criteria.

The appearance of favipiravir oral solution as a clear orange solution (Fig. 4) with raspberry flavor was the first criteria for quality control. On the basis that favipiravir raw material has already been well identified by both infrared spectroscopy and liquid chromatography, its identity in the drug product could be sufficiently confirmed based on RP-HPLC comparison with favipiravir reference standard. To ensure that the amount of active substance is in therapeutic range, the acceptance criteria for assay was set between 95.0% and 105.0%

labeled amount which aligns with both the specifications of favipiravir tablets currently available in the market and the 12th International Meeting of World Pharmacopoeias (IMWP) Monographs on Favipiravir and on Favipiravir tablets published by WHO.¹⁷ Although the IMWP monograph has also published an assay method for favipiravir tablets by isocratic HPLC, a validated in-house HPLC method was used in this study to allow simultaneous determinations of favipiravir along with organic impurities. As discussed previously, degradation of favipiravir in an aqueous oral solution is foreseeable, possibly through hydrolysis and oxidation (Fig. 3) as observed in a forced degradation study of favipiravir raw material during analytical method validation. Hence, both individual and total organic impurities need to be monitored. For the acceptance criteria, the concept of qualification threshold in ICH Q3B,¹⁸ which addresses the control of degradants in drug products, was considered. Based on the loading dose of favipiravir for COVID-19 treatments in adults weighing more than 90 kg, the maximum daily dose would be 4800 mg, and thus, the ICH Q3B qualification threshold would allow a limit of individual impurities only at 0.15%. However, this limit was expanded to 1.0% in our case when considering the short-term use of this product for COVID-19 treatments. This is very well in line with the concept of less than lifetime exposure to mutagenic impurities, an even more harmful class of impurities, described in the ICH M7 guideline¹⁹ allowing a higher acceptable limit based on shorter treatment duration. In contrast, a limit of 2.0% for total organic impurities was applied so that the amount of favipiravir remaining in the oral solution would still be in the therapeutic range.

Since the pH of an oral solution significantly impacts both the solubility and stability of favipiravir as demonstrated during formulation development, a rather narrow limit of 5.80–6.20 was suggested. In addition, the amounts of propylparaben and methylparaben were controlled under the antimicrobial preservative contents determined by RP-HPLC, and the acceptance limit between 90.0% and 110.0% labeled amount was assigned to ensure the effective and safety levels of preservatives. Last but not least, the microbial limits were also listed in the specifications to control the microbial contamination levels under the acceptance criteria that follows the USP general chapter (111) Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use.²⁰

The specifications designed for favipiravir oral solution were then used in the formulation screening during the development process, the stability studies for shelf-life and storage condition determinations, and the quality control tests for batch release.



Figure 4. Appearance of the actual favipiravir oral solution product from hospital compounding.

Table 3
Specifications of Favipiravir Oral Solution for Hospital Compounding.

Tests	Acceptance Criteria	Procedure
1. Appearance	Clear orange solution with raspberry flavor	Visual inspection
2. Identification	The retention time of the major peak in the chromatogram of the sample solution corresponds to that in the chromatogram of the standard solution, as obtained in the Assay	Validated RP-HPLC USP <621> Chromatography
3. Assay	95.0 - 105.0% labeled amount of favipiravir (C ₅ H ₄ FN ₃ O ₂)	Validated RP-HPLC USP <621> Chromatography
4. Organic impurities		Validated RP-HPLC USP <621> Chromatography
Any individual impurity	NMT ^a 1.0%	
Total impurities	NMT 2.0%	
5. Antimicrobial preservative contents		Validated RP-HPLC USP <621> Chromatography
MP ^b	90.0 – 110.0 %	
PP ^c	90.0 – 110.0 %	
6. pH	5.80-6.20	USP <791> pH
7. Microbial limits		USP <61> Microbiological examination of non-sterile products: Microbial enumeration tests
TAMC ^d	10 ² cfu/mL	
TYMC ^e	10 ¹ cfu/mL	
<i>Escherichia coli</i>	Absent in 1 mL	

^a NMT, not more than.

^b MP, methylparaben.

^c PP, propylparaben.

^d TAMC, total aerobic microbial count.

^e TYMC, total yeast and mold count.

^f cfu, colony-forming unit.

