AAPS PharmSciTech, Vol. 16, No. 5, October 2015 (© 2015)
DOI: 10.1208/s12249-015-0297-x

Brief/Technical Note

Dissolution Testing for Bioavailability of Over-the-Counter (OTC) Drugs—a Technical Note

Zongming Gao,[1,5] Lawrence Yu,[2] Stephanie Clark,[1] Mike Trehy,[1] Terry Moore,[1] Benjamin Westenberger,[1] Lucinda Buhse,[1] John Kauffman,[1] Benjamin Bishop,[3] Lydia Velazquez,[3] and Scott Furness[4]

Received 1 August 2014; accepted 19 January 2015; published online 14 February 2015

KEY WORDS: bioavailability; dissolution; OTC; over-the-counter drug; solubility.

INTRODUCTION

Over-the-counter (OTC) drug products are medicines that can be sold directly to a consumer without a prescription from a health-care practitioner. OTC drugs generally have these characteristics which have been summarized on FDA's website "1) their benefits outweigh their risks; 2) the potential for misuse and abuse is low; 3) consumers can use them for self-diagnosed conditions; 4) they can be adequately labeled; and 5) health care practitioners are not needed for the safe and effective use of the product" [1].

OTC monograph drugs play an increasingly important role in the health-care system. There are more than 80 therapeutic categories and an estimated 100,000 OTC drug products in the US market. Because of the sheer volume of OTC drugs on the market in 1972, the FDA decided that a product-by-product application review process would be impractical and consequently created the OTC monograph system to review categories of drugs and make a determination as to their monograph status and whether they are generally recognized as safe and effective (GRAS/E). This means that certain active pharmaceutical ingredients (API) and/or categories of OTC drugs may be marketed without FDA pre-review that is typically expected for New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs). This regulatory pathway is available to industry if they conform to the OTC monograph guidelines for the API and conform to OTC labeling requirements. Since the OTC monograph system regulates the APIs, instead of the specific drug product, manufacturers are free to include any excipients that serve a pharmaceutical purpose, provided that those excipients are recognized by Center for Drug Evaluation and Research (CDER) to be safe.

Recently there have been concerns within FDA regarding OTC monograph drugs, specifically low-solubility drugs, because their bioavailability can be formulation dependent. This paper presents results of solubility and dissolution testing of four OTC drug products for the purposes of exploring the possible impact of a drug product's formulation and various biorelevant dissolution media on its bioavailability. We chose four drugs for testing and made preliminary determinations on their solubility in order to have a range of drugs with varying solubilities and dissolutions. Two highly soluble drugs (dextromethorphan HBr and guaifenesin) and two poorly soluble drugs (meclizine HCl and phenazopyridine HCl) were selected for study. The solubility of each API was measured and classified according to the Bioequivalence Classification System (BCS) Guidance [2]. Dissolution testing of these drugs was also conducted. The US Pharmacopeia (USP) dissolution methods for the four drugs call for water or acid (0.1 N hydrochloric acid) as the dissolution media. Water as a dissolution media is usually a poor choice because there is no control of pH. Furthermore some patients may have compromised digestive systems, and even for healthy people, the pH in the GI tract can range from a pH of 1.2 in the stomach to 6.8 in the small intestine. Therefore, dissolution profiles of these four drug products were presented at the recommended conditions in their corresponding USP monograph and at pH values of 1.2, 4.5, and 6.8 as suggested in a FDA BCS Guidance [2].

[1] Division of Pharmaceutical Analysis, St. Louis, MO 63110, USA.
[2] Office of Pharmaceutical Quality, Silver Spring, MD 20993, USA.
[3] USPHS Officer assigned to Division of Nonprescription Regulation Development, Silver Spring, MD 20993, USA.
[4] Office of New Drug Quality Assessment, Silver Spring, MD 20993, USA.
[5] To whom correspondence should be addressed. (e-mail: zongming.gao@fda.hhs.gov)

MATERIALS AND METHODS

Materials

The drug substances examined in this study are shown in Table I. Dextromethorphan HBr (D9684-10, Lot#090M1298V), guaifenesin (#PHR1027, Lot# P500027), and phenazopyridine HCl (34076–100, Lot# SZBB172XV) drug substances were purchased from Sigma-Aldrich. Meclizine HCl standard substance (Lot#KOK260) was purchased from USP.

