Preparation and Stability Evaluation of Extemporaneous Oral Suspension of Valsartan Using Commercially Available Tablets

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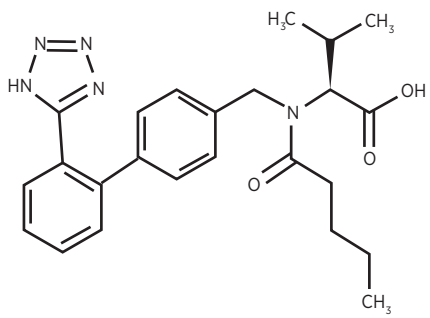
ABSTRACT

The aim of this study was to develop an extemporaneous valsartan suspension (80 mg valsartan/ 5 mL) starting from commercial tablets (80-mg/ tablet). A high-performance liquid chromatographic system was used for the analysis and quantification of valsartan in the samples studied. Samples of valsartan suspension for analysis were prepared as reported by the validated high-performance liquid chromatographic method and the dissolution tests were performed according to the U.S. Food and Drug Administration's method. The high-performance liquid chromatographic assay indicated that the 80-mg/5-mL valsartan suspension was stable for 30 days when stored at long-term and accelerated storage conditions. Valsartan release profile showed that approximately 85% of valsartan dissolved after 10 minutes and, accordingly, the calculation of similarity factor was not necessary. It is possible for the pharmacist to crush valsartan 80-mg tablets and prepare a suspension which has dosage flexibility that can be calculated according to body-surface area, kidney, and liver functions, without affecting the chemical stability of the active ingredient nor its dissolution profile and also have a cost-effective dosage form.

INTRODUCTION

Valsartan is chemically *N*-pentanoyl-*N*-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl] methyl}-L-valine (Figure 1.)

FIGURE 1. Chemical structure of valsartan.



Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT_1 receptor subtype present in many tissues, such as vascular smooth muscle and the adrenal gland.[1] Placebo-controlled trials have found valsartan to be both safe and effective for the treatment of hypertension.[2] When taken in a dosage of 80 to 320 mg once daily, the mean reduction in diastolic blood pressure is 6 to 9 mm Hg, and the mean reduction in systolic pressure is 3 to 6 mm Hg.[1] Studies have shown that it is as effective as enalapril, lisinopril, and amlodipine in the treatment of mild-to-moderate hypertension.[2-5] Valsartan also is rapidly absorbed from the gastrointestinal tract after oral administration and can be administered without regard to food intake.[6,7] The peak effect of valsartan is evident in 2 to 4 hours; the bioavailability is 25%. It has a half-life of 6 to 9 hours with approximately 24 hours of antihypertensive activity. Müller et al have shown that only 10% of the dose was excreted unchanged in urine. Regarding its liver metabolism, the enzymes responsible for its metabolism are unknown and no active metabolites have been identified.[8,9] Elimination occurs primarily in the bile (86%) and to a lesser extent via the kidneys (13%), largely as unchanged drug.5,10 This study aimed to evaluate the stability of valsartan suspension prepared from valsartan tablets.

MATERIALS AND METHOD

Materials and Chemicals

Valsartan USP reference standard (Lot K1K224; Holland Moran, Holon, Israel) was used. Valzan 80-mg tablets (Batch RD-07B12; expiry date 02/2014) were obtained from Pharmacare PLC, Ramallah, Palestine. Aerosil (Lot 3752112720) was obtained from Evonik Industries, Essen, Germany; xanthan gum (Lot 2B4886K) was obtained from CP Kelco, San Diego, Califor-

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nia; banana powder flavor (Lot D400262601) was obtained from Florasynth, Israel; titanium dioxide (Lot U0J001224) was obtained from Grenox GmbH, Germany; sugar (Lot 3003) was obtained from Sugat Ltd., Israel; hydroxypropyl cellulose (Lot 99636) was obtained from Hercules, California); sodium hydroxide (Lot B0817998) and monobasic potassium phosphate (Lot A0383573) were purchased from Merck, KgaA, Darmstadt, Germany.

