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PREPARATION AND CHARACTERIZATION OF AN OILY SUSPENSION OF OMEPRAZOLE FOR ADMINISTRATION IN PEDIATRICS

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ABSTRACT: The present research was focused on the development of an oily suspension for oral administration of omeprazole in Pediatrics. Currently, for the treatment of this population, extemporaneous preparations are used in hospitals with many limitations in their use as bad organoleptic features and loss of drug activity due to improper manipulation, causing the omeprazole to be sensitive to the acidic environment of the stomach, with the consequent loss of activity. The objectives are to achieve a stable formulation of omeprazole in normal storage conditions and to ensure that this formulation maintains the active ingredient protected from the hostile environment of the stomach, which causes degradation of the drug. An oily omeprazole suspension was elaborated and compared to three master formulas usually employed in hospitals (pellets suspension, xanthan suspension, Ora-Sweet® suspension). The omeprazole suspension has been characterized as follows: appearance and organoleptic characteristics, content uniformity test, viscosity, study of dissolution rate and formulation stability.

INTRODUCTION: Omeprazole or 5-methoxy-2-((4-methoxy-3,5dimetil-2piridinil) methylsulfinyl)-1H-benzimidazole, of molecular formula C17H19N3O3S is an antiulcer, gastric antisecretory. Its mechanism of action is to inhibit irreversibly (suicide inhibitor) and specifically dose-dependent ATPase H^+/K^+ at the membrane of gastric parietal cells[1]. It is a prodrug which at acidic pH undergoes an activation called "Smiles' rearrangement" beginning with protonation of benzimidazole ring, followed by addition of pyridine nitrogen, ultimately resulting in a hydrophilic sulfonamide which is not absorbed from the membrane of the small intestine.

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Therefore, it has not therapeutic effects. The efficacy and safety of omeprazole therapy in children and teenagers are not fully established. Therefore, manufacturers' laboratories provide no information on dosage within this population. Occasionally, it has been used orally in case of reflux esophagitis in children whose ages are between one month and 16. In adults, it has been used orally both in capsules and tablets. The usual dosage is 20 mg once a day, and produces a rapid and effective inhibition of gastric acid secretion day and night, having maximum effect in the first four days of treatment.

In case of difficulty in swallowing in older or sick patients who are unable to swallow solid forms, it can be overcome with the following recommendations: opening the capsules and mixing the pellets with slightly acidic foods or use nasogastric tubes to manage pellets suspended in a liquid. Such methods of administration do not lack drawbacks. Firstly, oral administration of pellets in

pediatric patients is not an easy task, because of the young age of some of them there can be issues with swallowing or chewing such preparation, with the consequent destruction of enteric film and inactivation of the molecule. Furthermore, it is not recommended to adjust the dose of these formulations in pellets for these patients because it is difficult to figure out the correct dosage [2-3].

On the other hand, the use of nasogastric tubes is not a quick method of administration, and may result with an obstruction in the tube. In heterogeneous dispersed systems, as liquid suspensions, a solid powder or small insoluble particles larger than 0,1 micron size (dispersed phase or internal phase) are dispersed in a liquid medium (dispersing phase or external phase). The use of liquid suspensions is recommended for the administration of active principles in neonatology and pediatrics in those cases where the preparation of capsules is not possible [4]. The development of liquid suspensions of omeprazole could allow the administration of these drugs to children and make the adjustment of the dose according to patient weight more comfortable. There are different formulations for preparing these suspensions. Some of them refer below: Dissolution of the enteric granules in 8,4% solution of sodium bicarbonate [5].
-Triturate the granules and suspend the drug with other solids in a vehicle of simple syrup [6].

However, these preparations may be inactivated in the presence of gastric pH, even in the presence of the alkaline medium of the formulation. Another limitation is that the flavor of the preparation is too alkaline and salty for children. Omeprazole is the first marketed drug that has become part of extemporaneous oral liquid forms to use in pediatrics. Initially the active ingredient was not available to prepare these formulas so they resorted to the commercial presentation of the pharmaceutical industry: gelatin capsules containing omeprazole pellets with enteric coating. The content of the capsules was diluted in sodium bicarbonate 8,4% w/v. Subsequently, laboratories in Spain were authorized to supply omeprazole pellets for a while [7].

