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A STATISTICAL PERSPECTIVE ON THE SELECTION OF A FLAVORING AGENT FOR OPTIMAL TASTE MASKING OF AZITHROMYCIN

Aiman A. Obaidat[1,2*], Asmaa M. Al-Tirawi[1,2a], Fares F. Almousa[1,2], Nawaf G. Aloufi[1,2] and Emad Masuadi[3]

[1]College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh 14611, Saudi Arabia.
[2]King Abdullah International Medical Research Centre, Riyadh 11481, Saudi Arabia.
[3]College of Medicine and Health Sciences, United Arab Emirates University, P.O. Box 15551, Al Ain, United Arab Emirates.
[a]Department of Pharmaceutics and Center for Pharmaceutical Engineering and Sciences, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298, USA; and Faculty of Pharmacy, Jordan University of Science and Technology, Irbid-Jordan.

***Corresponding Author: Prof. Aiman A. Obaidat**
College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh 14611, Saudi Arabia.

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ABSTRACT
Azithromycin is a macrolide antibiotic known for its unpleasant bitter taste. The specific aim of our study was to utilize a simple statistical approach to select the best flavoring agent that can optimally mask the taste of azithromycin by comparing our formulation to the originator product available in the Saudi market, Zithromax®. Four formulations with different flavoring agents have been prepared and tasted by a panel of 100 volunteers to evaluate and give a score for each on a scale of 1-5 where 1 is very poor and 5 is excellent. The formulation flavored with peppermint was the highly preferred one based on the scoring results in a pilot study. Further optimization and tasting of this formula using a cross-over design study indicated that it is similarly acceptable in taste compared to the originator product.

KEYWORDS: Azithromycin, taste masking, flavoring agents, palatability, bitter taste.

INTRODUCTION
Oral solutions and suspensions are convenient for pediatric, elderly and disabled patients who have difficulty in swallowing tablets or capsules. However, refusal of taking medications by children is a common and expected problem mainly due to bad taste and unpleasant odor of such formulations. There are two taste masking approaches, first approach involves the reduction of the solubility of certain drugs at the pH of saliva (5.6 - 6.8), while the second is by altering the affinity and nature of drug which will interact with the taste receptors.[1] Important factors to consider during the taste masking formulation process which are: bitter taste level of the active pharmaceutical ingredients (API), needed dose and dosage form, drug solubility and ionic characteristics, disintegration and dissolution rate of the finished product, desired bioavailability and release profile. Multiple taste masking technologies have been reported based on the above mentioned approaches. The highly used one was taste masking with flavors and sweeteners,[2] then polymer coating of drug,[3] formation of inclusion complexes,[4] ion exchange resin complexes,[5] solid dispersion,[6] micro-encapsulation,[7] and others.

Combination of sweeteners and flavors can be utilized to taste mask bitter drugs.[8] Sweeteners dissolve in the oral cavity and mask the taste buds, thus inhibiting the interaction of the bitter API with taste buds. Flavors would give a good special taste and they could be used alongside primary taste masking agent. Certain cooling flavorings like menthol numbs the taste buds and decreases bitter taste perception.[9] Moreover, other excipients such as bitterness inhibitors can also be added.[10] Matrix entrapment, which relies on putting the drug into a bulky matrix and with that contact with taste buds, can be minimized. Such matrix would contain polymeric, resinous, gelling, or lipoid materials.[11] Prodrug formation leads to physicochemical changes of bitter moieties and thereby inhibits or retards their interaction with taste receptors.[12] Salt formation usually decreases the solubility of the API in saliva and thereby decreases its taste perception.[1,8] Other methods such as granulation with polymeric materials, implementing effervescent excipients, and rheological modification of

liquid preparations can be used for masking the taste of bitter API.[13] Stimuli responsive drug delivery systems utilizing pH sensitive or ion sensitive polymers have also been developed to mask bitter API taste.[14] Lycopodium derived microcapsules were used for taste masking of ibuprofen. Techniques like nano hybridizing and wet spherical agglomeration is also used for taste masking.[15] Mixing macrolides with acidic powder of L-carbocysteine, or by administering the macrolide mixed with chocolate jelly resulted in a notable taste improvement.[1]

Macrolides, such as azithromycin, have a bitter taste and there is a need to develop and utilize taste masking methods for them to optimize patients' compliance and therapeutic outcome.[16] Several methods have been utilized for taste masking of azithromycin. Microparticles containing azithromycin loaded in dispersible tablets were prepared by solvent evaporation and spray drying methods. Comparing the test formulation and the original showed some improvements were the bitter threshold of azithromycin has been elevated.[17] A technique employed physisorption using Langmuir adsorption isotherm. According to this technique, titanium dioxide nanoparticles were chosen as adsorbate as it is insoluble at saliva pH, and azithromycin as an adsorbent. In this case titanium dioxide acts as a protector which makes the drug avoids interaction with taste receptors of the tongue.[18-19]