High-performance liquid chromatography (HPLC)-grade solvents of acetonitrile (ACN) (Lot I674930), methanol (MeOH) (Lot I669207), ammonium dihydrogen phosphate (Lot A0221826); glacial acetic acid (Lot K43718463), and diethyl ether (Lot I626929) were purchased from Merck; hexane sulfonic acid sodium (Lot A0216197001, Acros organics) was purchased from Holland Moran. High purified water was prepared by using a Millipore Milli-Q plus water purification system. The HPLC grade solvents of ACN and MeOH were used as received. All other reagents were analytical grade.

Instruments and Chromatographic Conditions

The HPLC system consisted of LaChrom (Merck-Hitachi) equipped with model L-7100 pump, L-7200 autosampler, L-7300 column oven, DAD L-7450 photo diode array (PDA) detector, and D-7000 software HSM version 3.1 (Merck Hitachi, Kent, England).

The HPLC experimental conditions were optimized on an octadecyl silane C18 chemically bonded column (125 mm × 3.0 mm i.d., 5 mcm particles) that was purchased from ACE, London, United Kingdom. The optimum mobile phase was prepared by mixing water, acetonitrile, and glacial acetic acid (500:500:1, v/v/v). The mobile phase was filtered by using a 0.45-mcm microporous filter and was degassed by sonication prior to use. A wavelength of 273 nm was used. The flow rate used was 0.4 mL/minute and the injection volume was 10 mcl. The Diluent was prepared by mixing acetonitrile and water in the ratio of (1:1).

The peak quantification was obtained by comparing sample and standard peak area ratios as a function of concentration. Weights were measured using an Ohous balance (Model DV215CD; Shekel Ltd., Israel), and pH was identified using a Toledo GmbH pH meter (Model S47-K; Agentek, Mettler Toledo, Switzerland).

Validation of the High-performance Liquid Chromatography Method

It should be mentioned that the chromatographic conditions used, HPLC column, mobile phase, ultraviolet (UV)-wavelength, injection volume, standard preparation, and others, are the same as that mentioned in the *United States Pharmacopeia 33–National Formulary 28* monograph of valsartan active pharmaceutical ingredient.[11] The method was validated in accordance to the International Conference on Harmonization guidelines.[12] Parameters such as system suitability, selectivity, linearity, range, accuracy (recovery), and precision (repeatability) were all validated. The method was found to be valid as shown from the results in Table 1.

Specificity (Placebo and Forced Degradation Interference)

The specificity of the method to valsartan was determined in the presence of its stress impurities. It was assessed by performing forced degradation studies on pure standards of the valsartan separately to indicate the initial results and on samples of valsartan suspension in presence of its potential degradants. The stress conditions studied are UV-light (254 nm), heat (105°C), acid hydrolysis (1.0 N HCl), base hydrolysis (0.5 N NaOH), and oxidation (3% H_2O_2). The stressed sample solutions were analyzed against freshly prepared standard and sample solutions. The assay and purity check for the stressed standard solutions were calculated as summarized in Table 2.

As the result and the chromatograms indicate, there was degradation for the main peak in five solutions (stress solution), there was no interference between

TABLE 1. Summary of the Study's High-performance Liquid Chromatography Method Validation Results.

PARAMETER	STATISTICAL MEASURE	RESULT	ACCEPTED CRITERIA
Selectivity	None	Complies	No interference between the active material peak and any other peaks due to placebo.
System Suitability	• % RSD • Tailing factor • Theoretical plates • Capacity factor	0.93% 1.28 3640 4.6	≤2.0% ≤2.0 ≥2000 ≥2
Linearity (0.04 mg/mL to 0.6 mg/mL)	Correlation coefficient	0.99987	Minimum 0.995
Accuracy • 0.04 mg/mL • 0.08 mg/mL • 0.24 mg/mL • 0.4 mg/mL • 0.6 mg/mL	Percentage of recovery	 • 98.3% • 100.8% • 99.7% • 100.1% • 101.6%	98.0% to 102.0%
Precision (0.4 mg/mL) for assay analysis	Coefficient of variation	0.40	Max 2.0%
Precision (0.08 mg/mL) for dissolution analysis	Coefficient of variation	1.46	Max 2.0%

TABLE 2. Summary of the Forced Degradation of Valsartan Standard.