Drug products used in this study were purchased on the US market, and the API and excipients labeled on the products are listed in Table II.

Equipment

Thermoforma Orbital Shaker (420-4, Waltham, MA) was used to shake sample solutions at 100 RPM and 37°C. Orion pH Meter (710-1, Pittsburgh, PA) was used to measure solution pH. Two-point calibration with pH reference solution was performed before use of the pH meter. A Distek dissolution apparatus (2100A-2, North Brunswick, NJ) was used to conduct dissolution testing. For dissolution methods that require UV-Vis as the determinative step, an Agilent UV-Vis Spectrophotometer (8453-1, Santa Clara, CA) was used. For dissolution methods that require HPLC, an Agilent 1290 HPLC system with DAD detector was used.

Solubility Measurements

The solubility of each API was determined at several pH values following the FDA BCS Guidance [2]. A solution saturated with drug substance was shaken at 37°C for at least 24 h before its concentration was determined by UV-Vis or HPLC. The solution pH values were 1.2, 3.0 (phthalate buffer), 4.5, 5.5 (acetate buffers), and 6.8 (phosphate buffer). Lab-deionized (DI) water was also used as a medium. Each medium pH was measured using a pH meter before and after analysis. A minimum of three replicate determinations of solubility in each pH condition were performed.

Dissolution Testing

The dissolution testing was conducted using dissolution apparatus 1 or 2 as noted in Table III following the USP

Table I. Summary of Drug Substances

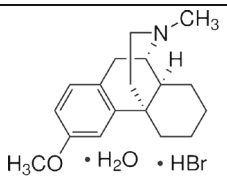
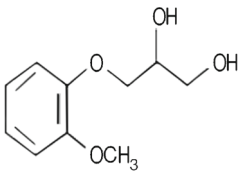
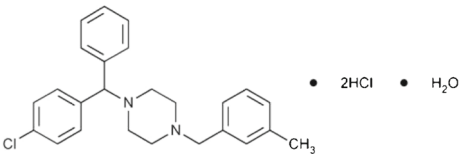
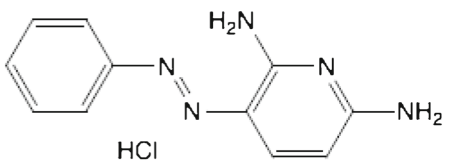
Chemical Name	Chemical structure	p*k*a	Molecular weight (g/mol)
Dextromethorphan HBr		8.3 [3]	370.3
Guaifenesin		15.6 [4]	198.2
Meclizine HCl		3.1, 6.2 [3]	481.9
Phenazopyridine HCl		5.2 [5]	249.7

