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CONVOLUTION STUDY AND THE ALCOHOLIC BEVERAGE EFFECT ON LANSOPRAZOLE DELAYED-RELEASE CAPSULES AND APPLICATION OF SIMILARITY FACTOR TO TWO-STAGE *IN - VITRO* DISSOLUTION PARADIGM

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Convolution, alcoholic beverage effect, prodrug, Lansoprazole Delayed-Release Capsules, FDA similarity factor f_2

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ABSTRACT: Lansoprazole, a proton pump inhibitor, is used to treat ulcers in the stomach and duodenum. In order to protect this acid labile drug from being degraded in the gastric medium, the marketed oral dosage forms are formulated into delayed release pellets and tablets. The aims of this research were (1) to investigate the principal site of drug release and absorption rate between an over-the-counter (OTC) product and a prescription brand, and (2) to explore the effect of ethanol on the in vitro release profile of the OTC product. For aim No. 1, the *in vitro* release profile conducted in our lab was convoluted with the lansoprazole plasma concentration time profile of an intravenous bolus reported by Gerloff, et al. For aim No. 2, the dissolution of OTC capsules was studied with 250 mL of 0.1 N HCl combined with equal volume of laboratory simulated beer and wine, which contained 5 and 11.5 % alcohol respectively to compare to its reference, 0% (n=6). Furthermore, the dissolution of the OTC formulation in the simulated alcoholic beverage showed no difference between 5 %, 11.5 % and 0 % ethyl alcohol (n=8, U.S. FDA similarity factor, $f_2 > 50$). We further explore the explanation why in spite that the biological half-life of lansoprazole is only 1.1 h, the over the counter products are designed to dose once daily.

INTRODUCTION: Excessive acid secretion exacerbates various gastrointestinal pathology (peptic ulcer disease, gastroesophageal reflux disease, and Zollingger-Ellison syndrome) [1, 2, 3]. Exposure to stomach acid to the proximal small intestine also makes the area susceptible to develop ulcers, the duodenum's most common problem. Lansoprazole is classified as a proton pump inhibitor which blocks the H^+/K^+ ATPase in the gastric parietal cell resulting in decreased acid secretion and allows the stomach and esophagus to heal [4].

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It is sparingly soluble in ethanol; and practically insoluble in water [5]. However, it has good permeability [6, 7]. Therefore, according to the Biopharmaceutical Classification System this drug is classified as BCS Class II [8].

The stability of lansoprazole decreases with the increase in the acidity in an aqueous medium. At 25°C the degradation half-life of lansoprazole is about 0.5 hour in pH 5.0, while it half-life in pH 7.0 is 18 hours [9]. This acid catalysis degradation of proton pump inhibitors (PPIs) was established by Lindberg et al in 1986 [10]. In the presence of proton in the media, the basic nitrogen of the benzimidazole ring become protonated and the acid catalysis degradation takes place after [11]. The rate of the degradation depends on the level of the proton or the acidity of the media. In couple of *in vitro* studies, Gupta et al. evaluated the rate of

degradation of three PPIs including lansoprazole in buffer phosphate media with different pH ranges of 3, 4, 5, 6 and 7.5, at 37 using differential pulse polarography to quantify proton pump inhibitors and their degradation products in a current-time manner. They found that as the pH of the medium increases, the degradation rates of proton pump inhibitors decrease. Also they found that lansoprazole degraded at pH up to 6 while it was stable at pH 7.5 [11].

Due to the acid labile nature of lansoprazole, many commercial products are formulated as enteric-coated pellets (15 mg, 30 mg) byDR REDDYS Labs Ltd., MATRIX Labs Ltd., SANDOZ, TAKEDA Pharms NA, and TEVA Pharms. TAKEDA Pharms NA, and TEVA Pharms also marketed this drug as DR orally disintegrating tablets [12]. In 2009, the only OTC lansoprazole product is manufactured by Novartis with a solo strength of 15 mg in 14, 28 and 42 capsules per package [9, 13]. Nowadays, there are three more OTC lansoprazole 15 mg by DR REDDYS Labs Ltd, PERRIGO R&D, and WOCKHAR Ltd., available in the market.

Although the formulation is product specific, one of the empirical formulations has been published [15]. Briefly described, lansoprazole was added into a medium to spray coat on sugar spheres **(Figure 1a & 1b).** After being dried in the same spray coater, the drug beads were further enteric coated with methacrylic acid and polyacrylate [14] in the case of Rx brand lansoprazole DR capsules and methacrylic acid copolymer in the case of OTC brand lansoprazole DR capsules **(Figure 1c)** according to the ingredients listed in the package inserts.

FIGURE1: EMPIRICAL FORMULATION PROCEDURE OF LANSOPRAZOLE DR 15 MG CAPSULES: (A) SUGAR SPHERES, (B) DRUG LAYERED PELLETS, AND (C) ENTERIC COATED PELLETS [14].

Co administration of alcoholic beverage with some drug products including the modified release formulations has been found can affect the release properties of such products and eventually will alter their bioavailability. In 2005, FDA withdrew one of the opiate controlled formulations, Palladone TM, from the market due to a fatal interaction with alcohol [15, 16]. This product was manufactured as a modified release pellets using ethyl cellulose, Eudragit RS (ammonia methacrylate copolymer type B) and stearyl alcohol [17].