NAME	STRESS CONDITION	DEGRADATION PERCENTAGE	PURITY[a]
Valsartan standard	Acidic/1.0 N Hydrochloride	79.8	0.9986
	Alkaline/0.5 N NaOH	22.3	0.9992
	Oxidative/3.0% H2O2	77.2	0.9999
	Thermal/105°C	23.6	0.9993
	Light/Ultraviolet-254 nm	22.1	0.9998

[a]The accepted criteria is >0.990.

the main peak and any other peaks in the chromatogram, and the purity check for the main peak in our results for all was higher than the accepted limit. As is clear from the results, the degradation preparations were well-resolved from the main peak, thus proving that the method is a reliable stability-indicating tool.

Formulation of Suspension

Suspensions were extemporaneously prepared to a final concentration of 80 mg/5 mL using 80-mg commercial tablets (see included formulation). Samples were taken for initial analysis, and the remaining samples stored at 25°C ± 2°C/60% RH ± 5% RH and at 40°C ± 2°C/75% RH ± 5% RH in order to be analyzed at 0, 1, 2, 3, 7, 14, and 30 days.

Rx

VALSARTAN SUSPENSION FROM VALSARTAN 80-MG TABLETS

For 25-mL suspension bottle

Valsartan crushed tablets (80 mg)		5 Tablets
Xanthan gum		0.02 g
Hydroxypropyl cellulose		0.02 g
Aerosil		0.11 g
Banana flavor		0.02 g
Trisodium phosphate, anhydrous		0.08 g
Titanium dioxide		0.001 g
Strawberry flavor		0.11 g
Sugar, fine		22.04 g
Water	qs up to	25 mL

METHOD OF PREPARATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Crush and mill well 5 valsartan 80-mg tablets.
4. Add the remaining powder components, using the geometric dilution method.
5. Add water and mix until achieving a pourable mass.
6. Fill into opaque plastic bottles.
7. Label.

Quality Control of Suspension

Assay of Valsartan in the Suspension

Samples of valsartan for analysis were prepared as reported by the validated HPLC method for the analysis of valsartan suspension. The amount of valsartan in each 5 mL was determined according to this analytical procedure. The summary of the analytical method is reported in Table 3.

TABLE 3. Summary of the High-performance Liquid Chromatography for Valsartan Assay and Dissolution.

PARAMETER	SPECIFICATION
Column	125 mm × 3.0 mm, 5.0 mcm, ACE 5 C18
Flow rate	0.4 mL/minute
Injection volume	10 mcL
Wavelength	273 nm
Mobile phase	Water: Acetonitrile: Glacial acetic acid (500:500:1, v/v/v)
Diluent used in assay	Water: Acetonitrile (1:1)

Preparation of Samples for Assay Analysis

The standard solution was prepared by transferring 40 mg of Valsartan USP reference standard to a 100-mL volumetric flask containing 80 mL of the diluent, shaken by mechanical means for five minutes, sonicated for two minutes and then diluted up to 100 mL with the same diluent, mixed well, and filtered using 0.45 mcm membrane filter before analysis. The obtained final solution contained 0.4 mg/mL of valsartan.

The sample solution was prepared by transferring 5 mL of the valsartan suspension (80 mg/5 mL) to a 200-mL volumetric flask containing 160 mL of diluent, shaken by mechanical means for five minutes, sonicated for two minutes and then diluted up to 200 mL with the same diluent, mixed well, and filtered using 0.45 mcm membrane filter before analysis. The obtained final solution contained 0.4 mg/mL valsartan.

Stability Study

Samples of the prepared suspensions were filled in opaque, well-sealed plastic bottles. For the stability studies, five bottles containing the suspension were stored in the refrigerator, another five bottles were stored in a stability chamber at 25°C ± 2°C/60% RH ±

5% RH condition, and another five bottles were stored in a stability chamber at 40°C ± 2°C/75% RH ± 5% RH condition. The suspensions were analyzed in duplicate by HPLC over the period of 0, 1, 3, 7, 14, and 30 days. The results are shown in Table 4. All valsartan concentrations were expressed as percentages of initial concentration. Stability was defined as studies conducted to generate information concerning the impact that environmental factors such as temperature, humidity, and light may, in time, have on the strength, purity, efficacy, quality, and safety of drug substances or preparations, and there should have been no significant change in the assay (i.e., 5% change from initial assay value, any specified degradation product exceeding spec. limit, dissolution exceeding the specification limits for 12 units, failure to meet specs for appearance, physical properties).