Table II. Summary of Drug Products

Drug	Drug product	Active ingredients	Inactive ingredients
Dextromethorphan HBr	Walgreen's cold daytime non-drowsy multi-symptom caplets	10-mg dextromethorphan HBr, 325-mg acetaminophen, 5-mg phenylephrine hydrochloride	Corn starch, croscarmellose sodium, crospovidone, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, silica gel, stearic acid, sucralose, talc, titanium dioxide, flavor
	Walgreen's cold/flu daytime non-drowsy liquid caps	10-mg dextromethorphan HBr, 325-mg acetaminophen, 5-mg phenylephrine hydrochloride	Edible ink, gelatin, glycerin, polyethylene glycol, povidone, propylene glycol, purified water, sorbitol
	Walgreen's cold/flu non-drowsy night time liquid caps	15-mg dextromethorphan HBr, 325-mg acetaminophen, 6.25-mg doxylamine succinate	Edible ink, gelatin, glycerin, polyethylene glycol, povidone, propylene glycol, purified water, sorbitol
Guaifenesin	Walgreen's mucus relief chest congestion tablets	400-mg guaifenesin	Magnesium stearate, microcrystalline cellulose, FD&C Blue #1, aluminum lake, hypromellose, maltodextrin, polyethylene glycol, povidone, silicon dioxide, sodium starch glycolate, stearic acid
	CVS chest congestion relief tablets	400-mg guaifenesin	Magnesium stearate, microcrystalline cellulose. May also contain (colloidal) silicon dioxide, (Co) povidone, dicalcium phosphate, maltodextrin, sodium starch glycolate, stearic acid.
Meclizine HCl	Walgreen's Wal-Dram II antiemetic travel sickness tablets	25-mg meclizine	Corn starch, FD&C Yellow #10, lactose, magnesium stearate, silica gel
	CVS motion sickness II less drowsy formula tablets	25-mg meclizine	Corn starch, FD&C Red 40 aluminum lake, lactose, magnesium stearate, silica gel, raspberry flavor, sodium saccharin
Phenazopyridine HCl	AZO standard tablets	95-mg phenazopyridine HCl	Microcrystalline cellulose, pregelatinized corn starch, croscarmellose sodium, hypromellose, polyethylene glycol, magnesium stearate, carnauba wax and vegetable, povidone, corn starch
	CVS urinary pain relief tablets	95-mg phenazopyridine HCl	Microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, hypromellose, polyethylene glycol, magnesium stearate, carnauba wax, maize starch, lactose, magnesium silicate, pharmaceutical glaze, povidone, sodium starch glycolate
	Uricalm maximum strength urinary discomfort relief tablets	99.5-mg phenazopyridine HCl	Microcrystalline cellulose, hypromellose, lactose, magnesium stearate, magnesium silicate, mineral oil, sodium starch glycolate, titanium dioxide, triacetin, cranberry

FD&C Federal Food, Drug, and Cosmetic Act

Table III. The USP Dissolution Methods for Each Drug Product

Drugs		USP dissolution methods (USP34NF29)
Dextromethorphan HBr	Tablet	Apparatus 2 (paddle), 50 rpm, 0.1 N HCl, 900 ml Tolerance: NLT 75% at 45 min HPLC method for analysis
	Capsule	Apparatus 1 (basket), 100 rpm, DI water, 900 ml Tolerance: NLT 75% at 45 min HPLC method for analysis
Guaifenesin	Tablet	Apparatus 2 (paddle), 50 rpm, DI water, 900 ml Tolerance: NLT 75% at 45 min UV-Vis method for analysis
	Capsule	Apparatus 1 (basket), 100 rpm, DI water, 900 ml Tolerance: NLT 75% at 45 min HPLC method for analysis
Meclizine HCl, tablet		Apparatus 1 (basket), 100 rpm, 0.01 N HCl, 900 ml Tolerance: NLT 75% at 45 min HPLC method for analysis
Phenazopyridine HCl, tablet		Apparatus 2 (paddle), 50 rpm, DI water, 900 ml Tolerance: NLT 75% at 45 min UV-Vis method for analysis

NLT not less than, *HPLC* high-performance liquid chromatography, *DI* deionized, *USP* US Pharmacopeia, *UV-Vis* ultraviolet-visible

monographs. Mechanical calibration of the dissolution apparatus was performed according to ASTM 2503–07 [6]. The dissolution medium was degassed using our published degassing procedure [7]. DI water (USP method), pH 1.2 simulated gastric fluid (SGF without enzyme), pH 4.5 acetate buffer, and pH 6.8 simulate intestinal fluid (SIF without enzyme) were used as dissolution media. All dissolution runs were conducted at 37°C in 900 ml dissolution medium. One dissolution run with six samples for each drug product was conducted in each dissolution medium, and the dissolution results at each time point were an average of six samples. For phenazopyridine HCl products, 12 samples were tested so as to conduct statistical comparison between brands using f_2, the similarity factor [2].

To obtain dissolution profiles, samples were withdrawn at 15-, 30-, 45-, and 60-min time points. The sample aliquots were filtered through a 45-μm filter disk (Distek, part# 5720-0275-1000, Lot# 404082) and analyzed using the USP monograph methods. The current USP dissolution methods for all four products and their tolerance are summarized in Table III.

RESULTS AND DISCUSSIONS

FDA BCS Guidance states "the solubility class assignment is based on the highest dose strength (HDS) of an immediate release (IR) product. A drug is considered highly soluble when the HDS is soluble in 250 ml or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 oz) of water" [2].