A study used the method of solvent diffusion where the microspheres of azithromycin with ethyl cellulose were mixed with other excipients to form orally dry suspensions. Results indicated that the suspension could considerably mask the bitter taste of azithromycin and the relative bioavailability of the suspension was also improved.[20-22] Other investigators studied taste masking of azithromycin by using sustained release ion exchange resins. These were prepared by suspension polymerization method, which was effectively used for taste masking.[23]

Azithromycin is an azalide antibiotic of macrolides, derived from erythromycin, with a methyl-substituted nitrogen atom incorporated into the lactone ring, thus making the lactone ring 15-membered.[24] Azithromycin prevents bacteria from growing by interfering with their protein synthesis. It is stable at gastric pH and has 37% oral bioavailability.[25] Azithromycin originator brand is Zithromax® produced by Pfizer pharmaceutical company and the available generic brands that are registered in Saudi Arabia are: Azimac® (Riyadh Pharma Company), Azi-once® (Jamjoom Pharmaceutical Company), Zerox® (Hikma Pharmaceutical Company), Zimax® (Spimaco), Azolid® (Cooper Pharma), Zocin® (The Arab Pharmaceutical Manufacturing Company, APM), and Azyn® (Bluepharma Genericos Comercio de Medicamentos).[26]

In this study, we have prepared a flavored powder mix of azithromycin that is ready for reconstitution to form an oral suspension in a concentration of 200 mg/5 mL where it is similar in its concentration to the originator product that is available in the Saudi market. We have tested different flavoring agents to improve the taste of this suspension formulation. The taste of the different formulations has been evaluated by a simple tasting experiment without swallowing through selecting a representative panel of subjects including academic staff and students. A simple statistical evaluation of the taste of the formulation has been conducted in comparison with Zithromax® which is the originator product available in the Saudi market.

METHODOLOGY

Materials

The API; azithromycin powder, in addition to other excipients that are anhydrous hydroxyl propyl cellulose (Klucel®), xanthan gum, peppermint powder, orange powder, were all obtained from Hikma-Jazeera pharmaceutical Industries (Riyadh-Saudi Arabia) as gift samples. Sucrose and sodium phosphate tribasic dodecahydrate, were obtained from our laboratories in the College of Pharmacy at King Saud bin Abdulaziz University for Health Sciences (KSAU-HS). The originator product (Zithromax® Suspension) was bought from local pharmacies in Riyadh, Saudi Arabia.

Methods

Different formulations have been prepared by simple mixing procedure using similar formula ingredients and quantities as Zithromax® to form a powder mixture ready for reconstitution and to produce a final concentration of the API in the oral suspension of 200 mg/5 mL[24]. Each formula has been given a certain code according to the flavoring agents used in that particular formula. In the pilot study, there were four different flavors mixtures: flavor I; orange, flavor II; peppermint, flavor III; orange with peppermint in 1:1 ratio, and flavor 4; orange with peppermint in 1:3 ratio. Table 1 shows the data collection sheet used to register the responses of the volunteers who participated in the pilot study. All were prepared and their tastes were evaluated by 12 subjects (6 males and 6 females) to select the best one of them that would be proposed for the final comparison against the brand formula (Zithromax®). The formula with the highest rating was selected for further development and testing.

Table 1: Sample data collection sheet for the pilot study to select the best flavor for final comparison against the originator brand; Zithromax®.

Please rate the taste of the formula by selecting one of the following choices. Write (X) in the space provided					
Formula Code	**Very Poor (1)**	**Poor (2)**	**Good (3)**	**Very good (4)**	**Excellent (5)**
Flavor I					
Flavor II					
Flavor III					
Flavor IV					

The inclusion criteria of the volunteers were age 18 years and above with no known allergies and nonsmoker. An informed consent was provided and signed by each participant explaining the purpose of the study and the procedure of taste evaluation in addition to being informed that they can freely leave the study at any time without providing any reasons. Tasting experiments were conducted in the premises of the KSAU-HS campus through selecting a representative panel of subjects from academic staff, administrators and students.