Table 4. Stability of Extemporaneously Prepared Valsartan Suspensions and Stored at 25°C ± 2°C/60% RH ± 5% RH and at 40°C ± 2°C/75% RH ± 5% RH.

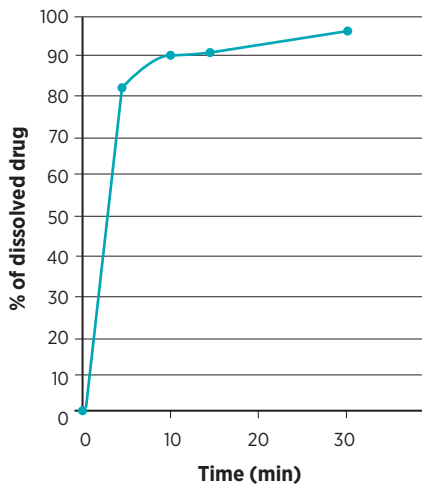
DATE OF ANALYSIS (DAYS)	STORAGE CONDITIONS 25°C ± 2°C/60% RH ± 5% RH PERCENTAGE OF VALSARTAN	40°C ± 2°C /75% RH ± 5% RH PERCENTAGE OF VALSARTAN
0	103.20	102.70
1	102.30	101.90
3	101.60	101.50
7	100.90	100.80
14	101.00	98.40
30	99.20	98.40

Dissolution of Valsartan in Suspension

In vitro dissolution studies were carried out using a dissolution apparatus USP (type II) at a paddle speed of 50 rpm. The dissolution medium was 1000 mL of phosphate buffer at pH 6.8. The buffer was prepared by dissolving 6.80 g of potassium dihydrogen orthophosphate in water; then the pH was adjusted to 6.8 using 0.2 M sodium hydroxide then diluted to 1000 mL using purified water). In all dissolution experiments, 10 mL of dissolution samples were withdrawn and replaced with equal volume of fresh phosphate buffer (pH 6.8) at regular intervals of 0, 5, 10, 15, 20, 25, and 30 minutes. The samples were filtered through a Millipore filter 0.45 mcm. The amount of valsartan in the samples was determined using the above validated HPLC method.

The dissolution profile of valsartan suspension was generated from the graph of the percent of valsartan released versus time using Microsoft Office Excel. The amount of valsartan in each sample was plotted against time as shown in Figure 2.

FIGURE 2. Dissolution profile of valsartan suspension (80 mg valsartan/5 mL) at pH 6.8 phosphate buffer.



Microbiological Stability

Bacterial contamination of the suspensions was assessed at 0, 1, 3, 7, 14, and 30 days after preparation. Aliquots of 100 mcL from each bottle were plated in duplicate on 5% sheep blood agar plates and stored aerobically at 30°C to 35°C (20°C to 25°C for fungi) for five days. Following the five-day incubation, agar plates were inspected for microbial growth and colony formation.

RESULTS

Visual and olfactory inspection of the prepared suspensions did not reveal any unacceptable changes during the study period in all tested bottles stored at the above-mentioned storage conditions. pH of the suspension remained around 5.4 until the last day of the study. The formulation was considered stable if the concentration of valsartan did not change by more than 5% from the initial value, and all other tests are within the specifications. The initial concentration of the drug was tested immediately after the compounding of the suspension. All subsequent concentrations were expressed as percentage of initial concentration, and they were close to 100%, showing a high degree of compliance with the *USP* requirement as reported in Table 3. There were no detectable degradation products at any time of the period of analysis. Despite the absence of preservatives in the formulation, the microbiological inspection of agar plates did not reveal any microbial growth in all the tested samples.

The percentage of valsartan release from suspension was within the accepted *Pharmacopeial* limits for immediate-release oral dosage forms at the end of the study period

of 30 days. Moreover, the valsartan release profile showed that not less than 85% of valsartan was dissolved after 10 minutes.

