

# REVIEWS OF THERAPEUTICS

## Extemporaneous Compounding of Oral Liquid Dosage Formulations and Alternative Drug Delivery Methods for Anticancer Drugs

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Oncology pharmacists face a constant challenge with patients who cannot swallow oral anticancer drugs, making extemporaneous oral liquid preparation a requirement. Improper extemporaneous preparation of these agents, especially with the traditional chemotherapy with a narrow therapeutic index, may increase the risk of over- or underdosing. In community pharmacies, multiple barriers exist that prevent these pharmacies from preparing extemporaneous oral anticancer drug formulations for a patient's use at home. In a home setting, patients or caregivers without proper counseling and education on how to safely handle chemotherapy are at increased risk for exposure to these drugs. Based on a review of the literature, compounding recipes are available for 46% of oral anticancer agents. A paucity of data exists on dose uniformity, bioequivalence, and stability of extemporaneous oral liquid formulations of anticancer drugs. Pharmacists must have an understanding of the basic scientific principles that are an essential foundation for the proper preparation of extemporaneous oral anticancer liquid formulations. The collaborative effort of a multidisciplinary team can also help identify different barriers in the community setting, especially in areas where community pharmacies may lack resources for the extemporaneous compounding of oral chemotherapy, and to find ways to coordinate better pharmaceutical care. There are great opportunities for oncology pharmacists, as well as community pharmacists, as a resource for educating and monitoring patients receiving oral chemotherapy to ensure dosing accuracy, safe administration, and proper disposal of hazardous drugs. Development of national guidelines to promote standards of practice in the community and/or home setting is urgently needed to help improve the safety of dispensing and handling oral chemotherapeutic agents, including extemporaneously compounded oral liquid formulations of these drugs.

**Key Words:** extemporaneous, compounding, stability, bioavailability, chemotherapy, oral anticancer drugs.

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### OUTLINE

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Major Factors Involved in Extemporaneous Oral  
Liquid Preparation  
Excipients  
Stability  
Bioavailability

Palatability  
Alternative Delivery Methods to Extemporaneous Oral  
Liquid Formulations  
Crushing Tablets or Opening Capsules  
Tablet or Capsule Dispersion  
Oral Administration from Injectable Form  
Extemporaneous Oral Liquid Preparation Through a

Feeding Tube  
Current Practices and Challenges of Extemporaneous  
Compounding in the Community Setting  
Adherence and Safe Handling of Oral Anticancer  
Agents in the Home Setting  
Role of the Pharmacist and Recommendations  
Conclusion

In the past 10 years, the use of oral anticancer agents for the treatment of various types of cancer has been increasing. Of all the cancer therapies under clinical development, 20–25% are expected to be oral.<sup>1, 2</sup> Currently in the United States, more than 40 oral agents have been approved for the treatment of cancer. The intravenous-to-oral switch process and the development of oral anticancer therapies for long-term daily use will most likely continue to evolve.

In adult oncology, patients with gastric or head and neck cancer, as well as the elderly, often experience swallowing problems or dysphagia. These patients may have difficulty with orally ingesting solid forms of drugs (e.g., tablets and capsules). Some of these patients may require feeding tubes to help them maintain normal nutrition. In nursing home or long-term care settings, a common practice for nurses is to crush pills and mix them in a liquid or other food for ease of administration for elderly patients with swallowing difficulties.<sup>3–7</sup> One survey found that some of the pills that were crushed in a nursing home included anticancer therapy such as tamoxifen.<sup>5</sup> This practice also occurs in a home setting where patients who cannot swallow pills, or their caregivers, are advised by some general practitioners or nurses to crush the pills and mix them into soft food or juices.<sup>8</sup> Because of limited availability of pediatric drug formulations, pharmacists commonly reformulate adult-strength drug products to meet the small dosing requirements for pediatric patients.<sup>9–14</sup> According to the United States Food and Drug Administration, no pediatric-specific formulation of any anticancer drug has been approved for the U.S. market.<sup>9</sup> Although most oral anticancer agents

are not controlled-release or enteric-coated products, most of them have a film coating designed to prevent health care personnel or patients from coming into direct contact with the drug and/or to mask the unpleasant taste.

Oncology pharmacists face the challenge of dealing with oral anticancer drugs that are not available in liquid dosage forms, and extemporaneous preparation of oral liquid formulations is required. Data on dose uniformity and stability of extemporaneous oral liquid formulations of oral anticancer drugs are scarce. Few studies have evaluated the bioequivalence and safety of administering extemporaneously prepared oral anticancer agents, either mixed with fluids or flushed through a feeding tube. When extemporaneously compounding oral chemotherapeutic agents with a narrow therapeutic index that are not properly prepared, one may also raise a concern of an increased risk of over- or underdosing, leading to increased adverse events or decreased effectiveness, respectively. In the community and home settings, oral chemotherapy agents are often dispensed or administered without proper safeguards.<sup>7</sup> Patients or caregivers without adequate counseling and education on how to safely handle these agents may also be at an increased risk of exposure to these hazardous drugs.<sup>7, 15</sup>

The goals of this article are to provide a general understanding of the fundamental principles of and major factors involved in extemporaneous preparation of oral liquids; to provide and discuss data on extemporaneous compounding and other alternatives to formulation of oral anticancer liquid dosage forms that were found in literature; to discuss the challenges that health care providers, patients, and caregivers face in terms of safe handling and disposal of extemporaneously prepared hazardous drugs in community and home settings; and to discuss the role of the pharmacist and provide recommendations.

## Literature Search

As a first step, all oral anticancer drugs available on the U.S. market and nine of the most commonly used adjunct agents in the oncology setting were identified. Then we performed a PubMed literature search (1966–May 2010) for all studies published in the English language by using the generic name of the identified drugs and the following search terms: extemporaneous formulations, oral liquid or suspension, compounding, anticancer therapy, antineoplastic agent, stability, pharmacokinetic, and bioavailability.

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Table 1. Summary of Extemporaneous Oral Liquid Preparation of Oral Anticancer Therapy and Stability Data

Drug	Dosage Forms	Extemporaneous Oral Liquid Formula
Altretamine <sup>20</sup>	Capsule (powder): 50 mg	No data
Aminogluthethimide <sup>21, 22</sup>	Tablet (uncoated, scored into quarters): 250 mg	No data
Anastrozole <sup>23</sup>	Tablet: 1 mg	No data
Azathioprine <sup>24–26</sup>	Injection, powder for reconstitution: 100 mg Tablet (scored): 25, 50, 75, and 100 mg	Method 1: 50-mg/ml oral suspension is prepared by crushing 120 x 50-mg azathioprine tablets into a fine powder in a mortar, transferring the powder into an amber glass bottle, and adding a sufficient quantity of a 1:1 mixture of Ora-Sweet SF and Ora-Plus, a 1:1 mixture of Ora-Sweet and Ora-Plus, or cherry syrup to make a final volume of 120 ml Method 2: 50-mg/ml oral suspension can be prepared by crushing 60 x 50-mg tablets into a fine powder in a mortar, transferring the fine powder into an amber glass bottle, adding 20 ml of methylcellulose followed by shaking the mixture to create a uniform paste, and adding the flavoring agent in a sufficient quantity of a 2:1 simple syrup:cherry syrup mixture to bring the volume to 60 ml
Bexarotene <sup>27, 28</sup>	Capsule (soft gelatin): 75 mg Gel: 1% 60-g tubes	1-mg/ml oral suspension can be prepared by first cutting a capsule in half, then the interior of the capsule is rinsed and suspended in 75 ml of water and used immediately
Bicalutamide <sup>29</sup> Busulfan <sup>30–34</sup>	Tablet (film-coated): 50 mg Injection, solution: 6 mg/ml (10 ml) Tablet (film-coated, scored): 2 mg	No data Method 1: 2-mg/ml oral suspension is prepared by crushing 120 x 2-mg tablets into a fine powder in a mortar, levigating with a small amount of simple syrup and mixing to make a uniform paste, adding simple syrup to almost 120 ml, transferring contents into a graduated cylinder, rinsing mortar and pestle with simple syrup, and transferring to the graduated cylinder, to make a final volume of 120 ml. Transfer contents of the graduated cylinder into an amber prescription bottle. Method 2: Busulfan tablets may be crushed and mixed with water for nasogastric tube administration
Capecitabine <sup>35–36</sup>	Tablet (film-coated): 150 and 500 mg	Place four 500-mg capecitabine tablets in approximately 200 ml of lukewarm water (50 ml/500-mg tablet) and stir for about 15 min until the tablets dissolve
Chlorambucil <sup>25, 37</sup>	Tablet (film-coated): 2 mg	2-mg/ml oral suspension can be prepared by crushing 60 x 2-mg tablets in a mortar, transferring the fine powder to an amber glass bottle, mixing the powder with 30 ml of methylcellulose, and adding sufficient quantity of syrup to make a final volume of 60 ml
Cyclophosphamide <sup>38–41</sup>	Injection, powder for reconstitution: 500 mg, 1 g, 2 g (contains mannitol 75 mg/cyclophosphamide 100 mg) Tablet: 25 and 50 mg	Method 1: 2-mg/ml oral suspension can be prepared by dissolving desired amount of lyophilized cyclophosphamide for injection in a sufficient quantity of aromatic elixir <sup>b</sup> in an amber glass bottle to make a final concentration of 2 mg/ml Method 2: 20-mg/ml oral suspension can be prepared by dissolving desired amount of lyophilized cyclophosphamide for injection in a sufficient amount of normal saline, compounded 1:1 with either simple syrup or Ora-Plus in an amber glass bottle Method 3: 10-mg/ml oral suspension can be prepared by dissolving 1 g of lyophilized cyclophosphamide for injection in 50 ml of 0.9% sodium chloride injection and adding a sufficient quantity of either simple syrup or Ora-Plus to a final volume of 100 ml in an amber glass bottle

Table 1. (continued)