Dextromethorphan HBr and guaifenesin are classified as highly soluble drugs because their BCS volumes are 22 and 2 ml, respectively. Meclizine HCl and phenazopyridine HCl are classified as low-solubility drugs because their BCS

Table IV. Summary of the Dissolution Results at 45 min and Medium pH After the Test

API	Product	Dissolution medium	%Dissolved at 45 min		Medium pH after dissolution tests
			Ave (6)	SD	
Dextromethorphan HBr	Walgreen's tablet 10 mg	0.1 N HCl (USP method)	96.7 (pass)	4.3	0.9
		pH 4.5 acetate buffer	92.2	2.8	4.4
		SIF (pH 6.8)	93.1	1.7	6.8
	Walgreens daytime capsule 10 mg	DI water (USP method)	96.8 (pass)	0.7	5.8
		0.1 N HCl	93.7	1.0	0.9
		pH 4.5 acetate buffer	95.4	0.8	4.5
		SIF (pH 6.8)	95.4	2.8	6.8
	Walgreens nighttime capsule 15 mg	DI water (USP method)	98.1 (pass)	0.6	5.7
		0.1 N HCl	94.7	0.9	0.9
		pH 4.5 acetate buffer	94.7	2.0	4.5
		SIF (pH 6.8)	94.8	2.3	6.8
Guaifenesin	Walgreen's mucus relief chest congestion tablet 400 mg	DI water (USP method)	91.4 (pass)	3.2	7.1
		SGF (pH 1.2)	88.1	4.2	1.0
		Acetate buffer (pH 4.5)	85.3	5.7	4.5
		SIF (pH 6.8)	87.3	2.3	6.8
	CVS chest congestion relief tablet 400 mg	DI water (USP method)	88.3 (pass)	1.2	5.6
		SGF (pH 1.2)	86.1	1.3	1.1
		Acetate buffer (pH 4.5)	87.6	1.7	4.5
		SIF (pH 6.8)	89.1	3.7	6.8
Meclizine HCl	Walgreens tablet 25 mg	0.01 N HCl (USP method)	99.3 (pass)	2.1	1.9
		pH 4.5 acetate buffer	41.2	1.4	4.5
		SIF (pH 6.8)	4.6	0.4	6.8
	CVS chewable tablet 25 mg	0.01 N HCl (USP method)	100.5 (pass)	3.3	1.9
		pH 4.5 acetate buffer	41.9	2.8	4.5
		SIF (pH 6.8)	3.1	0.4	6.8
Phenazopyridine HCl	AZO standard, 95-mg tablet	DI water (USP method)	99.72 (pass)	0.79	4.2
		SGF (pH 1.2)	63.85	2.54	–
		pH 4.5 acetate buffer	61.49	2.02	4.4
		SIF (pH 6.8)	16.19	4.93	6.8
	CVS, 95-mg tablet	DI water (USP method)	102.03 (pass)	3.94	4.3
		SGF (pH 1.2)	86.24	2.78	1.0
		pH 4.5 acetate buffer	54.32	8.57	4.5
		SIF (pH 6.8)	7.25	2.12	6.7
	Uricalm, 99.5-mg tablet	DI water (USP method)	105.52 (pass)	4.92	4.3
		SGF (pH 1.2)	85.50	2.73	1.1
		pH 4.5 acetate buffer	49.34	3.80	4.5
		SIF (pH 6.8)	11.48	3.43	6.7

USP US Pharmacopeia, *Ave* average, *SD* standard deviation, *SIF* simulate intestinal fluid, *SGF* simulated gastric fluid

volumes are larger than 250 ml when media pH is above 3. Early reports also show that these two poorly soluble drugs are BCS 2 drugs [8, 9].

The USP dissolution acceptance criteria (USP34NF29) for drug products examined in this study are not less than 75% (Q) at 45 min in the specified medium. The average dissolution results at 45 min are summarized in Table IV. All products tested in this study passed the USP acceptance criteria. For highly soluble drug products (dextromethorphan HBr and guaifenesin), the dissolution results at 45 min in all pH media were similar to those in the media specified in the USP monograph. However, the poorly soluble drug products (meclizine HCl and phenazopyridine HCl) exhibited different results when using alternative media. For both of these two drug products, the drug release decreased as the pH was raised.