A pharmacokinetic study conducted by the manufacture in which different concentrations of alcohol were administered simultaneously with this extended release opiate pellet product in order to explore the aforementioned fatal interaction. Co-ingestion with 240 mL of 40% v/v alcohol, which represents the spirit drink, resulted in six times increase in mean C_{max} in comparison to the control group who administered water (without 40% alcohol). In one volunteer, there was about 16-fold rise in the C_{max} observed. Co administration of 4% v/v alcohol drink resulted in twofold rise in C_{max} in some of the participants. Based on this possible interaction the FDA decided to develop regulatory decision framework to assess the risk of alcohol induced dose dumping for the oral MR products[18].

Routinely *in vivo* pharmacokinetics studies are not easily feasible since it poses a chance of risk to the participated patients in such clinical trials. Thus, the FDA necessitated the development of *in vitro* studies to examine the vulnerability and ruggedness of such MR formulations so that any defect could be circumvented at the early stage of the product development. Therefore, *in vitro* dissolution studies

can be used in this situation to explore the defect in the MR formulation coming from concomitant alcohol administration [18].

Therefore, the overall project goal can be divided into three aspects. First, it was to propose a three pH stage study (0.1 M HCl, phosphate buffer pH 4.0 and pH 6.5) to investigate lansoprazole 15 mg DR capsules. The current USP-NF [19] guidelines were to test in 0.1 M HCl for 1 hr and then progress to phosphate buffer pH 6.8 for another hour. Second, it was aimed to examine the OTC product of lansoprazole 15 mg DR capsules would have similar dissolution and simulated absorption profile to the Rx lansoprazole 15 mg DR Capsules. In order to achieve this aim,the USP dissolution apparatus 2, the U.S.FDA similarity factor (f_2), two-tail t-student test, lansoprazole IV plasma concentration time data retrieved from the literature (30)and convolution study using Kinetica 2000 would have to apply.

Out of the general concern regarding the potential effect of alcoholic beverage might alter drug release from an oral formulation is, the third aim of this project was to examine dissolution profile of the OTC product containing alcohol vs. no alcohol. Two common alcoholic drinks are 5 % representing beer and 11.5 % representing white and red wines[20].Since we could not test all beer and wine products available in the market, alcohol USPwas used in our laboratory to prepare into simulated beer and wine.

METHODS:

Market products:

Prescription (Rx) Prevacid® 15mg delayed-release capsules (Takeda Pharmaceuticals) were ordered from Cardinal Health (Dublin, OH) while OTC PREVACID 24 HR 15 mg (Novartis, lots 101493, 110158, 110179, 110538) was purchased from two different local pharmacies in Boston, MA.

Chemicals and reagents:

Lansoprazole USP (lot C142353) was ordered from PCCA (Houston TX). Hydrochloric acid (HCl, 36.5 - 38%), acetonitrile sodium hydroxide, sodium dodecyl sulfate, monobasic sodium phosphate anhydrous (NaH2PO4), 0.2 microns, 25 mm nylon membrane syringe filters were purchased from VWR (Bridgeport , NJ).

Standard preparation to calculate the sample concentrations:

Standard preparation was adopted from the USP37-NF32 [19]. Briefly described, a known quantity (10 mg) of lansoprazole reference standard was dissolved in 0.1 M HCl or phosphate buffer pH 6.8. Each medium contained 0.3% sodium dodecyl sulfate based on the suggestion in the lansoprazole monograph. Samples were scanned using a UV-Vis Spectrophotometer from 190 nm to 700 nm to identify the optimal wavelength at 285 nm.

Standard curve in each study medium which correlated between the responses of absorbance or AUC to a series of known concentrations in the working range (2, 8, 20, 40 µg/mL) was built. In addition to the acid stage medium (0.1 M HCl), Lansoprazole was spiked in three media to make into four concentrations respectively to construct standard curves. They were (1) lansoprazole in phosphate buffer pH 6.8, (2) lansoprazole in phosphate buffer pH 6.8 containing 5% alcohol and (3) lansoprazole in phosphate buffer pH 6.8 containing 11.5% alcohol. The standard preparations were then quantified using UV spectrophotometer as well as HPLC simultaneously.

The detection of the AUC in HPLC method and the absorbance in UV method were conducted in the same wavelength, 285 nm to establish the correlation between these two methods. The HPLC conditions adopted from USP-NF 2014 [20] were: (1) acetonitrile, water, and triethylamin (40:60:1), adjusted to pH 7.0 with phosphoric acid as the mobile phase, (2) 150 × 4.6 mm, 5 µm C18, 37°C were the column type and temperature, (3) flow rate 1.2 mL/min, (4) run time 10 min, (5) detecting wavelength 285 nm and (6) injection volume 50 microliters.

In vitro dissolution study: the USP two-stage and our proposed three-stage:

In acid stage, each vessel of the USP dissolution apparatus 2 was filled with 500 mL of 0.1 N HCl preheated to 37°C[19]. One capsule of Prescription (Rx) Prevacid®15mg DR capsules (Takeda

Pharmaceuticals) or a capsule of OTC PREVACID 24 HR 15 mg [12]was loaded into the 500 mL of 0.1 M HCl dissolution medium maintained at 37°C stirring at 75 rpm for 60 min. Eight mL of samples were collected at 20, 40 and 60 min for quantifying the drug release in the acid stage. In buffer stage, 8.175 g of monobasic sodium phosphate, 3.525 g of sodium hydroxide, and 1.5 g sodium dodecyl sulfate were dissolved in deionized water to make into 0.5 L of buffer concentrate.