Storage and Stability, and Label Information	Codes <sup>a</sup>	Comments
No data	A	
No data	A, C, J	Bioavailability of oral tablets is equal to that of solution
No data	A	
Method 1: 60 days at room temperature and under refrigeration at 5°C Shake well, protect from light Method 2: 56 days at room temperature, 84 days when refrigerated Shake well, refrigerate	A, C, F	
No data; drink the liquid immediately, then rinse glass with half a glass of water and consume to ensure administration of full dose	A, F, H, J	Oral suspension and oral swallowed capsules are bioequivalent Do not disperse capsules or drink the suspension with grapefruit juice
No data	A	
Method 1: 30 days when stored under refrigeration Shake well, refrigerate Method 2: No data	A, C, F, J	When stored at room temperature, stability is only 2 days at which only 95.7% of the drug remains, and after 3 days, only 90.8% remains Drug monitoring and individual dosage adjustment should be considered because of the variability in busulfan bioavailability and wide interpatient variability regardless of what oral formulation is used
No data; drink the liquid immediately, then rinse the glass with half a glass of water and consume to ensure administration of full dose	A, D, F	Bitter taste of the solution can be flavored with fruit juice or squash, but grapefruit juice should not be used; the solution may also be administered through a nasogastric tube or other enteral feeding tube
7 days when refrigerated Shake well, refrigerate, protect from light	A, C, F	Potency dropped < 90% in less than 24 hrs at room temperature
Method 1: 14 days when refrigerated Shake well, refrigerate Method 2: At least 56 days in both simple syrup and Ora-Plus when refrigerated; 8 days in simple syrup at room temperature and 3 days in Ora-Plus at room temperature Shake well, refrigerate The rate of degradation was not studied with respect to light conditions; the authors suggested storing the suspension in the dark or using amber syringes Physical stability (odor, color, and consistency of the suspension) remained unchanged at the end of the study There was no evidence of microbial growth Method 3: Storage at room temperature resulted in 10% degradation of the drug in 10.6 days in simple syrup and in 6.0 days in Ora-Plus	A, C, F	Tablets can be crushed but manufacturer recommends to use injection powder for reconstitution for making oral liquid Methods 2 and 3 may be preferred due to their simplicity in preparation and longer stability, and aromatic elixir is no longer commercially available

Table 1. Summary of Extemporaneous Oral Liquid Preparation of Oral Anticancer Therapy and Stability Data (continued)

Drug	Dosage Forms	Extemporaneous Oral Liquid Formula
Dasatinib <sup>42, 43</sup>	Tablet (film-coated): 20, 50, 70, and 100 mg	Add proper dose of dasatinib to 30 ml of chilled 100% orange juice or apple juice without preservatives, and let stand. After 5 min, swirl the contents of the drinking container for 3 sec, and repeat every 5 min until the total time is 20 min from when the tablet was added. Swirl the contents of the drinking container one last time, then drink immediately.
Erlotinib <sup>44-47</sup>	Tablet (film-coated): 25, 100, and 150 mg	Dissolve tablets in 100 ml of water with resulting suspension administered by gastric tube or swallowing. The container with the oral suspension should be rinsed twice with 40 ml of water and given by gastric tube to ensure delivery of full dose.
Estramustine <sup>48</sup>	Capsule (powder): 140 mg	No data
Etoposide <sup>49-54</sup>	Injection, solution: 20 mg/ml Capsule (soft gelatin): 50 mg	Method 1: Etoposide 10-mg/ml oral solution can be prepared by diluting a desired amount of etoposide injectable solution 20 mg/ml with sodium chloride 0.9% for injection to 10 mg/ml. Store in oral syringes or amber bottle. Method 2: Etoposide 50-mg oral solution can be prepared by drawing 2.5 ml of i.v. etoposide at a concentration of 20 mg/ml and storing in oral syringes. When administered, mix with 100 ml of water.
Exemestane <sup>55</sup>	Tablet (film-coated): 25 mg	No data
Everolimus <sup>56</sup>	Tablet: 5 and 10 mg	No data
Finasteride <sup>57, 58</sup>	Tablet (film-coated): 5 mg	May be crushed or broken if the patient finds it hard to swallow (see comments)
Fludarabine <sup>59, 60</sup>	Injection, solution: 25 mg/ml Tablet: (film-coated): 10 mg	No data
Flutamide <sup>17, 61</sup>	Capsule (powder): 125 mg (generic brand manufactured by Teva)	No data
Gefitinib <sup>62</sup>	Tablet (film-coated): 250 mg	Tablet may be placed, without crushing, in half a glass of noncarbonated drinking water (other liquid should not be used). Stir until the tablet is dispersed (~10 min), then administer immediately.
Hydroxyurea <sup>63, 64</sup>	Capsule (powder): 500 mg	100-mg/ml oral solution may be prepared by emptying the contents of 20 x 500-mg capsules and mixing 50 ml of room-temperature sterile water to first make a concentration of 200 mg/ml, then stir the mixed solution for several hours. The solution is then filtered to remove insoluble excipients, and 50 ml of flavored syrup is then added to the filtered solution to provide a final concentration of 100 mg/ml. Store in an amber plastic bottle.
Imatinib <sup>65</sup>	Tablet (film-coated, scored): 100 and 400 mg	Tablets, without crushing, may be dispersed in a glass of water or apple juice (50 ml for 100-mg tablet, and 200 ml for 400-mg tablet). Stir until disintegrated and administer immediately.

Table 1. (continued)

Storage and Stability, and Label Information	Codes <sup>a</sup>	Comments
No data; drink the liquid immediately, then rinse the glass with 15 ml of juice to ensure administration of complete dose; any unused suspension should be discarded 60 min after preparation	A, D, F	If necessary, the suspension preparation may be used for administration through a nasogastric tube at discretion of the physician Do not disperse the tablets or solution in grapefruit juice
No data; drink the liquid immediately, then rinse the glass with half a glass of water and consume to ensure administration of full dose	A, D, F	Do not disperse the tablets or solution in grapefruit juice
No data	A	Capsule should be taken 1 hr before or 2 hrs after meals Milk, milk products, calcium-containing products, magnesium, or other polyvalent ions should not be taken concomitantly with estramustine due to impairment of estramustine absorption
Method 1: 22 days at room temperature regardless of lighting conditions Method 2: No data	A, D, E, J	Etoposide at 1 mg/ml has acceptable stability when administered orally in orange juice, apple juice, and lemonade (not grapefruit juice) or flavored syrup with less than 1% loss over a 3-hr period. At this concentration, etoposide tends to precipitate out of solution; however, there was no loss of potency. To prevent precipitation, administer etoposide at concentrations $\leq 0.4$ mg/ml. Bioavailability of oral administration of i.v. etoposide and orally swallowed capsules is comparable Do not disperse the capsules or drink solution in grapefruit juice Capsules need to be refrigerated Doses should be taken 1 hr before or 2 hrs after meals
No data	A	No pharmacokinetic data are available. Crushing is not recommended; decision to crush or split tablet is based on clinical judgment.
No data	A	No pharmacokinetic data are available. Crushing is not recommended; decision to crush or split tablet is based on clinical judgment. Do not disperse the tablets or solution in grapefruit juice
No data	A, C, F	Women who are or may become pregnant, or are breastfeeding should not handle crushed or broken tablets because it may cause abnormalities of a male baby's sex organs. Tablets are coated and will prevent contact with active ingredient during normal handling.
No data	A	
No data	A, B, E, F	Contents of capsule may be opened and mixed with applesauce, pudding, or other soft foods, but not liquids Do not disperse the tablets or solution in grapefruit juice
No data; drink the liquid immediately, then rinse the glass with half a glass of water and consume to ensure administration of full dose	A, D, F	Oral liquid may be administered by a nasogastric tube Do not disperse the tablets or solution in grapefruit juice
3–9 mo at room temperature (only 5% loss in chemical activity over first 3 mo, and no additional loss out to 9 mo of room temperature storage)	A, B, E, F, I	Do not use heated water to prepare the solution since mildly heated water (41°C) can immediately reduce chemical stability by 40%
No data; drink the liquid immediately, then rinse the glass with half a glass of water or apple juice and consume to ensure administration of full dose	A, D, F	Do not disperse the tablets or solution in grapefruit juice



Table 1. Summary of Extemporaneous Oral Liquid Preparation of Oral Anticancer Therapy and Stability Data (continued)

Drug	Dosage Forms	Extemporaneous Oral Liquid Formula
Isotretinoin <sup>66-67</sup>	Capsule (soft gelatin): 10, 20, and 40 mg	Method 1: Place capsule(s) in a medicine cup or small bowl, and add warm (~37°C or 97°F) water or warm milk to cover the capsule(s). Wait 2–3 min until capsule is soft, and then drink the milk or water with the softened capsule, or swallow the softened capsule. Method 2: Puncture the capsule with a needle or cut the capsule with scissors. Squeeze the contents of capsule into 5–10 ml of warm milk or tube feed formula. Draw the mixture into an oral syringe, and then give by feeding tube. Flush feeding tube well with a minimum of 30 ml of milk or tube feed formula. Method 3: Puncture the capsule with a needle or cut the capsule with scissors. Draw contents into an oral syringe. Draw 1–5 ml of medium-chain triglyceride, soybean, or safflower oil into same syringe. Gently mix syringe to mix the contents, then give by feeding tube. Flush tube well with a minimum of 30 ml of milk or tube feed formula.
Lapatinib <sup>68</sup>	Tablet (film-coated): 250 mg	No data
Lenalidomide <sup>69</sup>	Capsule (powder): 5, 10, 15, and 25 mg	No data
Letrozole <sup>70</sup>	Tablet (film-coated): 2.5 mg	No data
Lomustine <sup>71</sup>	Capsule (powder): 10, 40, and 100 mg	No data
Megestrol <sup>18, 72-74</sup>	Tablet (scored): 20 and 40 mg Suspension, oral: 40 mg/ml (240 ml)	Place one 160-mg tablet into 20 ml of water, and let stand. Begin stirring, and continue until the tablets are completely disintegrated to form a fine particular suspension (dispersion time for 160-mg tablet is 2–5 min). Commercially available as 40-mg/ml oral suspension
Melphalan <sup>25, 75</sup>	Injection, powder for reconstitution: 50 mg Tablet (film-coated, scored): 2 mg	Not recommended; when melphalan is prepared in methylcellulose and simple syrup or wild cherry syrup, it decomposes too rapidly to make the suspension formulation feasible for extemporaneous compounding
Mitotane <sup>76, 77</sup>	Tablet (scored): 500 mg	No data
Mercaptopurine <sup>25, 78</sup>	Tablet (scored): 50 mg	50-mg/ml oral suspension can be prepared by crushing 30 x 50-mg tablets in a mortar and transferring the fine powder into an amber glass bottle, adding 5 ml of sterile water for irrigation, and shaking mixture to create a uniform paste. The flavoring agents are then added, including 10 ml of simple syrup and enough wild cherry syrup to make a final volume of 30 ml suspension.
Methotrexate <sup>80-85</sup>	Injection, powder for reconstitution (preservative-free): 20 mg, 1 g Injection, solution (as sodium): 25 mg/ml Injection, solution, (preservative-free): 25 mg/ml Tablet (film-coated, scored): 2.5, 5, 7.5, 10, and 15 mg	Preparation of stock diluent solution: mix 250 ml of 0.05% saccharin in cherry-flavored glycol or aqueous base, add sodium bicarbonate 20 g, then add a sufficient quantity of a chloroform water solution to a final volume of 1000 ml. (Chloroform water solution can be prepared by using 2.5 ml of pharmaceutical grade chloroform water and adding a sufficient quantity of distilled water to a final volume of 1000 ml.) To prepare a methotrexate solution of 40 mg/20 ml, use 1.6 ml of methotrexate from a 25-mg/ml methotrexate preservative-free vial, and bring to a total of 20 ml with the stock diluent solution.
Nilotinib <sup>86, 87</sup>	Capsule (powder): 200 mg	No data, but disruption of capsule may yield high blood levels that lead to increased toxicity