Final taste evaluation comparison between the best evaluated formula from the pilot study against Zithromax® has been conducted by reconstitution of the powder mix in purified water to prepare an oral suspension with a final concentration of 200 mg/5 mL. Taste evaluation of each formula has been examined by giving each test subject 5 mL of the suspension and instructing him/her to leave it in the mouth for 5-10 seconds and then spit it out without swallowing, then rinsing his/her mouth using drinking water. Then drinking only 10 mL of drinking water to wash the mouth before tasting the next formula. Each subject has been asked to evaluate the taste he/she experienced by rating it on a simple scale ranging from 1-5 as follows: very poor (1), poor (2), good (3), very good (4), and excellent (5). The approach has been applied by blind tasting experiment where the subjects were not given any information about the constituents of the tested formula. Each subject tasted two samples that were our prepared formula and the originator product (Zithromax®). All subjects have been asked to rate the prepared formula versus the originator product using the same approach. Subjects have been divided into two groups according to sequence of formula tested, in which Group 1; subjects (1-50) were given a scoring sheet in which A was the brand Zithromax® to be tasted first, and Y was our formula to be tasted secondly. While Group 2; subjects (51-100) were given another scoring sheet in which Y was our formula that is to be tasted first, and A was the brand Zithromax® to be tasted secondly. A cross-over design study has been conducted where all subjects have tasted both the originator product and our formula by switching the sequence of administration in the two groups. All subjects rated and scored their evaluation of the taste for each formula they tried.

All scoring sheets have been collected, tabulated using Excel® Software, and then analyzed by statistical approaches (Paired Samples Statistics, Independent T-test, ANOVA, and Kappa) to find the formula with the best taste and acceptability according to the rating given by the subjects who participated in the tasting experiment. The sampling technique was non-probability convenient sampling by including those who agree to be part of the study.

RESULTS AND DISCUSSIN

Using descriptive statistics for the pilot study tasting results, the formulation containing flavor II, which was peppermint only, showed a significant difference than other flavors regarding the acceptance of the taste (mean = 4.42 ± 0.9, P-value = 0.001). The ingredients to prepare 20 mL of this formula are shown in Table 2. Statistical assessment to compare the four formulations with different flavors is shown in Table 3. Peppermint flavor is known to have a cooling effect that numbs the taste buds and delay bitter taste perception. Sucrose has also been used in this formulation as a sweetener where it is highly water-soluble, dissolve in saliva and hide the taste buds, thereby retarding the interaction of bitter API with taste buds.[2,9] These results gave a strong predictor for the formulation that contains flavor II (peppermint). Therefore, it has been selected and scaled up to final tasting test comparison against the originator product, Zithromax®. As shown in Table 3, flavor II scored the highest mean regarding acceptance of the taste with a significant difference compared to flavors I, III and IV.

Table 2: Ingredients of the optimized formula that contains peppermint (Flavor II) as the formula with the highest taste rating in the pilot study.

Ingredient	**Q/20ml**
Azithromycin.$2H_2O$	840 mg
$Na_3Po_4.12H_2O$	162 mg
Klucel®	26 mg
Xanthan gum	26 mg
Peppermint Flavor	200 mg
Sucrose	15489 mg

Table 3: Descriptive statistics to compare the taste perception and acceptance by the volunteers of the pilot study to evaluate the formulations prepared with different flavors.

Formulation	Mean	SD	P-value
Flavor I	2.67	1.30	0.001
Flavor II	4.42	0.90	
Flavor III	2.67	0.89	
Flavor IV	2.67	0.78	
Mean Difference			
	Flavor II	Flavor I	< 0.001
		Flavor III	< 0.001
		Flavor IV	< 0.001

The study included 100 subjects and their demographic data regarding gender and age are shown in Table 4. They were divided into 2 groups where each group included 50 subjects of males and females. The study was conducted in a cross-over fashion where group 1 started by tasting the originator product (A) and group 2 started by tasting our formulation with flavor II (Y). Then the groups where crossed-over so that group 1 tasted Y and group 2 tasted A. This ensured that each volunteer has tasted the two formulations to compare and give a score for the taste of each.

Table 4: Baseline characteristics among 100 subjects who participated in the tasting experiment regarding their gender, age and distribution in the groups.

Characteristics		N	%
Gender	F	52	52.0%
	M	48	48.0%
Age (years)	18-24	46	46.0%
	25-29	13	13.0%
	30-39	27	27.0%
	40+	14	14.0%
Group 1	A then Y	50	50.0%
Group 2	Y then A	50	50.0%

The members of the two groups were distributed so that each group have almost equal number of males and females with almost same mean age in each group. The mean age in group 1 was 30.2 years and group 2 was 28.7 years with no significant difference between them (P-value = 0.11).