Four hundred and twenty-five mL of this buffer was added to the remaining 475 mL of acid stage solution, 0.1 N HCl, in each vessel with pH adjusted to 6.8, with either phosphoric acid or sodium hydroxide. The apparatus operation condition [21-24] remained the same as the acid stage (75 rpm, 37°C and 60 min) according to the USP dissolution guideline in the Lansoprazole monograph [19], but we voluntarily increased the run time of the Rx product in the buffer stage for additional 60 min because the release was found not completed by the end of buffer stage set by the compendium.

The Acid stage preparation of our three stage in vitro dissolution study was the same as the USP Method. In Buffer stage 1, we added 125 mL of simulated duodenum buffer concentrate which contained 5.13 g tribasic sodium phosphate and 1.5g of sodium dodecyl sulfate to the remaining solution in the vessel of acid stage to bring pH to 4.5 and let the USP dissolution apparatus 2 stir at 75 rpm for 15 min to simulate the retention time of capsule pelletsin duodenum.

In Buffer stage 2, 0.44 g of NaOH was dissolved in 300 mL deionized water to adjust dissolution medium to pH 6.5 to simulate the jejunum environment and stirred at the same rate until all capsule pellets were dissolved.

Convolution study:

Convolution program in Kinetica 2000™ (Inna Phase) was used to convolute the mean values of *in vitro* dissolution data for the two commercial products: Rx Prevacid® DR capsules and the OTC PREVACID 24 HR.

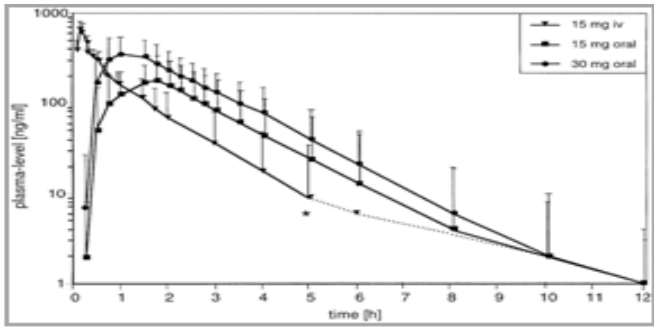


FIGURE 2: PLASMA LEVELS OF LANSOPRAZOLE (MEANS AND SD, N = 12) AFTER SINGLE DOSES OF 15 mg IV BOLUS, 15 mg ORALLY AND 30 mg ORALLY [25]

Both were 15 mg in strength (n = 6) with the plasma concentration time profile for IV bolus administration retrieved from a publication of Gerloff et al.[25] **(Figure 2).**It was performed by entering the cumulative drug release of *in vitro* dissolution of a study lansoprazole product into the OS (standing for by mouth) spreadsheet of the software and the plasma concentration time profile of lansoprazole intravenous bolus retrieved from literature.

Alcoholic Beverage Effect on Lansoprazole DR Capsules:

The USP dissolution apparatus 2 was used to study the alcoholic beverage effect on the lansoprazole release from its OTC brand of DR capsules.

Medium preparations of laboratory simulated beer and wine:

Alcohol USP of 13.16 mL was mixed with water to make into 250 mL to simulate a glass of beer (which contains 5% alcohol). Alcohol USP of 30.26 mL was mixed with water to make into 250 mL to mimic a cup of red or white wine (which contains 11.5% alcohol). 250 mL of water was prepared to simulate the administration of a DR capsule with water as the reference group. The simulating beer, simulating wine or water of 250 mL was further mixed with 250 mL of 0.1 M HCl to load into a dissolution vessel of the USP dissolution apparatus 2.

The Acid stage study was then conducted at 75 rpm with temperature maintained at 37°C and the duration for 1 h. Eight mL of medium was collected at 20 m 40 and 60 min with replenishment of fresh medium. The Buffer stage medium preparation, operation condition, and

sampling time were the same as those described in the Section 2.4: *In vitro* dissolution study.

U.S. FDA similarity factor, f_2 value:

The FDA similarity factor f_2 (Eq. 1) derived from mean-squared difference is a measure of similarity in the percentage dissolution between two dissolution profiles [26]. Thus, the similarity of two dissolution profiles, administration of the OTC lansoprazole DR capsules with water versus with an alcoholic beverage (test) at a particular time point can be determined.

$$f_2 = 50 \cdot \log\left\{\left[1+(1/n)\sum_{t=1}^{n}(R-T)^2\right]^{-0.5} \cdot 100\right\}$$

(Eq. 1)

Where f_2 is similarity factor,

n: time points,

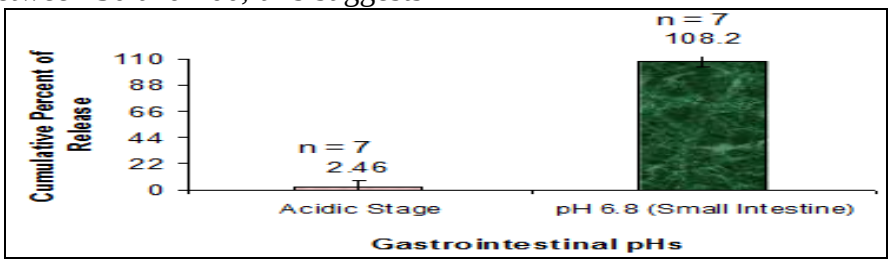
R: cumulative percent of the alcohol free sample as reference at the time point,

T: cumulative percent of the alcoholic beverage (test) sample at the time point.