Table 1. (continued)

Storage and Stability, and Label Information	Codes <sup>a</sup>	Comments
Methods 1, 2, and 3: No data; administer immediately after preparation	A, B, F, H	Capsules are inherently heat stable but are subject to degradation if exposed to light. Protect from light. To enhance absorption, some clinicians recommend giving with a fatty meal. Must not be administered in combination with vitamin A since symptoms of hypervitaminosis A could be aggravated.
No data	A	Should be taken 1 hr before or 1 hr after a meal Do not disperse the tablets in grapefruit juice
No data	A	
No data	A	
No data	A	
No data; suspension should be administered immediately after complete disintegration of the tablet(s). Rinse the glass several times with adequate amount of water and consume to ensure administration of the full dose. Commercially available suspension: According to expiration date on manufacturer's label Shake well	A, D, F, G	Megestrol acetate oral suspension is compatible with water, orange juice, apple juice, or Sustacal H.C. for immediate consumption
> 80% of melphalan decomposed within 24 hrs at room temperature, whereas > 50% decomposed within 7 days at 5°C Complete hydrolysis also occurs when melphalan solution is prepared in water (30 µg/ml) at 37°C after 8 hrs	A	Injectable form should be used as alternative for patients who cannot swallow pills
No data	A	Tablets should not be crushed according to the manufacturer
5 wks when stored at room temperature Addition of ascorbic acid at a concentration of 0.1% (weight/volume) to the standard formulation increased the shelf-life of the suspension at room temperature to 11 wks Shake well	A, C, F	
At least 1 month at room temperature and in refrigerator in a variety of storage containers, including clear and brown storage glass bottles	A, L, F	No significant difference in terms of bioavailability, $C_{max}$ , and AUC between tablets and oral solution. Mean bioavailability of the oral tablet and oral solution was 28% and 85–87% compared with the same dose given i.v. and i.m., respectively
No data	A	Do not disperse the capsules in grapefruit juice



Table 1. Summary of Extemporaneous Oral Liquid Preparation of Oral Anticancer Therapy and Stability Data (continued)

Drug	Dosage Forms	Extemporaneous Oral Liquid Formula
Pazopanib <sup>88</sup>	Tablet (film-coated): 200 and 400 mg	Not recommended; taking the drug with food or crushing the tablet will increase the rate of absorption, resulting in increased systemic exposure and potential toxicity
Procarbazine <sup>89, 90</sup>	Capsule (powder): 50 mg	10-mg/ml oral suspension can be prepared by emptying contents of 10 x 50-mg capsules into a mortar, adding a small amount (2 ml) of glycerin, and levigating the mixture to make a thick paste. Add 10 ml of strawberry syrup by geometric proportion and levigate until a uniform mixture is obtained. Transfer the mixture to an amber glass bottle, and add a sufficient quantity of strawberry syrup to a final volume of 50 ml by repeatedly rinsing the mortar and pestle with small amounts of the syrup.
Raloxifene <sup>91</sup>	Tablet (film-coated): 60 mg	No data
Sorafenib <sup>92-93</sup>	Tablet (film-coated): 200 mg	Place 2 x 200-mg tablets into a glass with 60 ml of water, and let stand; begin stirring after 5 min, and continue until the tablets are completely disintegrated to form a fine particular suspension. The suspension is ready for administration after 10 min. (Note that the brown tablet coating may initially form a thin film; however, it has no effect on dosing accuracy.)
Sunitinib <sup>94-97</sup>	Capsule (powder): 12.5, 25, and 50 mg	Method 1: Mix the contents of 3 x 50-mg capsules with 15 ml of a 1:1 mixture of Ora-Plus:Ora-Sweet solution to yield a final concentration of 10 mg/ml in an amber plastic bottle Method 2: Contents of capsules (up to 750 mg) may be mixed with 75 ml of apple juice
Tamoxifen <sup>19, 74, 98</sup>	Tablet: 10 and 20 mg Oral solution: 10 mg/5 ml	Place two 10-mg tablets into 40 ml of water, and leave to stand; begin stirring and continue until the tablets are completely disintegrated to form a fine particular suspension. (Dispersion time for 10-mg tablet is 2-5 min.) Commercially available as tamoxifen citrate oral solution (Soltamox 10 mg/5 ml)
Temozolamide <sup>99, 100</sup>	Injection, powder for reconstitution: 100 mg; Capsule (powder): 5, 20, 100, 140, 180, and 250 mg	10-mg/ml oral suspension can be prepared in a glass mortar by mixing the contents of 10 x 100-mg capsules and 500 mg of povidone K-30 powder. Add 25 mg of anhydrous citric acid dissolved in 1.5 ml of purified water, and mix to form a paste. Add 50 ml of Ora-Plus (add a small amount at first and mix, then add balance and mix), then transfer to an amber plastic bottle. Add enough Ora-Sweet or Ora-Sweet SF to bring to a total volume of 100 ml by rinsing the mortar with small amounts of Ora-Sweet; repeat rinsing 3 more times. Transfer to a plastic amber bottle.
Thalidomide <sup>101</sup>	Capsule (powder): 50, 100, 150, and 200 mg	No data
Thioguanine <sup>25, 102</sup>	Tablet (film-coated, scored): 40 mg	20-mg/ml oral suspension can be prepared by crushing 15 x 40-mg tablets in a mortar, then adding 10 ml of methylcellulose 1% (in small amounts). Transfer to a graduated cylinder, then add a sufficient quantity of syrup to a final volume of 30 ml. Transfer the solution to an amber glass bottle.
Topotecan <sup>103</sup>	Injection, powder for reconstitution: 4 mg Capsule: 0.25 and 1 mg	No data
Toremifene <sup>104</sup>	Tablet: 60 mg	No data

Table 1. (continued)

Storage and Stability, and Label Information	Codes <sup>a</sup>	Comments
No data	A	Should be administered without food (at least 1 hr before or 2 hrs after a meal) Do not disperse the tablets or solution in grapefruit juice
7 days at room temperature Shake well, protect from light	A, B, F	
No data	A	
No data; suspension should be administered within 1 hr after preparation. Stir suspension thoroughly and administer, and rinse the glass several times with a total of 6 oz of water and consume to ensure administration of full dose.	A, D, F, J	Take 1 hr before or 2 hrs after a meal since a high-fat meal can reduce bioavailability of oral tablets Mean relative bioavailability of sorafenib tablets is 38–49% compared with oral solution There is no significant difference in terms of absorption, $C_{max}$ , and AUC between intact tablets and oral suspension No data are available on administration of suspension by feeding tube or on using any fluids other than water to make the suspension
Method 1: 60 days at room temperature and at 4°C (maintains > 96% of initial concentration) Shake well Method 2: Consume within 2 hrs after mixing (maintains > 98% of initial concentration at 2 hrs at room temperature or under fluorescent light)	A, B, F	Physical stability (odor, color, and consistency of suspension) remained unchanged at the end of study No evidence of microbial growth Bioequivalency between oral liquid and capsules was not studied Oral suspension is fairly viscous One study showed that grapefruit marginally increased sunitinib exposure by 11%, which may not be clinically significant
No data; suspension should be administered immediately after complete disintegration of the tablet(s). Rinse the glass several times with an adequate amount of water and consume to ensure administration of the full dose Commercially available oral solution: According to expiration date on manufacturer's label	A, D, F, G	Do not disperse the tablets or solution in grapefruit juice Soltamox is a sugar-free, clear, colorless liquid, with licorice and aniseed odor and taste
7 days at room temperature with Ora-Sweet formulation, 14 days at room temperature with Ora-Sweet SE, or 60 days for both suspensions when refrigerated Shake well, refrigerate	A, B, F	It is essential to include povidone K-30 in the formulation to prevent crystal growth and to make the suspension more soluble and stable with an extended shelf-life Physical stability (color and consistency of suspension) remained unchanged at end of study. Pinkish color when refrigerated Color may become darkened when stored at room temperature
No data	A	
60 days at room temperature Shake well	A, C, F	
No data	A	Capsules need to be refrigerated Do not disperse the capsules in grapefruit juice
No data	A	

Table 1. Summary of Extemporaneous Oral Liquid Preparation of Oral Anticancer Therapy and Stability Data (continued)

Drug	Dosage Forms	Extemporaneous Oral Liquid Formula
Tretinoin (ATRA) <sup>16, 105–109</sup>	Capsule (soft gelatin): 10 mg	Method 1: Place capsule(s) in a medicine cup or small bowl, and add warm (~37°C or 97°F) water or warm milk to cover the capsule(s). Wait 2–3 min until capsule is soft, then drink milk or water with the softened capsule, or swallow the softened capsule. Method 2: Pierce the capsule and extract the appropriate volume of drug, knowing that tretinoin 10 mg = 0.17 ml of solution. Place the tretinoin liquid in a non-polyvinyl alcohol syringe and dilute with a sufficient quantity of medium-chain triglyceride oil to a final volume of 5 ml. Method 3: Place daily dose of ATRA in a sterile 50-ml tube. Add 20 ml of sterile water, then heat the tube in a water bath to 37°C until the capsules melt and the suspension is liquefied. The resulting fluid is administered by nasogastric tube. Method 4: Cut capsules open, and aspirate the contents with a 19-gauge needle into a syringe primed with 1 ml of soybean oil. Mix small amounts of soybean oil with the remaining contents in the capsule to allow more of the active drug to be drawn into the syringe. Uniformly stir the resulting mixture of ATRA and soybean oil and place in a glass syringe. Administer by nasogastric tube within 24 hrs of preparation. Method 5: Place 5 or 6 capsules (depending on dose) into a 20-ml syringe with 4 ml of sterile water for irrigation. Place syringe and contents under hot running tap water to speed dissolution of the capsules and contents. Shake to dissolve capsules and contents (~3 min). Add a sufficient quantity of canola oil to a final volume of 10 ml. Dispense in 10-ml oral syringe.
Vorinostat <sup>110, 111</sup>	Capsule (powder): 100 mg	50-mg/ml oral suspension can be prepared by adding 20 ml of either Suspensol S or Ora-Plus into at least a 4-oz amber or clear glass bottle. Add the contents of 20 x 100-mg capsules, and shake to disperse (could take up to 3 min); add 20 ml of Ora-Sweet, and shake to disperse to make a final volume of 40 ml.