To get a better view of drug release in dissolution medium, samples at three other time points (15, 30, and 60 min) were also collected. The dissolution profiles for drug products in the three different pH dissolution media are shown in Figs. 1, 2, 3, and 4. For higher solubility drug products, drug release was similar for each product in various biorelevant dissolution media as shown in Figs. 1 and 2 and Table IV. The results for various dextromethorphan HBr and guaifenesin products indicate that formulation, dissolution media, and dosage strength have no impact on highly soluble drugs.

The dissolution profiles for poorly soluble drug products are very different when tested in various biorelevant dissolution media (Figs. 3 and 4). The solubility results indicate that meclizine HCl and phenazopyridine HCl are highly soluble in DI water and acidic media and poorly soluble in pH 4.5 and 6.8 media. Reports on solubility and dissolution behavior of

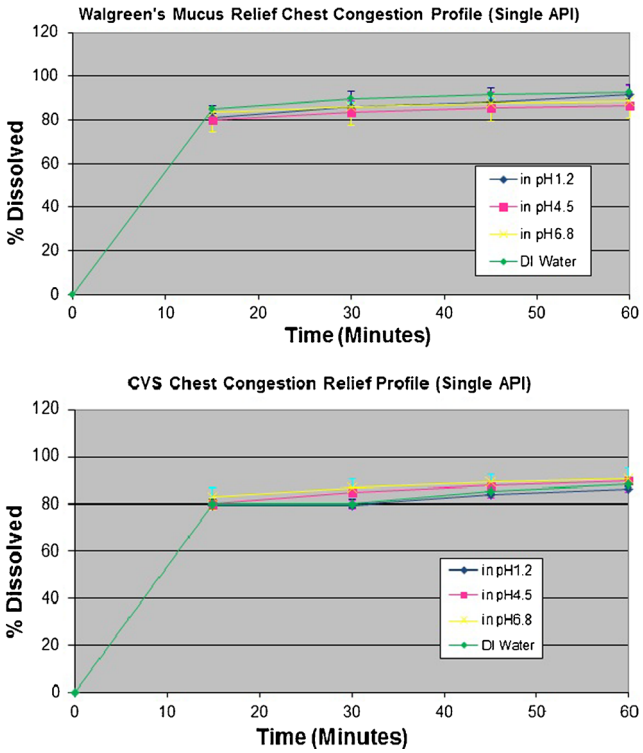


Fig. 2. Dissolution profiles of guaifenesin drug products in various dissolution media

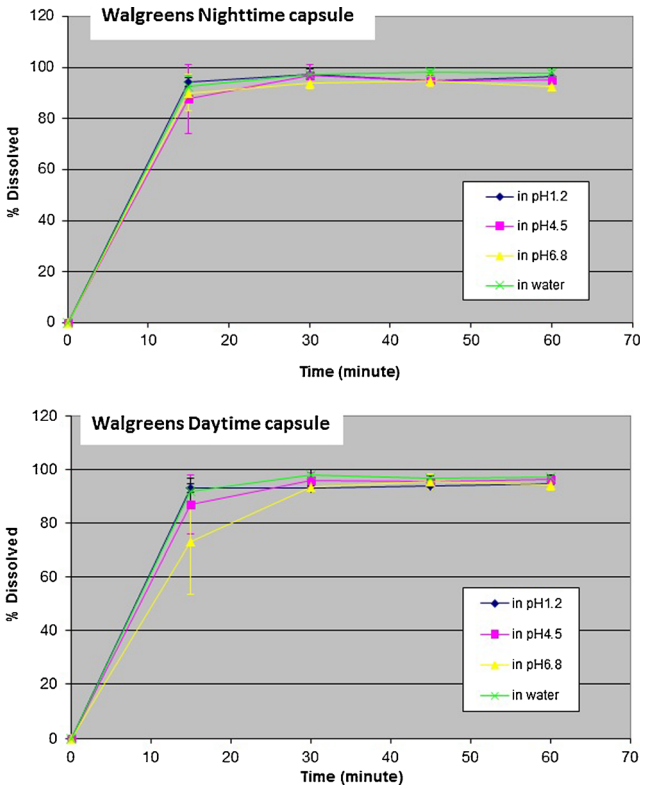


Fig. 1. Dissolution profiles of different dextromethorphan HBr drug products in various dissolution media