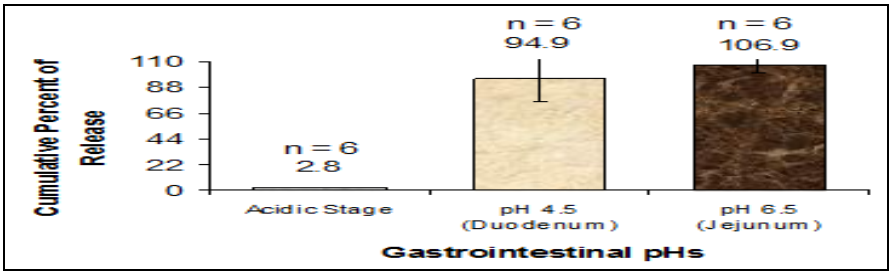
The f_2 value is the average sum of squares of the difference between test and reference profiles and fits the result between 0 and 100. A critical value of 50 is derived for similarity of dissolution profiles. If the f_2 value is between 50 and 100, this suggests that the dissolution profiles are similar. A f_2 value of 100 suggests that the test and reference releases are identical, and as the value becomes smaller the dissimilarity between two release profiles increases. Thus, the release from a test product should be rejected when the f_2 value is less than 50 [26].

RESULTS:

***In vitro* dissolution study: the USP two-stage vs. our proposed three-stage:** 2.46% of lansoprazole was released from a 15-mg Prevacid capsule in the Acid stage and completely released (108.2%) in the Buffer stage medium, pH 6.8 (n = 7, Figure 3a). Using our proposed three-stage method with four sampling points: 30 min and 60 min in acidic stage, 15 min at pH 4.5 and 15 min at pH 6.5, it was found 2.77% of a 15 mg Prevacid capsule was released in acidic pH, while 94.9% was released in duodenum pH (pH 4.5) in 15 min, and the release was completed in jejunum pH (pH 6.5) within additional 15 min (n = 6, Figure **3b**). Since the proposal has not yet gained recognition by the USP37-NF32, 2014 [19], because only one pharmaceutical product (Prevacid® 15 mg delayed-release capsule by Taketa) was studied, the present project proceeded with the dissolution method listed in the compendium.



(a)



(b)

FIGURE 3: COMPARISON OF LANSOPRAZOLE RELEASE AT DIFFERENT LOCATIONS OF THE GASTROINTESTINAL TRACT BETWEEN (a) THE USP TWO-STAGE DISSOLUTION METHOD [19]AND (b) OUR PROPOSED THREE-STAGE MODIFIED METHOD.

The *In vitro* dissolution study between Rx and OTC products:

The percentage dissolved versus time profile of Rx and OTC lansoprazole DR capsules products suggested that there was almost no drug release in Acid stage as the dosage form designed for (1.21 % ± 1.14 % for OTC product and 2.82 % ± 1.74 % for the Rx productat the end of one h, n = 6, **Figure 5).** However, the drug release at the end of 1 h buffer stage study were 101.2 % ± 10.72 % for the OTC brand and 94.33 % ± 5.59 % for Rx brand. The Buffer stage of the Rx brand was thus further extended for an additional hour and the drug release was finally completed with the results of 107.35 % ± 1.93 % (n = 6, **Figure 4)**.

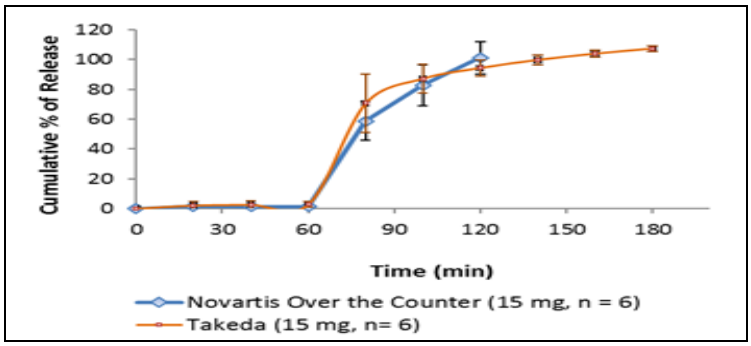


FIGURE 4: MEAN DISSOLUTION PROFILE OF 15 mg LANSOPRAZOLE Rx vs. OTC

Convolution Study:

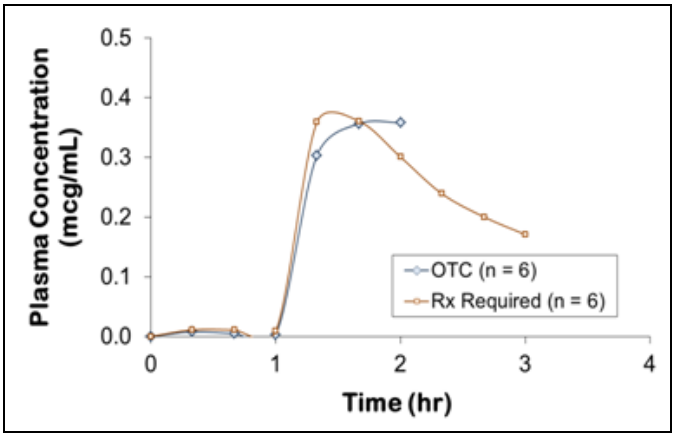
The Convolution results conducted using Kinetica 2000 software may be found in Table 1. The data were further plotted into (a) plasma concentration time profiles, (b) rate of absorption vs. time profiles for both OTC and Rx products. Convolution study suggested that following a one-dose administration of the Rx lansoprazole DR capsule, the C_{max} would reach 0.4µg/mL in about 1 hr 20 min **(Figure 5a).** The maximal absorption rate of the Rx capsules was 30.9 mg/h, while that of the OTC product was predicted as 26.1 mg/h **(Figure 5b)**.

TABLE 1: CONVOLUTION OUTPUTS OF KINETICA 2000 SOFTWARE, WHICH WAS DONE BY USING THE CUMULATIVE DRUG RELEASE OF *IN VITRO* DISSOLUTION OF A STUDY LANSOPRAZOLE PRODUCT TO CONVOLUTE THE PLASMA CONCENTRATION TIME PROFILE OF LANSOPRAZOLE IV BOLUS RETRIEVED FROM LITERATURE: (a) OTC BRAND, AND (b) Rx BRAND

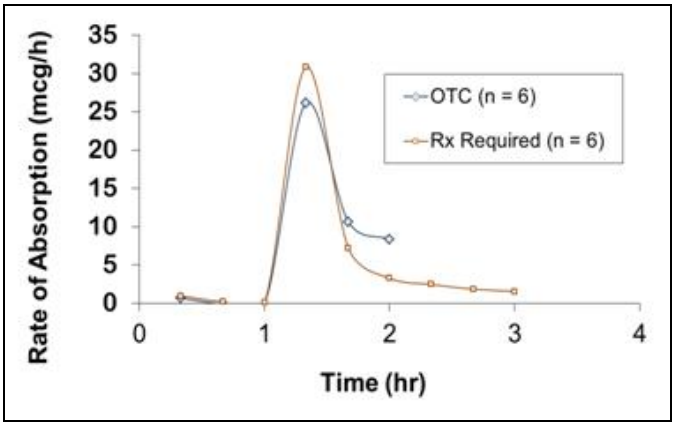
T_{os}	A(t)	C_{iv} extra (T_{os})	dA/dt	C_{os}
hr	mg	(mcg/ml)	(mcg)/(hr)	mcg/ml
0	0	0.452		0
0.33	0.22	0.352	0.667	0.008
0.67	0.19	0.228	-0.088	0.005
1.00	0.18	0.166	-0.030	0.003
1.33	8.80	0.138	26.121	0.303
1.67	12.42	0.101	10.647	0.357
2.00	15.18	0.067	8.364	0.358

T_{os}	A(t)	C_{iv} extra (T_{os})	dA/dt	C_{os}
hr	mg	(mcg/ml)	(mcg)/(hr)	mcg/ml
0	0	0.452		0
0.33	0.32	0.352	0.970	0.011
0.67	0.39	0.228	0.206	0.011
1.00	0.42	0.166	0.091	0.009
1.33	10.61	0.138	30.879	0.359
1.67	13.07	0.101	7.235	0.360
2.00	14.15	0.067	3.273	0.301
2.33	14.96	0.054	2.455	0.239
2.67	15.59	0.043	1.853	0.200
3.00	16.10	0.035	1.545	0.171

T_{os}: Time of oral administration;
A(t): Amount of drug absorbed;
C_{iv}: Extrapolated IV Concentration at the time of oral administration;
dA/dt: Rate of absorption;
C_{os}: Concentration obtained by oral administration;



(a)

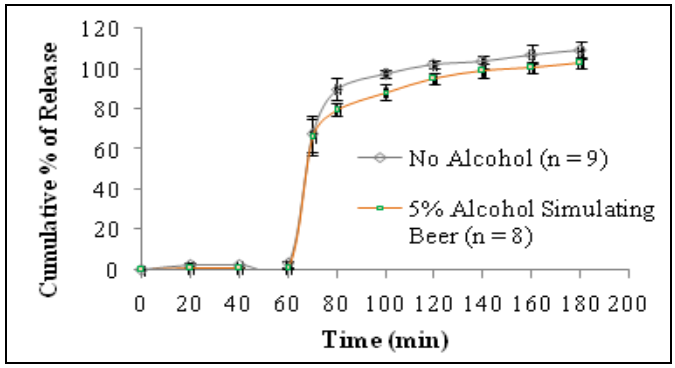


(b)