DISCUSSION

Although the compounding of extemporaneous formulations is a significant portion of a pharmacist's work in a healthcare setting, a very weak extemporaneous service is available in Palestine.[13] In fact, the U.S. Food and Drug Administration believes that pharmacists engaging in traditional pharmacy compounding provide an important medical service that is valuable to patient health for several reasons, such as the formulation of liquid dosage forms for pediatric and elderly patients who usually have swallowing problems, and for patients who have allergies to some additives (e.g., preservatives) present in the commercial formulation.[14]

Valsartan is a very important medication in hypertension. There are many patients, such as the elderly and pediatric patients, that may need to take this medication.[15] Valsartan is available in pharmacies only as tablets; therefore, in cases of patients having swallowing problems, such as previously stated, or if a patient is in a coma and they need to take this medication, the tablet dosage form becomes a problem and these patients may not be able to achieve benefits from this medication. Therefore, the formulation of valsartan into a stable, liquid dosage form starting from the commercially available tablets will be very useful for those patients.

In this study, an extemporaneous valsartan suspension was prepared starting from valsartan tablets as a source of raw material. Moreover, the last suspension was prepared without preservatives in order to investigate not only the chemical but also the microbiological stability in the absence of preservatives, which may cause undesirable side effects in certain patients.[16] The extemporaneous compounding of valsartan suspension starting from crushed commercial valsartan tablets would be a valid method to achieve the desired liquid dosage form with the desired strength if the obtained suspension can pass the Pharmacopeial requirements for suspension (e.g., dose uniformity, stability, dissolution profile). Accordingly, the first purpose of this study was the extemporaneous preparation of valsartan suspension starting from a commercially available product of valsartan tablets. The second purpose was to evaluate the characteristics of the obtained suspension with regard to microbiological stability, chemical stability, pH, and dissolution behavior according to the *USP* monograph of suspensions so as to ensure high quality of the obtained liquid dosage forms.

Valsartan 80-mg/5-mL suspensions being used as an antihypertensive agent should be compounded in a manner to bear its desired therapeutic effects within an eligible time period. The results of this study have shown that the formulated valsartan suspension was stable during the period and conditions of the stability study, since they passed the visual, olfactory, and other *Pharmacopeial* tests for liquid dosage forms. In fact, the obtained suspensions were stable for at least 30 days, regardless of the presence of preservative, when stored at 25°C ± 2°C/60% RH ± 5% RH or at 40°C ± 2°C/75% RH ± 5% RH. The dissolution test was carried out since the dissolution of drug from oral solid dosage forms is a critical criterion for drug bioavailability. In fact, dissolution studies can give an idea about the amount of drug available for absorption after oral administration. The amount of dissolved valsartan from the suspensions was more than 85% within the first 10 minutes.

According to the pharmaceutical bioclassification system, valsartan is a Class III drug, which suggests that valsartan immediate-release suspension may be biowaived from bioequivalence study if the release of valsartan from the dosage form is higher than 85% in 15 minutes.[17] Accordingly, the release behavior shown in this study encourages the compounding of valsartan suspension by crushing valsartan tablets; this will not affect the stability of the preparation nor its therapeutic response, since it releases most of its content within 10 minutes. Scientific information and directions should be provided by pharmaceutical manufacturers on how to prepare extemporaneous valsartan liquid dosage forms by using their commercial products as well as information on the expiry date of the obtained suspension, as this dosage form is not commercially available. In fact, this could be very useful for a broad range of patients with suitable valsartan dosage forms who can benefit from it. This may also promote the marketing of such tablets since pharmacists should use only tablets that have package inserts provided with such information. Publishing these results would be very helpful for pharmacists, especially in Palestine where there is a strong shortage of many drugs. Moreover, Palestinian pharmacists should be more acquainted with these aspects of pharmacy practice and be responsible in this important aspect of the profession.