AUC = area under the curve; C<sub>max</sub> = peak concentration.

\*Explanation of codes:

A = Procedures for proper handling and disposal of these oral anticancer drugs should be followed based on National Institute for Occupational Safety and Health recommendations. Skin contact or inhalation of contents of capsules or crushed tablets may have teratogenic effects; pregnant women or nonpregnant women of childbearing age who are caregivers should avoid direct contact.

B = Capsule may be opened and the contents may be crushed or chewed.

C = Tablet may be crushed.

D = Tablets, without crushing, may be placed in appropriate liquid until the tablet is dispersed by stirring.

E = Contents may be sprinkled into soft food such as applesauce or pudding.

F = No pharmacokinetic data on administration of suspension or solution by feeding tube are available. Administration of the liquid through a feeding tube (e.g., nasogastric tube) may be acceptable.

G = Liquid dosage forms of the product are commercially available.

H = Capsule may be opened and liquid contents removed for administration.

I = Skin contact of contents of capsules or crushed tablets may cause skin or mucosal irritation; avoid direct contact.

J = Bioavailability data are available.

<sup>b</sup>Aromatic elixir, used as a flavored vehicle, contains a variety of ingredients including suitable essential oil(s), syrup, talc, alcohol, and purified water.

References of relevant articles, product packaging, and manufacturer information, as well as the Internet, Micromedex,<sup>16</sup> and Lexi-Comp,<sup>17</sup> were used as a source to capture all the pertinent information that may not have been found through the PubMed search.

A total of 46 oral anticancer agents and the nine most common adjunct agents used in oncology were reviewed. None of the oral anticancer agents, except megestrol acetate<sup>18</sup> and tamoxifen,<sup>19</sup> are commercially available in an oral

liquid dosage form. Table 1<sup>16–111</sup> and Table 2<sup>16–17, 112–139</sup> provide a summary of the methods for extemporaneous oral liquid preparation and stability data, if any, for these agents. Recipes on how to prepare extemporaneous oral liquid formulations were available for 21 (46%) of the 46 oral anticancer drugs. Fourteen of the 21 drugs have been tested for chemical stability, and of these 14 drugs, only three included additional physical stability data. Pharmacokinetic data on the bioavailability of the extemporaneously

Table 1. (continued)

Storage and Stability, and Label Information	Codes <sup>a</sup>	Comments
Methods 1, 2, and 3: No data; administer immediately after preparation	A, B, F, H	To enhance absorption, some clinicians recommend administering with a fatty meal
Method 4: 24 hrs at room temperature		Must not be administered in combination with vitamin A since symptoms of hypervitaminosis A could be aggravated
Method 5: No data; administer immediately after preparation		No bioavailability data comparing oral capsules and oral liquid are available, but one pharmacokinetic study suggests that absorption is highly variable among patients
2 wks at room temperature (does not require refrigeration)	A, B, F, I	

prepared oral solution from the solid dosage forms were found for only seven oral anticancer agents.

### Major Factors Involved in Extemporaneous Oral Liquid Preparation

Before an oral liquid formulation is prepared extemporaneously, it is essential to have an adequate understanding of the pharmacokinetic characteristics of the drug, the chemical compatibility of an active drug with excipients, as well as stability, palatability of the final solution, ease of administration, and safety concerns.<sup>140–143</sup> With a thorough understanding of these basic scientific principles, pharmacists will be able to design a formula for extempo-raneous preparation of oral liquid formulations if no suitable formula is available in the literature.

#### Excipients

Excipients used for preparation of oral liquid formulations include suspending agents, vehicles

(syrup or flavors to enhance taste), color additives, and preservatives.<sup>140–143</sup> Since most drugs are not completely soluble in water, a suspending agent is required to prepare an extemporaneous oral liquid from tablets or capsules.<sup>140</sup> Carboxymethylcellulose and methylcellulose are the most common suspending agents to enhance dose uniformity and physical stability.<sup>140–142</sup> Concentrated syrup usually serves as a vehicle because it not only improves the taste due to its high content of sugar or sucrose, but also provides a preservative effect resulting from its high osmolality.<sup>140, 143</sup> The most commonly used, commercially available suspending agent and vehicle are Ora-Plus (Paddock Laboratories, Inc., Minneapolis, MN) and Ora-Sweet (Paddock Laboratories, Inc.), respectively. Ora-Plus, which is buffered to an acidic pH of 4–4.5 and contains preservatives, is designed to meet the widest range of potential uses.<sup>142, 144</sup> Ora-Sweet is a citrus-berry-flavored syrup with a buffered pH of 4–4.5.<sup>144</sup> For patients with diabetes mellitus, a sugar-free product (Ora-Sweet SF [Paddock

Table 2. Summary of Extemporaneous Oral Liquid Preparations and Stability Data of Most Commonly Used Ancillary Drugs in Oncology

Drug	Dosage Forms	Extemporaneous Oral Liquid Formula
Allopurinol <sup>25, 26, 74, 112–115</sup>	Injection, powder for reconstitution (as sodium): 500 mg Tablet (scored): 100 and 300 mg	Method 1: 20 mg/ml suspension can be prepared by using 24 x 100-mg tablets with glycerin or distilled water to levigate; add 40 ml of methylcellulose and a sufficient quantity of a 2:1 simple syrup:cherry syrup mixture to bring the volume to a final volume of 120 ml Method 2: An oral suspension for use in desensitization protocols is prepared by crushing 2 x 100-mg tablets in a mortar, adding 33 ml of methylcellulose 1% solution to make a slurry, and adding 4 ml of cherry-flavored and simple syrup and mixing to a total volume of 100 ml. 10 ml of the suspension is then further diluted with the same ingredients to 100 ml to yield a final concentration of 1 mg/5 ml or 200 µg/ml. Method 3: Crush tablets to make a 5 mg/ml suspension in simple syrup Method 4: Place each 100-mg tablet or half of a 300-mg tablet into 20 ml of water, and let stand. Begin stirring and continue until the tablets are completely disintegrated to form a fine particular suspension. (Dispersion time is 1–2 min for 100-mg tablet and 2–5 min for half a 300-mg tablet.)
Aprepitant <sup>116–118</sup>	Injection, solution: fosaprepitant dimeglumine 115 mg/10 ml Capsule (blended beads): 40, 80, and 125 mg	Method 1: 20-mg/ml oral suspension can be prepared by emptying the contents of 4 x 125-mg capsules into a mortar. Grind capsule contents to a fine powder using a pestle (takes 10–15 min). Do not allow capsule contents to soak in Ora-Blend <sup>b</sup> before grinding. Add small amount of Ora-Blend to the fine powder and triturate to a smooth paste, ensuring that there are no lumps. Add more Ora-Blend to make a liquid, then transfer to a graduated cylinder. Rinse out mortar with Ora-Blend and add to graduated cylinder. Then add a sufficient quantity of Ora-Blend to bring the final volume to 25 ml, and transfer the solution to an amber glass bottle. Method 2: Empty the contents from the capsule, and sprinkle on soft food (e.g. applesauce, pudding) immediately before administration, or place the contents in water, and immediately administer by feeding tube followed by flushing the tube with additional water to ensure complete delivery of the drug
Dolasetron <sup>119, 120</sup>	Injection, solution: dolasetron mesylate 20 mg/ml Tablet (film-coated): 50 and 100 mg	Method 1: 10-mg/ml suspension may be prepared by grinding 12 x 50-mg tablets to a fine powder in a mortar (takes 10–15 min); transfer powder to an amber glass bottle. Mix powder with Ora-Plus and strawberry syrup or Ora-Plus and Ora-Sweet in 1:1 ratio to make a final volume of 60 ml. Method 2: Injection may be mixed with apple or apple-grape juice for oral administration in children
Eltrombopag <sup>121</sup>	Tablet (film-coated): 25 and 50 mg	No data
Granisetron <sup>122–125</sup>	Injection, solution: 0.1 and 1 mg/ml Solution, oral: 2 mg/10 ml Tablet: 1 mg Transdermal patch: 3.1 mg/24 hr	Method 1: 0.2-mg/ml oral suspension may be prepared by crushing 12 x 1-mg tablets and mixing with 30 ml of water and a sufficient quantity of cherry syrup to provide a final volume of 60 ml Method 2: 0.05-mg/ml oral suspension may be prepared by pulverizing 4 x 1-mg tablets using a mortar and pestle, then adding 80 ml of methylcellulose 1% in simple syrup NF or a 1:1 mixture of Ora-Sweet (40 ml) and Ora-Plus (40 ml) to make a final volume of 80 ml
Leucovorin <sup>16, 126, 127</sup>	Injection, powder for reconstitution (as calcium): 50, 100, 200, 350, and 500 mg Injection, solution (as calcium): 10 mg/ml Tablet (scored): 5, 10, 15, and 25 mg	Method 1: 5-mg/ml oral suspension can be prepared by crushing 24 x 25-mg tablets to a fine powder in a glass mortar and pestle; transfer powder to an amber glass bottle. Add 30 ml of Cologel, and shake the mixture. Bring suspension to volume with a flavoring agent (2:1 mixture of simple syrup and wild cherry syrup) to a final volume of 120 ml. Vigorously shake bottle to mix thoroughly. Method 2: Disperse 5-mg tablets in an 8-oz glass of water, and let stand for 5 min. Then stir the solution with a spoon; tablets should readily go into solution.