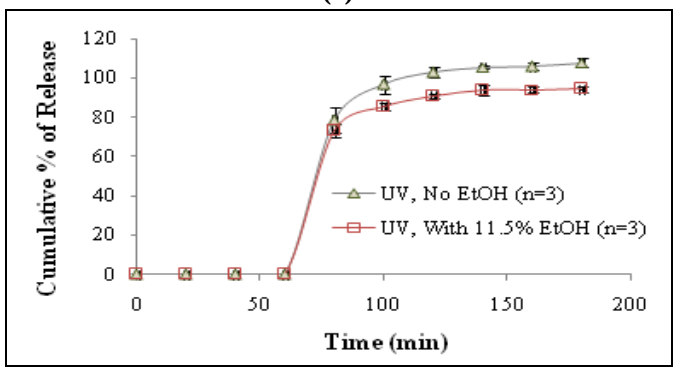
FIGURE 5: CONVOLUTION PREDICTED PLASMA CONCENTRATION TIME PROFILES AND ABSORPTION RATES OF THE TWO STUDY PRODUCTS. (a) After the Rx brand product and OTC product being taken by mouth, the drug concentration of the Rx brand product was predicted to reach its C_{max} at 0.4 mcg/mL in about 1 h and 20 min, while the OTC product reached its C_{max} between 1 h 40 min to 2 h. **(b)** The maximal absorption rate was predicted as 30.9 mg/h for the Rx brand and 26.1 mg/h for the OTC brand (see text)

Alcoholic beverage effect on Lansoprazole DR capsules

Both 5% and 11.5% alcohol did not impact lansoprazole release in acidic stage from its delayed release capsule **(Figure 6a)**. The *in vitro* dissolution profiles indicated that lansoprazole was released significantly different from the DR Capsules into the simulated medium containing 11.5% alcohol versus containing no alcohol (Figure **6b)**, but not those quantified by HPLC **(Figure 6c)**, because both the drug and degradant absorbed wavelength at 285 nm. The peak of the degradant only appeared in high drug concentrations and the AUC of degradant was very small in comparison to the main drug peak **(Figure 7).**



(a)



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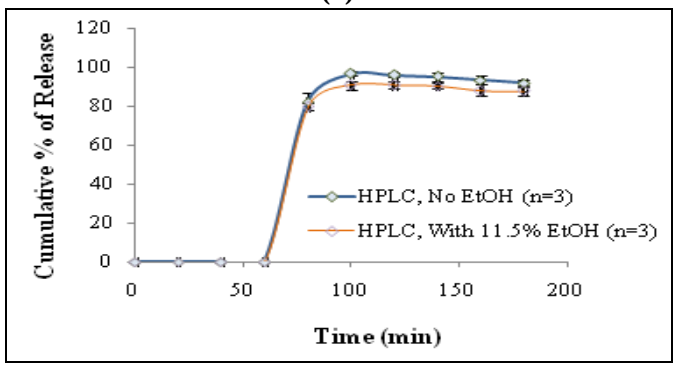

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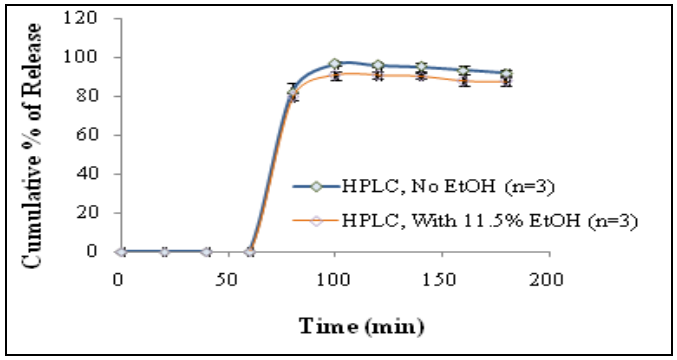

(d)

FIGURE 6: TWO-STAGE IN VITRO DISSOLUTION PROFILES OF LANSOPRAZOLE DR CAPSULES IN (a) 5 % alcohol, containing (representing cup of beer) and alcohol-free media assayed by UV spectrophotometer, **(b)** 11.5 % alcohol-containing (representing a glass of wine) vs. alcohol-free medium quantified by UV spectrophotometer, **(c)** 11.5 % alcohol-containing vs. alcohol-free medium quantified by HPLC, and **(d)** profiles from the same sample sets quantified by UV versus by HPLC

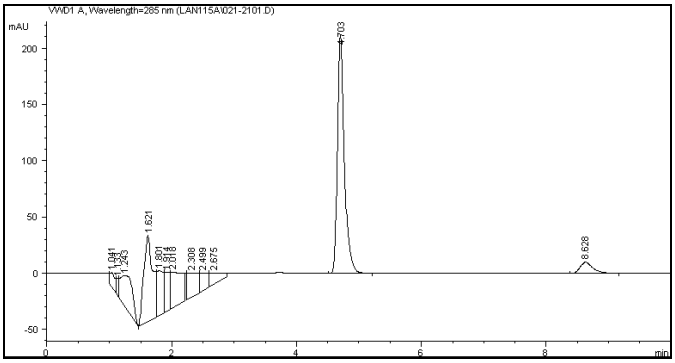

FIGURE 7: CHROMATOGRAM OF A LANSOPRAZOLE DISSOLUTION SAMPLE SIMULATING THE ADMINISTRATION OF THE DRUG WITH A CUP OF LABORATORY PREPARED WINE. THE RETENTION TIME OF THE DRUG PEAK WAS 5 MIN WHILE AN UNIDENTIFIED PEAK WAS ALSO PRESENT AT 9 MIN IN THE SAMPLES COLLECTED AT 60 MIN AND AFTER. THE DEGRADANT PEAK WAS RATHER SMALL IN COMPARISON TO THE MAIN DRUG PEAK.