Stability of Favipiravir Oral Solution

The main goal of this study was to develop a sufficiently stable favipiravir formulation for patient use under hospital monitoring, and therefore, a one-month period was considered practical. The physicochemical and microbiological stabilities of our favipiravir oral

solution, including the two hospital production lots of CRAFV018 and CRAFV019, were evaluated under four conditions, i.e., 5°C ± 3°C, 25°C ± 2°C/75% RH ± 5% RH, 30°C ± 2°C/75% RH ± 5% RH, and 40°C ± 2°C/75% RH ± 5% RH, in either a refrigerator or a stability chamber. All tests in the specifications, except for identification, were performed. Interestingly, the appearance of our oral solution remained

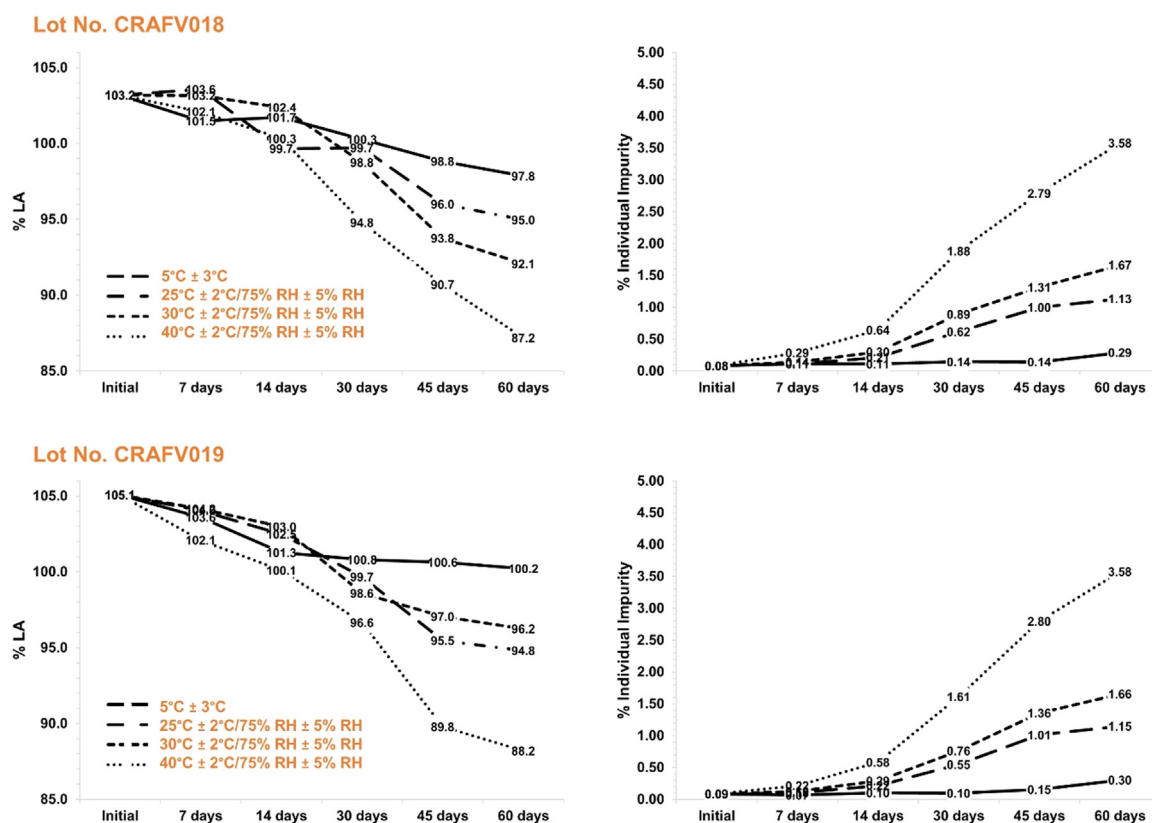


Figure 5. Assay (shown as %LA) and individual impurity results from the stability studies of the favipiravir oral solution from Lot No. CRAFV018 and CRAFV019 during up to 60-day storage at 5°C ± 3°C, 25°C ± 2°C/75% RH ± 5% RH, 30°C ± 2°C/75% RH ± 5% RH, and 40°C ± 2°C/75% RH ± 5% RH.

Table 4
Stability Study of the Favipiravir Oral Solution from Hospital Compounding at 30°C ± 2°C and 75% RH ± 5% RH.