Table 2. (continued)

Storage and Stability, and Label Information	Codes <sup>a</sup>	Comments
Method 1: 8 wks when refrigerated Shake well, refrigerate Method 2: No data Method 3: 14 days when refrigerated Shake well, refrigerate Method 4: No data; the suspension should be administered immediately after complete disintegration of the tablet(s). Rinse the glass several times with an adequate amount of water and consume to ensure administration of the full dose.	B, C, D, E, G	
Method 1: 90 days at 4°C Stability was reduced when stored at room temperature Shake well, refrigerate Method 2: No data; administer immediately	A, D, E, G	Blended beads from the capsule may be crushed into fine powder No bioavailability data are available on the oral suspension Do not disperse the capsules or solution in grapefruit juice
Method 1: 90 days at room temperature and when refrigerated Shake well Method 2: Use within 2 hrs of dilution at room temperature	B, D, E, G	Both preparations may have a bitter aftertaste; mixing chocolate syrup with the suspension in 1:1 ratio may mask the bitter aftertaste and improve palatability, especially for children Do not disperse the tablets or solution in grapefruit juice
No data		Tablets must not be taken within 4 hrs of any products containing polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc) due to a significant decrease of plasma eltrombopag exposure by 70%
Method 1: 14 days at room temperature or when refrigerated Shake well Method 2: 91 days at room temperature or when refrigerated when prepared in either one of the suspending agents Shake well	B, D, E, G	2-mg/10 ml oral solution and transdermal patch also commercially available Do not disperse the tablets or solution in grapefruit juice
Method 1: up to 4 wks when refrigerated (≥ 90% potency preserved) Storage at room temperature is not recommended due to rapid degradation Shake well, refrigerate Method 2: 2 hrs at room temperature	B, D, E, G	

**Table 2. Summary of Extemporaneous Oral Liquid Preparations and Stability Data of Most Commonly Used Ancillary Drugs in Oncology (continued)**

Drug	Dosage Forms	Extemporaneous Oral Liquid Formula
Mesna <sup>128–130</sup>	Injection, solution: 100 mg/ml Tablet (film-coated, scored): 400 mg	Parenteral solution is diluted in cold beverages such as milk, juice, or carbonated beverages to mask the unpalatable taste (since the bioavailability of oral mesna is 50%, the dose based on the i.v. formulation should be doubled for oral administration)
Ondansetron <sup>131–134</sup>	Infusion (as hydrochloride) (premixed in 5% dextrose in water): 2 mg (50 ml) Injection, solution: 2 mg/ml Solution: 4 mg/5 ml (strawberry flavor) Tablet (film-coated): 4 and 8 mg Tablet, orally disintegrating: 4 and 8 mg	Method 1: The injectable form of ondansetron can be mixed with orange juice, cola, or cherry syrup. Ondansetron 8-mg/4 ml injection was stable in 26 ml of orange juice or cola; ondansetron was mixed in cherry syrup at a concentration of 0.533 mg/ml Method 2: 0.8-mg/ml syrup may be made by crushing 10 x 8-mg tablets; flaking of the tablet coating will occur. Mix thoroughly with 50 ml of the suspending vehicle, Ora-Plus, in 5-ml increments. Add a sufficient quantity of cherry syrup USP, Syrpalta, Ora-Sweet, or Ora-Sweet SF to make a final volume of 100 ml.
Tranexamic acid <sup>74, 135–139</sup>	Injection, solution 10%: 100 mg/ml Tablet: 500 mg	Method 1: 5% oral solution can be prepared by diluting 5 ml of 10% tranexamic acid injection with 5 ml of sterile water Method 2: Place each 500-mg tablet into 20 ml of water, and let stand. Begin stirring and continue until the tablets are completely disintegrated to form a fine particular suspension. (Dispersion time for each 500-mg tablet is 2–5 min.)

<sup>a</sup>Explanation of codes:

A = Capsule may be opened and contents may be crushed or chewed.

B = Tablet may be crushed.

C = Tablets, without crushing, may be placed in appropriate liquid until the tablet is dispersed by stirring.

D = Contents may be sprinkled into soft food such as applesauce or pudding.

E = Contents may generally be administered through a nasogastric tube with an appropriate fluid provided that entire contents are washed down the tube.

F = Liquid dosage forms of the product are commercially available.

G = The taste of the product in a liquid form would likely be unacceptable to the patient; administration through a nasogastric tube should be acceptable.

H = Tablets are made to disintegrate under the tongue.

<sup>b</sup>Ora-Blend consists of a 1:1 combination of Ora-Sweet and Ora-Plus.

Laboratories, Inc.]) is also available. Ora-Blend consists of a 1:1 combination of Ora-Sweet and Ora-Plus.<sup>144</sup> The pH of Ora-Plus–Ora-Sweet suspension is 4.2–4.4, and the pH of 1% methylcellulose syrup suspension is about 6.8.<sup>142, 144</sup> It is important to note that some common oral excipients, including benzyl alcohol as a preservative, ethanol, or propylene glycol as a solvent, have known neurotoxic effects on neonates and young children.<sup>145</sup>

### Stability

Stability is defined as the extent to which a product retains the same properties and charac-

teristics as it possessed at the time of its manufacture, or within specified limits, throughout its period of storage and use.<sup>146</sup> The United States Pharmacopeia (USP) defines five types of stability for extemporaneous compounding: chemical, physical, microbiologic, therapeutic, and toxicologic (Table 3).<sup>141, 146</sup> The USP also provides a general guideline on stability and beyond-use dates for extemporaneously compounded prescriptions.<sup>140, 146</sup> For microbiologic reasons, unless published data support a longer expiration time, the beyond-use date for any water-containing formulation prepared from ingredients in solid form is limited to 2 weeks, and the liquid must be stored in the refrigerator.<sup>140, 146</sup> Based on



Table 2. (continued)

Storage and Stability, and Label Information	Codes <sup>a</sup>	Comments
Undiluted formulation is stable for at least 9 days in standard polypropylene syringes at room temperature, 35°C, or when refrigerated When diluted in a 1:2 or 1:5 ratio, suspension is stable at room temperature for at least 7 days	B, E, G	Patient who vomits within 2 hrs of taking oral mesna should repeat the dose or receive i.v. mesna
Method 1: Ondansetron 8 mg (4 ml) prepared from injectable form was stable in 26 ml of orange juice or cola (final concentration 0.27 mg/ml) for up to 1 hr when stored at room temperature. Ondansetron 168 mg (84 ml) prepared from injectable form was stable in 231 ml of cherry syrup (final concentration 0.53 mg/ml) for 7 days at room temperature or when refrigerated. Method 2: 42 days when refrigerated Shake well, refrigerate	B, D, E, F G, H	Do not disperse the tablets or solution in grapefruit juice
Method 1: 5 days when refrigerated Refrigerate and protect from light Method 2: No data; the suspension should be administered immediately after complete disintegration of the tablet(s). Rinse the glass several times with an adequate amount of water and consume to ensure administration of full dose	B, C, E, G	

Table 3. Five Types of Stability Defined by the United States Pharmacopeia for Extemporaneously Compounded Formulations<sup>141, 146</sup>

Type of Stability	Definition
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits
Physical	Original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained
Microbiologic	Sterility or resistance to microbial growth is retained according to the specified requirements; antimicrobial agents that are present retain effectiveness within the specified limits
Therapeutic	Therapeutic effect remains unchanged
Toxicologic	No significant increase in toxicity occurs

the literature, most of the earlier studies that evaluated extemporaneously compounded oral anticancer liquid formulations reported chemical stability data only, which was the main limitation of these studies. Only very few studies assessed

physical and/or microbiologic stability.

Chemical stability of an active ingredient in the selected vehicle is usually examined by high-performance liquid chromatography (HPLC), which is the most commonly used stability-indicating assay.<sup>140</sup> The USP specification range of the potency of an active drug is within 90–110%, and a standard cutoff of 90% of the initial concentration remaining is used to determine a recommended beyond-use date.<sup>140, 146</sup>

Factors that affect stability include pH, temperature, excipients, solvent, light, air (oxygen), carbon dioxide, humidity, particle size, microbial growth, formation of polymorphs, crystallization, vaporization, and adsorption.<sup>140–143</sup> Hydrolysis, oxidation, and reduction are the most frequently encountered destructive processes in extemporaneous oral liquid preparations.<sup>141</sup> Drugs that are esters or that contain chemical groups such as substituted amides, lactones, and lactams are most susceptible to hydrolysis. Other drug types including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils are prone to deterioration through oxidative processes.<sup>141</sup>

The rate of these reactions can be affected by temperature and pH.<sup>140, 141, 143</sup> For example, when hydroxyurea oral solution 100 mg/ml was extemporaneously prepared with mildly heated water at 41°C in an attempt at facilitating dissolution, the mild heating of the water statistically significantly reduced the chemical stability by 40% compared with the preparation using room-temperature sterile water.<sup>64</sup> Azathioprine is more rapidly hydrolyzed to 6-mercaptopurine at alkaline pH than under acidic or neutral conditions.<sup>147</sup> Temozolamide is stable at acidic pH less than 5 and labile at pH greater than 7, and it is rapidly hydrolyzed to an active metabolite at neutral and alkaline conditions.<sup>99</sup>

Melphalan is insoluble in water; rapid hydrolysis occurs when the drug is prepared in water, whereas the rate of reaction slows down in an acidic condition.<sup>75, 148, 149</sup> It was observed that the melphalan 2-mg/ml oral suspension prepared in methylcellulose and simple syrup or wild cherry syrup started to decompose between time of preparation and time of assay.<sup>25</sup> More than 80% of the drug decomposed within 24 hours at room temperature, whereas more than 50% decomposed within 7 days at 5°C.<sup>25</sup> It is unknown if the potency remains within the USP-specified limits when the liquid formulation is administered immediately after preparation, or if the stability may last longer when the drug is prepared with a more acidic excipient and/or vehicle, or at a different concentration. Therefore, the practice of mixing crushed tablets or emptying contents of capsules with any solution without knowing stability data is discouraged.

The selection of appropriate excipients and determination of the optimum pH range are crucial steps during the compounding process to maintain the stability or to extend the shelf-life of a final product. An acidic pH of 5–6 is usually required to maintain optimal stability for most hydrolyzable drugs.<sup>141</sup> Some pharmaceutical excipients may be used to increase the stability to minimize the hydrolytic and oxidative processes.<sup>141</sup> For example, when temozolamide oral suspension is prepared, it is essential to add povidone K-30 in the suspension to prevent crystal growth so as to make the formulation more soluble and stable with an extended shelf-life.<sup>100</sup>

Another example is that mercaptopurine is known to undergo oxidation in alkaline solutions.<sup>25, 78</sup> The addition of ascorbic acid as an antioxidant at a concentration of 0.1% (weight/volume) to the standard formulation of mercaptopurine has been shown to increase the suspen-

sion's shelf-life at room temperature from 5 weeks to 11 weeks.<sup>79</sup> Other commonly used antioxidants used in aqueous preparations include sodium sulfite, sodium bisulfite, and hypophosphorus acid.<sup>141</sup>

One should note that the stability of two oral liquid formulations using the same active ingredient but prepared extemporaneously with different vehicles, different final concentrations, excipients, water content, and/or the changes of light or temperature condition may be different from each other. For example, the potency of chlorambucil 2-mg/ml oral suspension decreases to less than 90% in less than 24 hours at room temperature, but remains stable for 7 days when it is kept refrigerated in a light-resistant container.<sup>25</sup> Another example is that the chemical stability of cyclophosphamide oral suspension prepared at a final concentration of 2 mg/ml in aromatic elixir is 14 days when refrigerated,<sup>39</sup> but at least 56 days at the same temperature when it is prepared at a concentration of 20 mg/ml in simple syrup or Ora-Plus.<sup>40, 41</sup> Therefore, any liquid preparation that can maintain its stability only at a specified temperature or light condition should be properly labeled on the prescription bottle to avoid a loss of potency and to minimize drug waste. It is also important to note that the excipients found in commercially available tablets or capsules may reduce the chemical stability of the extemporaneously prepared oral liquid by changing the pH to a value that may cause the rate of degradation to increase.<sup>143</sup>

An unpleasant or foul odor and the presence of turbidity in an oral liquid may result from microbial growth that could also adversely affect its appearance and palatability.<sup>140–143</sup> After an extemporaneous oral liquid formulation is prepared, the pharmacist should examine any change in the color, odor, or texture of the formulation. A good suspension should have uniform particle-size distribution and viscosity.<sup>143</sup> If caking, difficulty in resuspending, crystal growth, microbial growth, or discoloration is observed, it may indicate instability, and the product should be discarded.<sup>141, 143</sup>

If no published stability data are found, one should consult the pharmaceutical companies or large research centers since they may be able to provide some useful unpublished stability information or share their own institutional experiences.