CONCLUSION

The HPLC assay and dissolution indicated that the 80-mg/5-mL valsartan suspension was stable for at least 30 days when stored at 25oC ± 2oC/60% RH ± 5% RH and at 40oC ± 2oC/75% RH ± 5% RH. The dissolution profile of the suspension indicates immediate and high release of valsartan, which is an essential condition to ensure the required absorption. This study is of great importance for elderly and pediatric patients who have swallowing problems, so the community pharmacists can prepare good, quality suspensions with the desired valsartan content using Valsan (80-mg valsartan tablet) as the source of active ingredient. In those cases, pharmaceutical manufacturers should provide their package inserts with scientific information and directions on how to transform their commercial immediate-release tablets into suspension as well as information on the expiry date of the obtained suspensions.

REFERENCES

1. Criscione L, de Gasparo M, Bühlmayer P et al. Pharmacological profile of valsartan: A potent, orally active, nonpeptide antagonist of the angiotensin II AT1-receptor subtype. *Br J Pharmacol* 1993; 110(2): 761–771.

2. Oparil S, Dyke S, Harris F et al. The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. *Clin Ther* 1996; 18(5): 797–810.
3. Black HR, Graff A, Shute D et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: Efficacy, tolerability and safety compared to an angiotensin-converting enzyme inhibitor, lisinopril. *J Hum Hypertens* 1997; 11(8): 483–489.
4. Corea L, Cardoni O, Fogari R et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: A comparative study of the efficacy and safety against amlodipine. *Clin Pharmacol Ther* 1996; 60(3): 341–346.
5. Holwerda NJ, Fogari R, Angeli P et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: Efficacy and safety compared with placebo and enalapril. *J Hypertens* 1996; 14(9): 1147–1151.
6. Zaid AN, Cortesi R, Qaddomi A et al. Formulation and bioequivalence of two valsartan tablets after a single oral administration. *Sci Pharm* 2011; 79(1): 123–135.
7. Flesch G, Müller P, Lloyd P. Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist, in man. *Eur J Clin Pharmacol* 1997; 52(2): 115–120.
8. Müller P, Flesch G, de Gasparo M et al. Pharmacokinetics and pharmacodynamic effects of the angiotensin II antagonist valsartan at steady state in healthy, normotensive subjects. *Eur J Clin Pharmacol* 1997; 52(6): 441–449.
9. Waldmeier F, Flesch G, Müller P et al. Pharmacokinetics, disposition and biotransformation of [14C]-radiolabelled valsartan in healthy male volunteers after a single oral dose. *Xenobiotica* 1997; 27(1): 59–71.
10. Brookman LJ, Rolan PE, Benjamin IS et al. Pharmacokinetics of valsartan in patients with liver disease. *Clin Pharmacol Ther* 1997; 62(3): 272–278.
11. United States Pharmacopeia Convention, Inc. *United States Pharmacopeia 36–National Formulary 31*. Rockville, MD: US Pharmacopeial Convention, Inc.; 2012: 5537–5542.
12. ICH Expert Working Group. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. *ICH Harmonized Tripartite Guideline: Validation of Analytical Procedures: Text and Methodology Q2(R1).* Geneva, Switzerland. November 2005. Available at: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1_Guideline.pdf. Accessed January 13, 2014.
13. Zaid AN, Al-Ramahi R, Shahed Q et al. Determinants and frequency of pharmaceutical compounding in pharmacy practice in Palestine. *Int J Pharm Pract* 2012; 20(1): 9–14.
14. U.S. Department of Health & Human Services. U.S. Food and Drug Administration. *Drugs: Compounding and the FDA: Questions and Answers*. [FDA Website.] December 2, 2013. Available at: www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm. Accessed January 13, 2014.
15. Meyers KE, Lieberman K, Solar-Yohay S et al. The efficacy and safety of valsartan in obese and non-obese pediatric hypertensive patients. *J Clin Hypertens (Greenwich)* 2011; 13(10): 758–766.
16. Rowe RC, Sheskey PJ, Quinn ME, eds. *Handbook of Pharmaceutical Excipients*. 7th ed. London, UK: The Pharmaceutical Press; 2012.
17. Kumaresan C. *In vitro and in vivo studies in pharmaceutical development.* [Pharmainfo.net Website.] April 13, 2008. Available at: www.pharmainfo.net/reviews/vitro-vivo-studies-pharmaceutical-development. Accessed January 13, 2014.

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