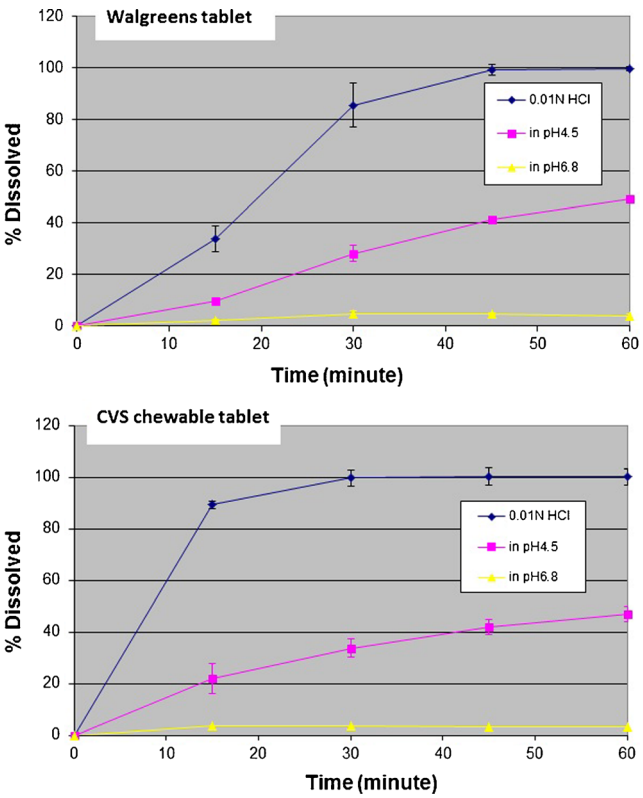


Fig. 3. Dissolution profiles of two meclizine HCl drug products in various dissolution media