### Bioavailability

Since the bioavailability of most oral anticancer drugs is known to be substantially variable,<sup>150</sup> the

differences in absolute bioavailability between the oral solution and the solid dosage form must be minimized. When reviewing the literature, data on the bioavailability and pharmacokinetics of oral anticancer solid dosage forms administered as a liquid suspension were scarce and found only for a very few oral anticancer drugs including aminoglutethimide,<sup>22</sup> bexarotene,<sup>28</sup> busulfan,<sup>32</sup> capecitabine,<sup>36</sup> etoposide,<sup>51, 52</sup> methotrexate,<sup>82-85</sup> and sorafenib.<sup>93</sup> The bioavailability of these agents, except for busulfan,<sup>32</sup> when extemporaneously prepared as an oral solution, was equal to that of solid dosage forms. A randomized, crossover, bioavailability study with a washout period of 14 days was conducted in six patients receiving a single dose of aminoglutethimide 500 mg as an oral solution.<sup>22</sup> The tablets had a 9% larger mean area under the concentration-time curve (AUC) value than the solution and a 5% lower peak plasma concentration ( $C_{\max}$ ) value, which were not considered to be significant differences.<sup>22</sup> The authors concluded that the bioavailability of oral tablets was similar to that of oral solution. Another group evaluated the pharmacokinetics of oral busulfan in pediatric patients and reported wide interpatient variability after oral administration of the drug.<sup>32</sup> The investigators reported that the variability may have been related to the different administration formulations of the drug (tablet, gelatin capsule, crushed tablet), administration technique (nasogastric vs oral, administration of crushed vs intact tablets, administration in gelatin capsules), age, differences in bioavailability, and hepatic metabolism. It was suggested that drug monitoring and patient-specific dosage adjustment should be considered.

Capecitabine tablets are supplied as immediate-release and film-coated tablets, and are water soluble.<sup>36</sup> One pharmacokinetic study evaluated patients with solid tumors who were given a solution of a single dose of capecitabine 2000 mg; the drug was provided in powder form and reconstituted in 200 ml of water.<sup>36</sup> The study showed that the absorption of the drug was rapid and almost complete. Eighty-four percent of the dose was recovered in the urine in the first 12 hours, indicating rapid excretion of capecitabine and its metabolites.

Two pharmacokinetic studies evaluated the bioavailability of oral etoposide solution prepared from the intravenous etoposide solution.<sup>51, 52</sup> A phase I study evaluated the pharmacokinetics and pharmacodynamics of oral etoposide 25–75 mg/m<sup>2</sup>/day as three equally divided daily doses

for 21 days in pediatric patients with solid tumors.<sup>51</sup> Etoposide oral solution was prepared as a 1:2 dilution of intravenous etoposide solution with 0.9% normal saline solution. Patients were instructed to further dilute each dose immediately before administration either in orange juice, lemonade, apple juice, or flavored syrup. Pharmacokinetic data were collected on day 1 of therapy in 18 children and again on day 21 in 14 of those patients. The bioavailability of oral etoposide solution in the study was assumed to be 50% of the intravenous doses. The results indicated no significant difference between the AUC values measured on days 1 and 21, although the pharmacokinetic results revealed substantial inpatient variability. The degree of neutropenia correlated best with the duration of systemic exposure to the drug when the steady-state plasma concentration was maintained above 1 µg/ml, rather than the AUC,  $C_{\max}$ , dose, or other patient characteristics.

In the second study, the bioavailability of etoposide was examined after oral administration of a single dose of intravenous etoposide solution in eight adult patients with cancer.<sup>52</sup> A dose of oral etoposide 50 mg (2.5 ml) was prepared from 20-mg/ml intravenous etoposide solution, and was further diluted in 100 ml of water. The patients were instructed to take the dose after an overnight fast, 30 minutes before breakfast. Multiple blood samples were collected at different time intervals after oral administration for determining the plasma etoposide concentration by using HPLC, as well as pharmacokinetic parameters such as  $C_{\max}$ , time to reach  $C_{\max}$ , and AUC. Plasma concentrations of etoposide were above 1 µg/ml in seven of eight patients, and the mean  $C_{\max}$ , time to  $C_{\max}$ , half-life, and AUC were 2.38 µg/ml, 1.19 hours, 7.5 hours, and 12.83 µg•hour/ml, respectively. The authors used the pharmacokinetic data of other studies in which the therapeutic responses could be achieved with a mean plasma etoposide concentration of 1 µg/ml to conclude that intravenous etoposide solution produced adequate bioavailability compared with the oral capsule form.<sup>51, 53</sup> The limitation of both studies was that there was not a direct comparison with the control in a crossover design.

One pharmacokinetic study of methotrexate evaluated the effect of subdivision of the dose using three different formulations (oral tablets, oral liquid, and intravenous infusion) and the timing of the methotrexate within the chemotherapy cycle.<sup>82</sup> The patients in the study acted

as their own controls. A 2-mg/ml oral solution was prepared from mixing methotrexate injection with sodium bicarbonate, syrup, and chloroform water. The results showed that mean bioavailability for all the oral methods of administration was 28% of the same dose given intravenously. There were no significant differences in terms of absorption, AUC, and  $C_{\max}$  between oral tablets and the extemporaneous oral liquid.<sup>81</sup> These results were consistent with those of other pharmacokinetic studies.<sup>83–85</sup>

The bioavailability of sorafenib tablets administered as a liquid suspension compared with intact tablets was evaluated in a crossover manner.<sup>93</sup> Twenty-six healthy male volunteers were randomized into two groups who received either two 200-mg tablets administered with 8 oz of water or an oral suspension of two 200-mg tablets disintegrated in 2 oz of water over 10 minutes, followed by 6 oz of water for rinsing. The two study arms were separated by a 10–14-day washout period. Serial blood samples were collected before, immediately after, and for up to 144 hours after each dose of sorafenib. Sorafenib was assayed by liquid chromatography–mass spectrometry, and AUC,  $C_{\max}$ , and time to  $C_{\max}$  were assessed. There was no significant difference in absorption and in the geometric means of the pharmacokinetic parameters between the two groups. The mean relative bioavailability of sorafenib tablets was 38–49% compared with oral solution. Although the clinical significance of this bioavailability finding is unknown, caution is advised if sorafenib is administered as an oral solution. Patients should be monitored for potential increased toxicities of the drug. No pharmacokinetic data of the oral sorafenib solution using any fluids other than water were available. Neither the stability of oral sorafenib suspension nor the administration of the suspension through a feeding tube was studied. Therefore, it is advised that the suspension be administered within 1 hour after preparation.<sup>93</sup>

### Palatability

Young children and the elderly often have difficulty swallowing solid dosage forms. Small pill size or liquid dosage forms are better suited for these patient populations. The main problem with using an oral liquid is its palatability since taste sensation differs from one person to another and is age dependent.<sup>143</sup> The appropriate choice of taste, odor, color, palatability, and sweetness of an oral liquid preparation may encourage drug

therapy adherence, especially in children.<sup>142</sup> The active ingredient of some of the drugs may produce an unpleasant taste, and the manufacturer usually applies a flavored sweetened film coating onto the tablets to improve palatability.<sup>143</sup> Most oral anticancer drugs are also surrounded by a wax matrix to prevent exposure to the health care worker. If these tablets are crushed, the patient would be subjected to the unpleasant taste, which could impair drug adherence.

### Alternative Delivery Methods to Extemporaneous Oral Liquid Formulations

When a patient cannot swallow a tablet or capsule, a commercially available oral liquid formulation should be preferred before considering the extemporaneous compounding method. Examples of oral anticancer liquid formulations that are commercially available include megestrol and tamoxifen.<sup>18, 19</sup>

Ideally, the source of an active drug for preparation of an extemporaneous oral liquid should be a pure drug. Since the pure drug is usually not easily available, it is common practice to obtain the pure drug from injectables, tablets, or capsules.

### Crushing Tablets or Opening Capsules

The most common method of preparing an extemporaneous oral liquid formulation from the solid dosage form is pulverization using a mortar and pestle.<sup>140</sup> Before a tablet is crushed or a capsule is opened to empty the contents, it is important to understand the pharmacokinetics of the drug and to research if any stability data are available in the literature. Almost all oral anticancer agent tablets are film coated to protect the handler from direct contact with the active ingredient. In addition, a coating is necessary for tablets that have an unpleasant taste, and a smoother finish makes large tablets easier to swallow.<sup>143</sup> Coatings are also useful to extend the shelf-life of pharmaceutical ingredients that are sensitive to moisture or oxidation.<sup>143</sup>

The practice of crushing a tablet or opening a capsule of an oral anticancer agent is generally not recommended because it raises the concern of unreliable dosing as well as posing a hazard to human health. Certain tablets, although they are not designed to be extended release or enteric coated, may not be crushed because it can alter the pharmacokinetics or bioavailability of the drug. For example, a pharmacokinetic study



showed that administration of a single pazopanib 400-mg crushed tablet increased the AUC and  $C_{\max}$  by 46% and by approximately 2-fold, respectively, as well as decreased time to  $C_{\max}$  by 2 hours compared with administration of a whole tablet.<sup>88</sup> Because of the potential of an increased rate of absorption that may lead to an increase in systemic exposure and drug toxicities, pazopanib tablets should not be crushed.