The U.S. FDA similarity factor, f_2 value:

Since both the OTC and Rx products were DR oral dosage form, there was almost no drug release in the acid stage, we further used the dissolution data of the in vitro dissolution study of OTC product in laboratory prepared alcohol beverage as the test group and alcohol free as the reference group to determine how to calculate the FDA similarity factor in a DR dosage form. Should it be computed (1) from Acid stage to Buffer stage, or (2) from Buffer stage alone? When this equation was used to conduct from Acid stage to Buffer stage, the f_2 values for all profiles were above 50 suggesting the release profiles were similar.

However, when the equation was used to conduct the Buffer stage only (without the data from the Acid stage as they were almost no drug release in this stage protected by the enteric coat), the f_2 value, 48.8 and 47.6 (< 50), the second column of **Table 2** from the right) indicated that the release profiles between the 11.5% alcohol vs. alcohol free were different after being in Buffer stage for 20 min. The pellets were expected to transit through the duodenum and into the jejunum region. We further confirmed this finding by using t-test to examine the release from time point by time point which aligned closer to the conclusion of the f_2 value computed from Buffer stage alone (the first two columns from the right of **Table 2).**

TABLE 2: THE FDA SIMILARITY FACTOR OF OTC AND RX DRUG PRODUCTS COMPUTATION DONE FROM ACID STAGE TO BUFFER STAGE VERSUS THE BUFFER STAGE ONLY. THE RESULTS WERE COMPARED TO THOSE OF T-TEST

Stage	Cumulative Time (min)	Cumulative % of Release		Similarity Factor (f_2)		P Value
		11.5% EtOH (n = 8)	No EtOH (n = 9)	From Acid to Buffer Stages	Buffer Stage Alone	
Acid	20	1.3	2.45	91.1	Not Applied	< 0.001*
	40	1.4	2.44	91.4	Not Applied	0.007*
	60	1.6	2.98	90.4	Not Applied	0.015*
Buffer	70	60.3	67.56	70.5	56.8	0.082** (NS)
	80	78.5	90.02	60.2	50.7	< 0.001**
	100	85.5	97.58	56.1	48.8†	< 0.001**
	120	89.2	101.96	53.5	47.6†	< 0.001**

† < 50 suggesting different profiles between the OTC brand and Rx brand

* Mann-Whitney Rink Sum Test;

** t-test;

NS: No Significant Difference

DISCUSSION: Lansoprazole, an acid labile pro-drug, prevents gastric acid secretion by selective covalent inhibition of H+/K+ ATPase, the last step in acid secretary pathway. It needs the acid catalyzed reaction in order to convert to the active form. This active entity will form a sulfide bond with the active site of ATPase enzyme in the parietal cell [3, 29]. However, this acid catalyzed pathway is preferred not to take place before lansoprazole is absorbed into the blood stream. The gastric juice is known rather acidic with the presence of abundant protons present. If lansoprazole is released from its dosage form into the stomach, an undesired acid catalyzed reaction may occur. That is, a proton will interact with the basic nitrogen on the imidazole ring to form an

intermediate compound which leads to the formation of lansoprazole dimer. To prevent this interaction form occurring in the stomach, lansoprazole is thus formulated as enteric coated beads with a pH sensitive polymer [9, 13-14].

But two questions related to formulation were raised here. First, both Eudragit L100-55 and Eudragit L100 [17] have been used as enteric coating ingredient. As seen in **Figure 1c**, this pro-drug degraded linearly while the formation of dimer increased linearly when it was allowed to be exposed to this pH 6.0 longer.

Therefore, Eudragit L100 (dissolution threshold at pH 6.0) should be better than Eudragit L100-55 (dissolution threshold at pH 5.5). Second, have the commercial products been formulated into delayed release followed by immediate release (DR-then-IR) or delayed release followed by extended release (DR-then-ER) based on the drug release pattern? Two reasons led us to believe that it is DR-then-ER were (1) the biological half-life of lansoprazole is 1.1 hr, (2) PREVACID 24 HR 15 mg is marketed for once a day, the release is expected to be in aslow and extended manner after the enteric coat is dissolved. But Figures 2a and 2b suggest that lansoprazole was formulated as DR-then-IR based on the release pattern. We further explored the rationale of making into DR-then-IR through literature search.

Based on the study of Beel et al.[30], once lansoprazole reaches the parietal cells from the systemic circulation, it will block the ATPase enzyme, thus reduce the secretion of protons into the stomach with the half-life of 22 hr. Thus, it is reasonable to fabricate the beads into DR-then-IR pattern instead of DR-then-ER by suspending lansoprazole in a medium to spray on sugar spheres. Once dry, they were further coated with an enteric coat [14].

Any small change in the formulation of such products could result in variation of the bio-pharmaceutical properties. Dissolution test is an important tool to understand the release behavior of various pharmaceutical formulations and the effect of alcohol on these formulations [12, 17, 27, 28]. The appropriate selection of an analytical method, such as ultraviolet spectrophotometry or high performance liquid chromatography for *in vitro* dissolution study plays major role in the accuracy of the data.