Applying paired sample statistics on the scores of tasting collected from the volunteers in the two groups showed that there was no significant difference between A and Y and they were almost identical (P-value = 0.951). The results of this analysis are illustrated in Table 5. This indicates that our optimized formulation flavored with peppermint is as competitive as the flavor of the marketed originator brand, Zithromax®.

Table 5: Paired sample statistics showing mean score values for tasting of A and Y.

Paired Samples Statistics				
Test Formula	**Code**	**Mean**	**SD**	**P-value**
Zithromax®	A	3.64	1.12	0.951
Formulation with Flavor II	Y	3.63	1.06	

Table 6 shows independent T-test results regarding the groups and the gender preference of the test formula. The results showed no significant difference between the two sequences of taste scoring of the two groups; A then Y or Y then A (P-values are 0.067 and 0.742, respectively). This statistical test showed significant differences in gender preference of drug A (Female 3.3, Male 4, with P-value = 0.006), while in the other side there was no significant difference in gender preference with drug Y. This means that the brand Zithromax® was highly preferred by males more than females but our optimized formula with peppermint flavor (Flavor II) was generally and equally similarly accepted by both genders.

Table 6: Independent T-test showing means and P- values among the two groups and the two genders.

			A		Y	
			Mean	**SD**	**Mean**	**SD**
Independent T-test	**Group**	A then Y	3.9	1	3.7	1.1
		Y then A	3.4	1.2	3.6	1
		P-value	0.067		0.742	
Independent T-test	**Gender**	F	3.3	1.3	3.6	1.1
		M	4	0.8	3.7	1
		P-value	0.006		0.605	

Tasting was also conducted based on age grouping where 4 age groups have been used to taste our formula against the originator product. Using ANOVA analysis and as illustrated in Table 7, drug A showed a significant difference between age groups (P-value = <0.001). In this test, three age intervals (25-29, 30-39 and 40+) gave significantly higher preference of about 4 out of 5 for formulation A; Zithromax®, while the younger age

interval (18-24) gave a score of about 3 out of 5. However, there was no significant difference regarding formulation Y among all the four age intervals. This indicates that the optimized formula with Flavor II is again more significantly accepted by general population regardless of the age group.

Table 7: Analysis of Variance (ANOVA) showing mean scores for both drugs according to different age groups.

Age (Years)	A		Y	
	Mean	SD	Mean	SD
18 - 24	3.1	1.2	3.5	1.2
25 - 29	3.9	1.1	3.8	1
30 - 39	4.1	0.8	3.7	0.9
40+	4.1	0.7	3.9	0.9
P-value	<0.001		0.501	

Kappa analysis was also performed to evaluate the taste preference for A or Y and the results are shown in Table 8. Kappa analysis of the scoring results showed that 47% of the participants were in favor of drug A while 46% were in favor of drug Y and 7% gave identical score for both drugs. This statistical assessment also confirms the competiveness of the formula with peppermint flavor in comparison with the originator brand Zithromax® as the scores for both of them were approximately similar.

Table 8: Kappa analysis showing % of participants in favor of A (Zithromax®), % of participants in favor of Y (Flavor II), and % of participants who gave identical score for both formulations.

A*Y Cross Tabulation (% of Total)								
		Y					Total	
		Very poor	Poor	Good	Very good	Excellent		
A	Very poor	0.0%	2.0%	0.0%	3.0%	0.0%	5.0%	46.0%
	Poor	0.0%	0.0%	4.0%	5.0%	1.0%	10.0%	
	Good	2.0%	2.0%	0.0%	11.0%	12.0%	27.0%	
	Very good	0.0%	5.0%	16.0%	3.0%	8.0%	32.0%	
	Excellent	0.0%	4.0%	10.0%	8.0%	4.0%	26.0%	
Total		2.0%	13.0%	30.0%	30.0%	25.0%	100.0%	
		47.0%						7.0%

CONCLUSION

The flavor of liquid dosage forms plays an important role in compliance of pediatric and elderly patients who usually have difficulty in swallowing solid dosage forms. In this study, and based on a simple statistical approach, our formulation in which peppermint was used as the flavoring agent was highly comparable to the originator brand among general population in terms of average acceptance of the taste. Moreover, the flavor of our formula is more acceptable regardless of age and gender groups and sequence of tasting. Based on these results, we recommend further optimization of this formula along with stability studies to investigate its stability under different ambient conditions.

STATEMENT OF ETHICS

The study was approved by the Institutional Review Board at King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia (IRBC/1283/19).

CONFLICT OF INTEREST

The authors declare there is no conflict of interest associated with this study.

AUTHOR CONTRIBUTION

The authors contributed equally the same in conducting tasting experiments, data collection, analysis and manuscript writing.

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