Although some oral anticancer drugs such as azathioprine,<sup>25, 26</sup> busulfan,<sup>33</sup> chlorambucil,<sup>25</sup> finasteride,<sup>17</sup> mercaptopurine<sup>25</sup> and thioguanine<sup>25</sup> may be crushed, no formal pharmacokinetic studies evaluating efficacy and safety of extemporaneously prepared oral liquids from the crushed tablets have been conducted. These liquid formulations, as well as those made by emptying the contents from capsules, should be prepared at least under a class I biologic safety cabinet or bench-top hood with high-efficiency particulate air (HEPA) filters as required by the National Institute for Occupational Safety and Health (NIOSH).<sup>151</sup>

When preparing an oral liquid from a soft gelatin capsule that contains liquid content (e.g., tretinoin or isotretinoin), one may place the capsule and warm fluid (water or milk) inside an oral syringe to allow the capsule to dissolve. The suspension can be administered orally or through a nasogastric tube.<sup>67, 109</sup>

### Tablet or Capsule Dispersion

As most of the drugs are not completely soluble in water, some agents may be dispersed in water or other fluids to form a suspension before administration. One study showed that neither tablet hardness nor partial removal of film coating of tablets appeared to affect the dispersion time.<sup>74</sup> Oral anticancer agents that can be dispersed into water or other fluid, but must be administered immediately after preparation due to lack of stability data, include bexarotene,<sup>28</sup> capecitabine,<sup>36</sup> dasatinib,<sup>43</sup> erlotinib,<sup>45–47</sup> gefitinib,<sup>62</sup> imatinib,<sup>65</sup> isotretinoin,<sup>67</sup> megestrol,<sup>74</sup> sorafenib,<sup>93</sup> tamoxifen,<sup>74</sup> and tretinoin.<sup>109</sup> The active ingredients of some of the drugs may have an unpleasant taste. The dispersed solution may be administered with a flavored beverage to mask the bitter taste. However, when choosing a beverage to be mixed with a drug, one should be aware of any potential drug-food interactions. Grapefruit or grapefruit juice is one of the most widely studied foods shown to interact with many drugs.<sup>152, 153</sup> It appears that grapefruit juice

mostly affects drugs with a high first-pass metabolism mediated by cytochrome P450 (CYP) 3A4 or as substrates of P-glycoprotein.<sup>152, 153</sup>

Although no formal studies evaluated the interaction between grapefruit juice and oral agents used in oncology, including aprepitant,<sup>116</sup> dasatinib,<sup>42</sup> erlotinib,<sup>44</sup> gefitinib,<sup>62</sup> and imatinib,<sup>65</sup> interactions may be possible. The manufacturers recommend that these drugs should not be mixed with or be dispersed in grapefruit juice due to potential changes in the plasma concentration and AUC of these drugs that may lead to increased toxicities or reduced effectiveness. One group of authors demonstrated a clinically significant interaction between grapefruit juice and nilotinib,<sup>87</sup> whereas another study evaluating the interaction between sunitinib and grapefruit juice showed a marginal increase in sunitinib exposure, which may not be clinically significant.<sup>97</sup> Grapefruit juice has been shown to reduce the plasma concentration of etoposide, which is a CYP3A4 substrate.<sup>54</sup>

Other citrus or fruit juices such as orange juice and apple juice appear to have inhibitory effects on organic anion-transporting polypeptides and have been shown to interact with some drugs *in vitro*.<sup>154–156</sup> However, until more studies are available to determine if these particular fruit juice–drug interactions are clinically significant, specific recommendations on avoiding the mixing of the fruit juices other than grapefruit juice with oral anticancer therapies cannot be made.<sup>156</sup> The rate, extent of absorption, or bioavailability of some oral anticancer agents (e.g., estramustine) may be impaired by products that contain milk, calcium, magnesium, or other polyvalent ions.<sup>48</sup> These products should not be taken concomitantly with these anticancer agents.

### Oral Administration from Injectable Forms

In patients who cannot swallow pills, the use of an injectable drug given parenterally should be ideal. However, it may not be the most convenient route if the treatment needs to be given on a long-term basis. In some cases, after careful consideration of compatibility, excipients in the injectable form, stability, bioavailability, and drug absorption changes, an injectable formulation may be considered for oral use. However, injectable drugs that are chemically destroyed by gastric acid should not be used for oral administration.<sup>143</sup> An advantage of using the injectable form of a drug orally is that the mess of

handling the powder pulverized from the crushed tablets or opened capsules can be avoided. More important, it can prevent or minimize exposure to hazardous drugs through aerosolization during the compounding process. Some examples of injectable drugs that can be taken orally include cyclophosphamide,<sup>38–41</sup> etoposide,<sup>50</sup> mesna,<sup>130</sup> and antiemetics such as dolasetron<sup>120</sup> and ondansetron.<sup>133</sup>

When the injectable form of a drug is used to prepare an oral formulation, the dosing may be different depending on the extent of first-pass metabolism, resulting in poor oral bioavailability of the drug.<sup>143</sup> For example, the bioavailability of etoposide<sup>52</sup> and mesna<sup>129</sup> is about 50%. When these drugs are given orally, the dose should be twice the intravenous dose. The extemporaneous oral solution of these drugs prepared directly from the injectables often produces a bitter or unpleasant taste. It is recommended that these drug solutions be mixed with orange or apple juice or flavored syrup before administration.<sup>50, 51, 130</sup>

When extemporaneous oral liquid formulations of oral anticancer drugs are prepared and administered, especially in the hospital or nursing home setting, specialized oral syringes, not standard slip tip or Luer-Lock (BD, Franklin Lakes, NJ) syringes, should always be used.<sup>157</sup> This is particularly important when the oral liquid formulations are prepared directly from the intravenous dosage form (e.g., cyclophosphamide, etoposide, mesna) to prevent inadvertent intravenous administration.

### Extemporaneous Oral Liquid Preparation Through a Feeding Tube

No formal pharmacokinetic studies evaluating the efficacy and safety of extemporaneously prepared oral anticancer liquid formulations administered through feeding tubes were found during the literature review. Nevertheless, it is a common practice, especially in a pediatric setting where the extemporaneously prepared oral liquids are given through nasogastric or feeding tubes in infants or children who are unable to swallow tablets.<sup>32, 34, 50, 51, 67, 109</sup> Since most of these compounded oral liquid formulations given through feeding tubes have not been pharmacokinetically validated, whether the patient receives appropriate or adequate dosing is not known. If unavoidable, it is good general practice to hold the tube feeding at appropriate intervals before drugs are given through the feeding tube to allow

optimal absorption of the drug, followed by flushing the tubing with adequate amounts of water to ensure delivery of the entire dose.<sup>158</sup> The health care providers should also check for any significant interactions with the feeding tubes or enteral feedings to ensure appropriate delivery of the intended doses.<sup>159</sup> When handling and administering hazardous oral drugs through a feeding tube, nurses or caregivers should wear nonpermeable gowns and double gloves.<sup>151, 160</sup>

### Current Practices and Challenges of Extemporaneous Compounding in the Community Setting

There is a paucity of data in terms of stability, bioequivalence, and safety of extemporaneously compounded oral anticancer liquid formulations compared with solid dosage forms. These unlicensed drug preparations may pose a greater risk of potentially harmful medication errors and adverse drug reactions because of the inherent risks associated with the compounding process.

Several organizations including the American Society of Health-System Pharmacists, NIOSH, and USP Chapter 797 have published national guidelines detailing the procedures and requirements for compounding chemotherapy to prevent work-related injury and illness caused by exposure to hazardous drugs.<sup>151, 160, 161</sup> These guidelines are also intended to set standards of practice that appear to be primarily applicable to traditional settings, including hospitals and ambulatory infusion clinics, but have not adequately addressed the safety of handling and administration of oral chemotherapy in the community and home settings.

The reasons why only very limited compounding information is provided in manufacturers' package inserts include the following: the hazardous nature of these drugs that requires specific safe handling and disposal, nonapproved pediatric use of most oral anticancer drugs, lack of financial resources and insufficient investment in clinical trials, limited research on drug disposition in various pediatric populations worldwide, the complexity of performing bioavailability and pharmacokinetic and pharmacodynamic studies, and cumbersome legal issues.<sup>142, 162</sup>

There are also barriers that prevent community pharmacies from preparing extemporaneous oral anticancer drug formulations for a patient for home use. Very few community pharmacies have the capacity to compound oral anticancer liquids largely due to lack of financial incentives (low

volumes of such prescription requests, purchase of the costly equipment such as a biologic safety cabinet or bench-top hoods with HEPA filters), low comfort and confidence levels due to inadequate experience with chemotherapy, minimal access to relevant information sources, the unwillingness to comply with cumbersome laws and regulations for handling and disposal of hazardous drugs, and time consumption on stringent chemotherapy compounding training for pharmacy staff.

Oral chemotherapy drugs are generally dispensed in the retail pharmacy setting; however, no data have been published that specifically evaluate the chemotherapy compounding pattern in outpatient pharmacies. One group of authors conducted a survey on the extemporaneous compounding practices among all U.S. compounding pharmacies.<sup>163</sup> Five hundred twenty-two surveys were mailed, and 117 completed surveys were returned and analyzed, for a response rate of 22%. Although oral chemotherapy compounding was not addressed in the study, one may raise a concern that one third of respondents claimed that their pharmacies neither had compounding policies and procedures, nor provide staff training in compounding.<sup>163</sup> Another issue is, in real-life community pharmacy practice, compounding oral drugs is often performed by trainee staff who may not be adequately qualified to reformulate a preparation.<sup>164–165</sup>

Another survey study assessed community pharmacists' attitudes toward and knowledge of oral chemotherapy in terms of indications, general dosing principles, drug interactions, adverse effects, and special handling precautions.<sup>166</sup> The response rate in the study was 22.5%. The average scores with regard to knowledge about general dosing principles and chemotherapy adverse effects were reported as 69% and 45%, respectively. In terms of knowledge of proper handling of oral chemotherapy, the average score was low at 25%. Only 35% of pharmacists knew that crushing cyclophosphamide tablets at a patient's request was inappropriate, and 95% of respondents reported that their pharmacy did not have a separate counting tray for cytotoxic drugs. The results of these two survey studies have indeed raised a concern about inadequate training and education on the safety of dispensing and handling of oral chemotherapy in community pharmacies.

When a hospitalized patient needs to continue an extemporaneously compounded oral anticancer liquid drug at home, inpatient pharmacies at

most institutions cannot dispense these oral liquids on an outpatient basis because most third-party insurance companies would not pay for them. In some cases, a patient may be able to take the prescription to an outpatient pharmacy that is affiliated with the hospital, and the oral liquid is compounded using an inpatient chemotherapy hood and is then dispensed and billed by the outpatient pharmacy. Most oncology pharmacies in an ambulatory care setting may not have a separate retail license to dispense oral chemotherapy and are not legally liable to prepare extemporaneous oral anticancer liquid drugs from prescribed oral tablets that a patient may bring from a retail pharmacy. Such drug prescriptions may be prepared only in a specialty compounding pharmacy, which may result in delaying treatment, especially if a patient lives in a rural area where there is no local specialty compounding pharmacy. In addition, compounded drugs may not always be reimbursed by third-party payers.