To assure the quality of the release profile, dissolution studies are conducted and the FDA similarity factor f_2 are compared. Also to make sure that different brands of the same formulations can provide similar pharmacokinetic parameters such as C_{max}, t_{max} and absorption profiles, these dissolution experiments can provide a great insight to these parameters. We cannot say that the method that was advised by the USP to analyze the dissolution samples of lansoprazole by the UV spectrophotometer is invalid just because the HPLC gave us different or more accurate results. The rational is that in the dissolution apparatus, these is more chance for this pro-drug to degrade unlike what would happen *in vivo*.

In other words, lansoprazole is classified as class II drugs, which means it is going to be absorbed rapidly once it is released in the small intestine. As a result, the susceptibility of lansoprazole to breakdown *in vivo* will be lower than in the *in vitro* dissolution study. That means less amount of its byproducts will interfere with the UV reading. Therefore, UV is suitable for quantifying the dissolution samples of this BCS class II drug. Our finding is consistent with the analytical tool listed in Lansoprazole monograph of USP-NF 2014 [19]. However, ultra performance of liquid chromatography (UPLC) would be an even better too if available.

CONCLUSION: The project examined the absorbance wavelengths of the two-phase *in vitro* dissolution study for lansoprazole and found 288 nm was more sensitive than the 331 nm. Both wavelengths are superior to 306 nm which is suggested in USP-NF for the acid stage. Both our study and the USP-NF 2013 agree that 285 nm is the suitable detecting wavelength for lansoprazole in the buffer stage dissolution study. Correlating the detective strength between ultraviolet/visual spectroscopy and HPLC showed linearity. However, UV spectrophotometer only reported the sum absorbance of drug and its degradant, while HPLC was able to quantify them individually. The two-stage *in vitro* drug release profiles between Rx and OTC lansoprazole products were compared. There was almost no release between the two products in the acidic stage, 0.1 N HCl (1.21±1.14% for OTC product and 2.82±1.74 for Rx brand, n = 6 each). This finding adheres to the claim of the dosage form

design as delayed release capsule. Nevertheless, judging from the time course of *in vitro* dissolution study and the convolution study combining the data collected in the lab with the plasma concentration time profile of the IV bolus retrieved from literature [25], the Rx release the drug slightly faster in the buffer stage reflecting that this product possibly was designed to target at the duodenum while the OTC brand started drug release in duodenum and completed its release in the proximal jejunum.

The pharmacokinetic parameters that I obtained from convulsion study suggested that both products showed simulated plasma concentration peak that fell within the range of 1.5 to 2 h after administration. This finding is relevant to the range that is obtained from the clinical studies conducted by Freston JW et al. [31].

In vitro dissolution study was conducted to examine the effect of coadministration of alcoholic beverage, such as beer (containing 5% alcohol) or wine (containing 11.5% alcohol), on the dissolution properties of OTC enteric coated lansoprazole pellets. Our finding suggested that there was no significant effect of the simulated cup of beer. The same study in the simulated wine quantified by UV showed the drug release in the alcohol-free medium was higher than the group in alcohol-containing medium in the Buffer stage **(Figure 7b)**, However, the same observation was not remarkable when the same sets of dissolution samples were quantified by HPLC **(Figure 7c)**.

It was found that in addition of drug peak (which retention time is 4.7 min in the stated HPLC method), there was an unidentified chromatographic peak (which retention time was 8.6 min) in both alcohol-free and alcohol-containing groups. The HPLC study proved that drug molecules and degradant molecules absorbed wavelength at 285 nm, which explained the difference in the study results between UV and HPLC. The merit of HPLC is that it is a technology of better separation and selection. However, the run time is longer (10 min per cycle in this case) than UV (5 sec in this case), when the study drug, lansoprazole, is degradable in any proton containing medium, including phosphate butter pH 6.8, degradation might continue during the assay. To avoid this problem, UPLC instead of HPLC should be tried in the future.

It should be noted that fermented alcoholic beverages, such as beer and wine, could increase gastric acid secretions [33]. Therefore, peptic ulcer patients should avoid consumption of such beverages. Future study on whether higher alcohol concentrations (such as two glasses or three glasses of laboratory simulated wine) on lansoprazole DR capsules may increase the chance of pre-drug release in the stomach and result in drug inactivation should be conducted with an in vitro approach but not in human subjects with the disease, because the ulcerative condition may be worsened.

Last but not least, this project is insightful in gaining the knowledge of pharmaceutical formulation. Through the step-by step investigation of this dosage form, the merit of making this pro-drug into DR-then-IR beads were explored. We also comprehend that although lansoprazole is more stable in pH 7.0, there is not much medium in the proximal colon for drug dissolution.

Therefore, targeting to the small intestine is appropriate in this case, because the drug absorption is much effective in this region than in the colon due to the presence of abundant microvilli. However, we also identified a formulation drawback. From the literature Eudragit L100-55 polymer was less favored than Eudragit L100 to be used in the formulation work which dissolution threshold is pH 5.5 causing the conversion of lansoprazole into a dimer more than that in pH 6.0. Since the dimer cannot block the ATPase to reduce proton secretion, the conversion may be reduced by properly selecting the Eudragit polymer in the subtype of L100.

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