Tests	Acceptance Criteria	Lot no. CRAFV018						Lot no. CRAFV019					
		Initial	7 days	14 days	30 days	45 days	60 days	Initial	7 days	14 days	30 days	45 days	60 days
		Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
1. Appearance	Clear orange solution with raspberry flavor	103.2	103.2	102.4	98.8	93.8	92.1	105.1	104.2	103.0	98.6	97.0	96.2
2. Assay	95.0 – 105.0%	0.08	0.14	0.30	0.89	1.31	1.67	0.09	0.12	0.29	0.76	1.36	1.66
3. Organic impurities	NMT 1.0%	0.08	0.23	0.42	1.29	1.61	2.69	0.09	0.19	0.40	0.76	1.72	2.56
Any individual impurity	NMT 2.0%	101.5	NA ^a	NA	NA	NA	100.9	101.6	NA	NA	NA	NA	101.2
Total impurities	90.0 – 110.0%	92.5	NA	NA	NA	NA	94.3	96.9	NA	NA	NA	NA	98.5
4. Antimicrobial preservative contents	90.0 – 110.0%	6.00	5.98	5.97	5.93	5.91	5.87	6.01	5.99	5.98	5.95	5.90	5.87
MP ^b	90.0 – 110.0%	< 100	NA	NA	NA	NA	< 100	< 100	NA	NA	NA	NA	< 100
PP ^c	90.0 – 110.0%	< 10	NA	NA	NA	NA	< 10	< 10	NA	NA	NA	NA	< 10
5. pH	5.80–6.20	Absent	NA	NA	NA	NA	Absent	Absent	NA	NA	NA	NA	Absent
6. Microbial limits	< 100 cfu/mL												
TAMC ^d	< 10 cfu/mL												
TYMC ^e	Absent in 1 mL												
<i>Escherichia coli</i>													

^a NA, not applicable.

^b MP, methylparaben.

^c PP, propylparaben.

^d TAMC, total aerobic microbial count.

^e TYMC, total yeast and mold count.

^f cfu, colony-forming unit.

unchanged under all testing conditions through the end of 60-day storage. While the pH was well within the acceptance limit, a slightly drop below 6.0 might be explained by the degradation of favipiravir to an acid degradant²¹ shown in Fig. 3. This assumption was substantiated by the significant changes observed during the assay and organic impurity determination, in which the individual impurities from the degradation of favipiravir were rising as the %LA dropped (Fig. 5). These results also confirmed the direct effects of storage temperature on drug degradation. As expected, when stored in a refrigerator, the favipiravir content was maintained above the lower limit of 95.0% until the end of study, whereas the samples from Lot No. CRAFV019 that were exposed to accelerated conditions of 40°C ± 2°C/75% RH ± 5% RH failed the assay test upon 30-day storage, and the %LA dropped below 90% after 60 days. The same trend was observed with the organic impurities. For example, under refrigerated conditions, the degradation of favipiravir was slowed down such that the levels of individual impurities remained below the acceptance limit of 1.0% throughout the 60-day period of stability studies. Interestingly, favipiravir precipitation was not observed after refrigerated storage, which helps lessen a common concern when handling poorly soluble drug substances. Although the best storage condition for favipiravir oral solution was 5°C ± 3°C in a refrigerator, a more practical option of 30°C ± 2°C/75% RH was selected to correspond with most patients' preference of storing medicine under ambient conditions despite Thailand being in a hot and humid climate zone. Based on the stability data at 30°C ± 2°C/75% RH from Table 4, the shelf-life of favipiravir oral solution was determined to be 30 days, after which the individual impurities increased above 1.0% limit although all other quality attributes still met the acceptance criteria. Because 30 days period is a practical shelf-life for drug distribution and patient use, storage at 30°C ± 2°C/75% RH was suggested. In the case where a longer shelf-life is needed, the recommended storage condition would be refrigeration, and the shelf-life could be extended to 60 days.

Conclusion

Our collaborative efforts between hospital, academia, and industry have led to a successful development of a favipiravir oral solution in response to an urgent demand for COVID-19 treatments in pediatric patients requiring an alternative dosage form to ease drug administration and improve compliance over that of conventional tablets. Albeit with time constraints during the crisis, we utilized pharmaceutical science concept for formulation development and simplified the manufacturing process for hospital compounding. The quality attributes and specifications of our favipiravir oral solution were justified according to ICH quality guidelines and pharmacopeial monograph to ensure safety and efficacy of the formulation. Stability studies were also performed to determine suitable storage conditions and shelf-life. The finished product from this work has been helping thousands of pediatric patients during COVID-19 outbreak in Thailand.

Declarations of Interest

The authors declare no conflict of interest.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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