#### **Adherence and Safe Handling of Oral Anticancer Agents in the Home Setting**

As more oral anticancer agents are prescribed in an outpatient setting for patients to self-administer at home, adherence and safe handling of these hazardous agents have become major concerns because nonadherence and improper handling or administration may negatively affect the treatment outcomes and lead to serious medication errors. According to one report, adherence rates for oral chemotherapy vary from less than 20% to 100%.<sup>167</sup> The reasons for nonadherence are multifactorial and include complex treatment regimens, poor communication with health care providers, history of mental illness, inadequate social support, patient dissatisfaction with care, history of nonadherence, and substantial behavioral change required.<sup>167</sup> In addition, drug adherence for patients with cancer can be even more challenging because the substantial increased cost of cancer treatment, as well as an increased use of oral anticancer therapies. For today's cancer care, patients need to assume more or even total responsibility for managing their oral anticancer drugs at home. For those who cannot swallow pills and require an extemporaneous method of preparing their drugs, there is the potential of further decreasing the adherence rate and increasing dosing errors.

In a pediatric ambulatory care setting, although parents of pediatric patients may be more



conscientious about drug administration, the complexity of chemotherapy regimens, different dosing schedules, and the number of other required drugs can be overwhelming to caregivers without training and education. One study that evaluated the rate of medication errors in children with acute lymphocytic leukemia who received chemotherapy at home reported that a medication error occurred for almost 10% of chemotherapy agents prescribed for these patients.<sup>168</sup> More than two thirds of medication errors detected were related to administration.

One group of authors reported that the drug adherence rate was increased from 16.8–21% to 45–48% for patients with hematologic malignancies who received education programs during home visits; education about the disease, adverse effects of drugs, and adherence to drug regimens; and training on pill taking including practicing self-medication in a controlled environment.<sup>169, 170</sup>

As previously discussed, one of the barriers of practicing safe handling of oral anticancer therapy at home in patients unable to swallow pills is the lack of proper counseling and education, and the limited access to preparation of extemporaneous oral anticancer liquid in an outpatient setting. Health care providers, patients, or caregivers who prepare extemporaneous oral anticancer liquid formulations should be properly trained and educated by following standard procedures and by using established precautions and required personal protection equipment.<sup>160, 161</sup> In general, for intact film-coated oral chemotherapy pills, no specific handling procedures are necessary.<sup>36</sup> Although the data on the ability of personal protection equipment to protect against drug exposure from handling oral agents are unclear, wearing gloves and gowns as well as thorough hand washing should be considered when administering an oral anticancer liquid formulation to minimize the risk of skin exposure in case of splashing and contamination of the hands.<sup>7</sup> Spill kits should always be available in case of a spill.<sup>7</sup>

Oral anticancer drugs are not only potentially carcinogenic, but also teratogenic. Although little or no data are available to evaluate the adverse effects on reproductive health in female family members or caregivers resulting from the exposure to antineoplastic drugs, studies have shown an association between occupational exposure to these hazardous drugs and miscarriages and stillbirths among nurses and pharmacists.<sup>171–177</sup> These risks are directly related to the extent of exposure and the potency and

toxicity of the hazardous drug. Based on these data, caregivers who are pregnant or are breastfeeding should avoid direct contact with, or the handling of, these drugs, especially when an extemporaneous oral liquid preparation method needs to be used for administration.

### Role of the Pharmacist and Recommendations

Since the prescribing of oral anticancer therapies often takes place in the outpatient setting, pharmacists can play an essential role in educating patients and caregivers on the proper use of these drugs and in verifying dosing. Oncology clinics provide an ideal opportunity for oncology pharmacists to collaborate with the oncology group to establish pharmacist-managed oral chemotherapy protocols to coordinate better pharmaceutical care and optimize treatment outcomes. Through the implementation of these protocols, oncology pharmacists can assist physicians in providing more in-depth patient education on adverse effects, safe handling of these hazardous agents at home, as well as close monitoring for adverse effects and drug adherence through routine phone and/or clinic visit follow-up.

When an extemporaneous preparation of oral anticancer liquid by a specialty pharmacy is required, an oncology pharmacist may assist patients in locating a specialty compounding pharmacy in their area to prevent potential delay in administration and nonadherence. For a hospitalized patient who needs to continue extemporaneously prepared oral anticancer therapy at home, continuity of care as an outpatient can be coordinated between a prescriber and an on-site outpatient pharmacy, if available, to help avoid unnecessary delay in administration of therapy.

Since some private oncology clinics do not have oncology pharmacists, effective communication between prescribers, oncology nurses, and community pharmacists may also help improve the safe delivery and administration of oral anticancer agents. One survey reported that after the Internet, community pharmacists were considered the second major source of information on oral chemotherapy for caregivers of pediatric cancer patients.<sup>11</sup> Therefore, community pharmacists should become knowledgeable about oral chemotherapy and educate patients and caregivers on their adverse effects and management, as well as proper procedures for handling and disposal of these drugs.

With regard to certain oral anticancer liquid formulations that can be prepared simply by dispersing a tablet in water or other beverages, oral instructions as well as patient-friendly written educational materials (e.g., leaflets or pamphlets) in lay language can be provided to patients and caregivers. An example of this type of educational information for patients taking capecitabine is shown in Appendix 1. This information should include the name of the drug and its indication, preparation method, dosing and schedule instructions, administration technique, storage conditions, proper disposal of contaminated medicine cups, adverse effects, and symptom management. These teaching tools have been shown to be very effective at improving patient education and for enhancing absorption and understanding of the information.<sup>178–181</sup> The Multinational Association for Supportive Care in Cancer has recently developed a teaching tool for assisting health care providers in the assessment and education of patients receiving oral agents for treatment of cancer.<sup>182</sup>

Implementation of policies and procedures for preparing, administering, handling, and disposing of these oral hazardous agents, including extemporaneous oral liquids, in both hospital and outpatient settings, is important to minimize exposure and to ensure the safety of the patients, nurses, or caregivers who administer the drugs.<sup>160</sup> An organization can establish a compounded drug formulary to promote appropriate compounded drug utilization by creating a uniform standard for compounding practice, providing a database of dynamic and uniform standard compounding recipes based on clinical evidence, reducing variation in compounded products, and identifying and eliminating problems in compounding practice.

The pharmaceutical industry and national pharmacy organizations may bring researchers together to promote research and to organize charitable activities to fund research in this area. Manufacturers can also make an effort to include the bioavailability, variability, and stability data for extemporaneous oral compounding of any new oral anticancer agents. It has been recently proposed by pediatric oncology experts that the development of pediatric formulations be seriously considered when promising data emerge from adult trials, when a commitment is made to begin phase I trials in adults, or when there is enthusiasm in the pediatric oncology community about the drug in question.<sup>9</sup>

Research in designing a formula for an extemporaneous oral anticancer liquid should be universally acceptable and as simple as possible. The use of unnecessary or uncommonly available ingredients as excipients should be avoided if possible. Stability and bioavailability data should also be validated through well-designed pharmacokinetic studies. Investigators should always be encouraged to share the formulation details and their institutional experiences on the extemporaneous preparation of oral anticancer liquid dosage forms with other health care professionals through publications and/or national pharmacy conferences.

As more oral anticancer agents are being developed and approved, development of national guidelines to promote standards of practice in nontraditional settings such as long-term care facilities, community pharmacies, and/or patients' homes is urgently needed to help improve the safety of dispensing and handling of oral chemotherapy, including extemporaneous compounding of oral liquid formulations of these drugs.

## Conclusion

This review provided an overview of the recipes and stability data for extemporaneous compounding of oral anticancer liquid dosage formulations and alternative drug delivery methods available in the literature. Although compounding recipes have been found in about 46% of the currently marketed oral anticancer agents, there is a paucity of data in terms of stability, bioequivalence, and safety of these extemporaneously compounded oral formulations. Currently, in community and home settings, oral chemotherapy agents are often dispensed or administered without proper safeguards. In addition, multiple barriers exist that prevent community pharmacies from preparing extemporaneous oral anticancer liquid drugs. Development of national guidelines to promote standards of practice in these nontraditional settings may help improve the safety of dispensing and handling of oral chemotherapy, including extemporaneously compounded oral liquid formulations of these hazardous drugs.

An ideal opportunity exists for oncology pharmacists, as well as community pharmacists, to play a significant role in educating and monitoring patients who receive oral chemotherapy in order to ensure dosing accuracy, safe handling, and proper disposal of these hazardous drugs.

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**Appendix 1. Sample of Patient Education Information on Oral Chemotherapy Using Capecitabine as an Example**

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Generic name: Capecitabine

Brand name: Xeloda

Uses:

- For the treatment of various types of cancer such as colon, rectal, and breast cancer.

How to store this drug:

- You should store the drug in the original prescription bottle or a chemotherapy pill box at room temperature.
- Keep the drug away from heat, small children, and pets.

How to take this drug:

- You will take \_\_\_\_\_ 500-mg tablets and \_\_\_\_\_ 150-mg tablets by mouth twice/day, 10–12 hours apart with a glass of water for 2 weeks, followed by 1 week off.
- You may take the pills with food or within 30 minutes after you have eaten.
- The tablets come in 500-mg and 150-mg sizes.

What you can do if you cannot swallow the pills:

- Crushing or splitting tablets should be avoided.
- You may disperse the capecitabine tablets in an appropriate amount of lukewarm water (approximately 20–50 ml of water for each 500-mg tablet), and stir the mixture for about 15 minutes until the tablets dissolve. You should drink the mixture immediately, then rinse the cup with some water, and consume the water to ensure administration of the full dose.
- A bitter taste of the solution can be flavored with a fruit juice or squash, but the use of grapefruit juice should be avoided.
- If you have a feeding tube, you may also draw the mixture into an oral syringe, then administer the solution through the tube. Make sure to flush the feeding tube well with a minimum of 30 ml of warm water.

Other precautions you should take when handling the chemotherapy pills or solution at home:

- Do not become pregnant while taking this drug.
- Caregivers who are pregnant or of childbearing potential or who are breastfeeding should avoid exposure to crushed and/or broken tablets.
- It is recommended that you or your caregiver wear gloves when handling this drug.
- You should wash your hands before and after touching the pills.
- When the drug is prepared in a liquid form, it is advisable to place a plastic-backed absorbent pad on the work area in case of a potential for spilling, spraying, or splashing while pouring the liquid into the medicine cup, or administering the drug by oral syringe.
- You should have a spill kit and hazardous drug waste container ready; these may be obtained from your oncology health care providers.
- Any disposable oral syringes and medicine cups contaminated with the chemotherapy agent should be placed in a sealable plastic bag, and must be discarded into the hazardous drug waste container.
- Wash hands thoroughly with soap and water after removing gloves.
- Return the filled hazardous drug waste container to the oncology clinic for proper disposal.

Possible side effects and management:

- Please refer to drug-specific information that is provided by your health care provider.

Possible drug-food or drug-drug interactions:

- Please consult the pharmacist, physician, or nurse in your clinic.
-