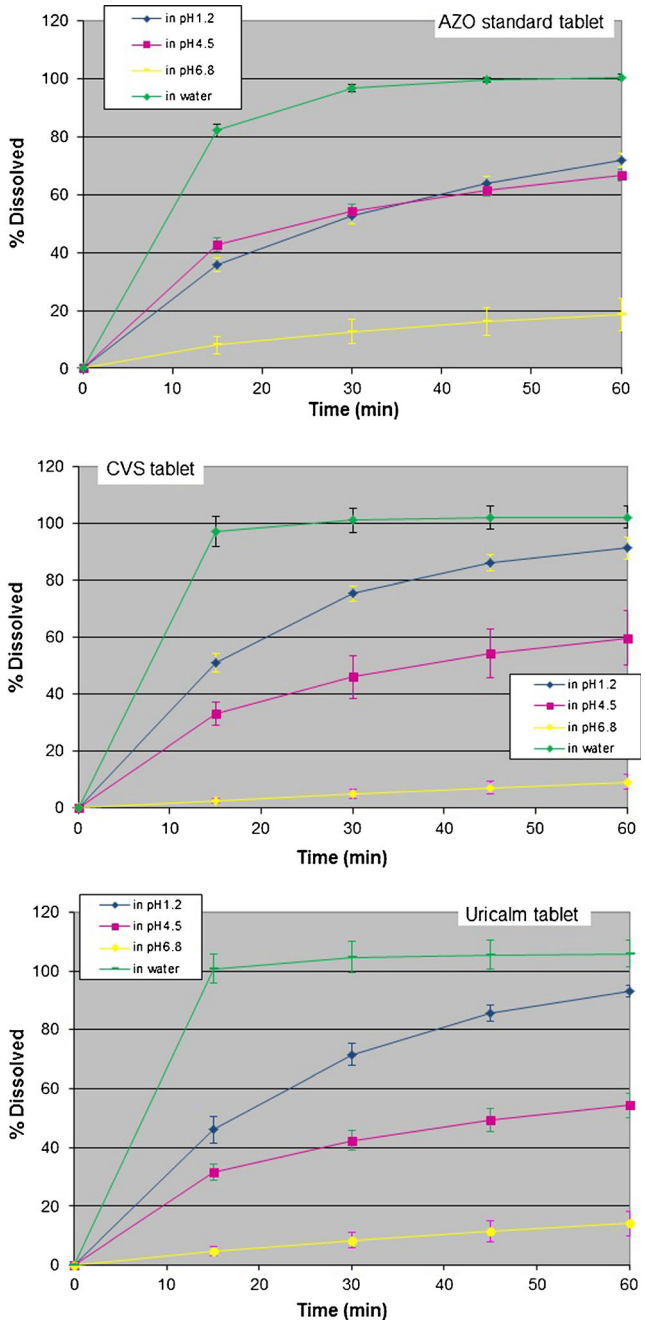


Fig. 4. Dissolution profiles with three phenazopyridine HCl products in various dissolution media

some pharmaceutical hydrochloride salts show that the solubility changes are caused either by common ion suppression of the solubility product equilibrium or by the conversion from the hydrochloride salt to the free base form [6, 10–13]. Our results on two low-solubility hydrochloride salts (meclizine HCl and phenazopyridine HCl) are in agreement with previous reports. Dissolution results show a completed drug release in the acidic medium but less drug released in the pH 4.5 and 6.8 buffers. Review of the p*K*a of the two APIs (see Table I) indicated that the low percent dissolution in high pH medium may be due to the conversion of the hydrochloride salt to its less soluble free base.

To address concerns on possible formulation-dependent drug bioavailability, especially for low-solubility OTC monograph drugs, different manufacturers and dosage strengths for phenazopyridine HCl drug products were compared in this study. The similarity factor (f_2) was calculated between products from three manufacturers of the phenazopyridine HCl drug products from their dissolution profiles (Table V). The FDA guidance for industry on dissolution testing of immediate release solid oral dosage forms [2] notes that f_2 values between 50 and 100 indicate similarity of two dissolution profiles. The results in Table V show that, in each medium, dissolution profiles are similar for these phenazopyridine HCl products except for pH 1.2 SGF. In SGF, the CVS and Uricalm products have similar dissolution profiles, but the AZO product has a lower dissolution rate. The product labels indicate that there are some excipients in the AZO product that are not in CVS and Uricalm products, and magnesium silicate is in CVS and Uricalm products and is not in the AZO products. Other formulation factors such as particle size, mixing, granulation and compression/encapsulation, *etc.* may also be affecting the dissolution of phenazopyridine HCl drug. Clinical data would be necessary to determine if the dissolution differences are manifested *in vivo*.

The FDA Guidance defines bioavailability as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action [14]. The small intestine with its large surface area is a major absorption site, and a drug should have sufficient aqueous solubility to dissolve in the gastric fluids at the absorption site. The studied highly soluble drugs showed dissolution results that met USP specifications and did not change when tested in the other biorelevant media, even though the drug products were from different manufacturers. However, drug release profiles for the studied poorly soluble drugs indicate that there may be potential bioavailability problems, even though they meet the USP acceptance criteria. In our case studies, both meclizine HCl and phenazopyridine HCl are poorly soluble in pH 6.8 SIF, and their drug products show very low dissolution results. A published paper performed a dissolution test using modified flow-through method with phenazopyridine HCl drug product, simulating the conditions in the GI tract by testing the drug in SGF for 1 h and then changing the medium to SIF [15]. The results show that after changing the medium to SIF, no additional drug was released, and the phenazopyridine became supersaturated then gradually precipitating in the SIF. This drug concentration drop in the SIF may reflect a potential reduction of the bioavailability of phenazopyridine HCl depending on the site of absorption or the stomach pH environment of the patient.

Table V. Statistical Comparisons (f_2) of Three Different Phenazopyridine HCl (N=12) Drug Products in Four Dissolution Media

Dissolution medium	Similarity factor, f_2		
	CVS *vs.* AZO	Uricalm *vs.* AZO	CVS *vs.* Uricalm
DI water	55	48	72
SGF (pH 1.2)	35	37	73
pH 4.5 acetate buffer	55	49	71
SIF (pH 6.8)	55	70	73

DI, deionized, *SGF* simulated gastric fluid, *SIF* simulate intestinal fluid

CONCLUSIONS

Four high volume OTC drug products sold in the US market were studied. Based on the BCS Guidance, two of them (dextromethorphan HBr and guaifenesin) were found to be highly soluble drugs and the other two (meclizine HCl and phenazopyridine HCl), poorly soluble drugs.

The dissolution measurements showed that all drug products met USP dissolution acceptance criteria of not less than (NLT) 75% in 45 min in specified dissolution medium.

The dissolution profiles for the two highly soluble drugs did not change when tested under a range of pH media, suggesting that these highly soluble drugs should be bioavailable regardless of the fluid pH in the GI tract. However, the dissolution profiles for the poorly soluble drug products differed when tested in various biorelevant media. In addition, when a statistical f_2 similarity factor was applied to compare phenazopyridine HCl drug products that were formulated by three different manufacturers, the results show that the different formulations do have statistically different dissolution results at certain conditions.

The results demonstrate that the release of poorly soluble drugs (meclizine HCl and phenazopyridine HCl) depends on both solubility and pH, which may ultimately affect drug performance. As a result, drug bioavailability may depend on drug formulation and the patient's GI condition, regardless of whether the product meets the USP acceptance criteria. How to factor this into development of OTC drug monographs is a challenge to be addressed, as the current monograph system does not have requirements for pre-approval of new formulations. In the meantime, these potential issues may affect consumers, even if they are not aware of them when selecting the right drug product for their condition.

Disclaimer Opinions expressed in this report are those of the authors and do not necessarily reflect the views or policies of the FDA.

REFERENCES

1. Drug applications for over-the-counter (OTC) drugs, http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/over-the-counterdrugs/default.htm. Accessed on 10/19/2012
2. FDA Guidance for Industry. "Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System". Food and Drug Administration, Center for Drug Evaluation and Research, August 2000.
3. pKa's of drugs and reference compounds, http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/A%20Practical%20Guide%20to%20Contemporary%20Pharmacy%20Practice/pdf/pKa-table.pdf. Accessed on 3/23/2012.
4. Drug Bank, http://www.drugbank.ca/drugs/DB00874. Accessed on 7/17/12.
5. Abu TM, Serajuddi N, Charle S, Jarowsk I. Effect of diffusion layer pH and solubility on the dissolution rate of pharmaceutical bases and their hydrochloride salts I: phenazopyridine. J Pharm Sci. 1985;74(2):142–7.
6. ASTM method E2503-07, Standard practice for qualification of basket and paddle dissolution apparatus.
7. Moore TW. Dissolution testing: a fast, efficient procedure for degassing dissolution medium. Dissolution Technol. 1996;3:3–5.
8. World Health Organization. Proposal to waive *in vivo* bioequivalence requirements for the WHO model list of essential medicines immediate release, solid oral dosage forms. Geneva; October 2005.
9. Wu C, Benet LZ. Predicting drug disposition *via* application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res. 2005;22:11–23.
10. Miyazaki S, Oshiba M, Nadai T. Precaution on use of hydrochloride salts in pharmaceutical formulation. J Pharm Sci. 1981;70(6):594–6.
11. Miyazaki S, Oshiba M, Nadai T. Unusual solubility and dissolution behavior of pharmaceutical hydrochloride salts in chloride-containing media. Int J Pharm. 1980;6:77–85.
12. Miyazaki S, Nakano M, Arita T. A comparison of solubility characteristics of free bases and hydrochloride salts of tetracycline antibiotics in hydrochloric acid solutions. Chem Pharm Bull. 1975;23(6):1197–204.
13. Miyazaki S, Oshiba M, Nadai T. Common ion effect of chloride on the dissolution properties of papaverine hydrochloride. Chem Pharm Bull. 1981;29(11):3414–7.
14. Guidance for industry bioavailability and bioequivalence studies for orally administered drug products—general considerations, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070124.pdf. Accessed on 1/7/2013.
15. Gao Z. Development of a continuous dissolution/absorption system—a technical note. AAPS PharmSciTech. 2012;13(4):1287–92.