Therefore, the overall objective of this work is the development of an oily, semisolid dosage form of omeprazole for pediatric administration. Nowadays, one oily suspension of omeprazole is available to use in primates, llamas, dogs and cats. The aim of this paper is the preparation and characterization of an oily suspension of omeprazole for administration in Pediatrics. In preliminary studies by our research group [8], sedimentation volume, some of organoleptic characteristics, viscosity, studies drug-excipient compatibility, by thermal methods such as differential scanning calorimetry (DSC) of our suspension were reported.

Therefore, achieving this overall objective entails compliance with the following specific objectives:

1. To achieve a stable formulation of omeprazole in normal storage conditions.

2. Ensure that the formulation maintains the active ingredient protected from the hostile environment of the stomach, which causes degradation of the drug.

MATERIALS AND METHODS:

Materials:

Omeprazole (Uquifa S.A., Barcelona).

Omeprazole pellets (Fagron, Barcelona).

Sesame oil (Acofarma, Barcelona).

Compritol® 888 ATO (Gattefosse, Paris).

Soy lecithin (Acofarma, Barcelona).

Calcium carbonate (Acofarma, Barcelona)

Aspartame (Fagron, Barcelona).

Labrafac® (Gattefosse, Paris).

Vanilla flavor (Symrise, Barcelona).

Aroma candy (Symrise, Barcelona).

Sodium bicarbonate (Acofarma, Barcelona).

Xanthan gum (Fagron, Barcelona).

Sodium saccharin (Fagron, Barcelona).

Ora-Sweet ®(Paddock, Minneapolis).

Method of preparation of the final formula:

The viscosizing agent (Compritol®) was fused, and the oily vehicle was added. It was also preheated to 60°C, using IKA Werke IKA EuroStart system

equipment, provided with blades and temperature control, with a stirring rate of 150 rpm for 25 minutes. The mixture was allowed to cool to 45°C. Then, the soy lecithin was added, until it was dispersed with a stirring speed of 200 rpm for 15 minutes. On the other hand, omeprazole was mixed with calcium carbonate in a biconical mixer model WAB System Schatz. The solid mixture was slowly incorporated to the oily vehicles at controlled temperature of 30°C using a homogenizer IKA Ultra-Turrax T18 basic model for 150 minutes, keeping constant temperature using an ice bath. The sweetener was added using a homogenizer IKA Ultra-Turrax T18 basic model, for 10 minutes, maintaining constant temperature of 30°C in an ice bath. The suspension was allowed to cool down to 25°C, and then it was flavored according to specifications using a stirrer IKA Werke Euro Start to 250 rpm for 5 minutes.

Preparation of suspensions of reference used in hospital setting:

Finally, omeprazole was compared to three master formulations, which nowadays are used in hospital pharmacy, to observe which had better results. The formulas used in the comparison were pellets suspension, xanthan suspension and Ora-Sweet® suspension. The formulation using pellets is reported in **Table1**. Firstly, an alkaline solution of sodium bicarbonate was prepared. Secondly, the solution was refrigerated at least ten minutes in a freezer. Finally, pellets were placed in the stirrer IKA Werke Euro Start and were slowly stirred to 50 rpm for 10minutes. [9]

TABLE 1: COMPONENTS OF PELLETS SUSPENSION

Omeprazole pellets	Sodium saccharin	Sodium bicarbonate	Purified water q.s.
300 mg	200 mg	100 mg	100 ml

Table 2 reports the xantan suspension. 0,5 g of xanthan gum was slowly dispersed in 49,5 ml of water in the IKA Werke Euro Start stirrer. It was then agitated properly and it was heated to 50°C (phase 1). 8,4 g of sodium bicarbonate were later dispersed in 100 ml of purified water. Sodium saccharin was added. This dispersion was not dissolved as saturation concentration could not be exceed (phase 2).Vanilla essence was then added to phase 1 with soft agitation. Phase 1 was mixed with phase 2. Finally, the omeprazole base was added and it was homogenized using an IKA Ultra Turrax T18 basic model machine for 15 minutes. The final appearance of the suspension was white, homogeneous and viscous, with a pH equal to 9.

TABLE 2: COMPONENTS OF XANTHAN SUSPENSION

Omeprazole Base Fagron	Sodium bicarbonate	Xanthan gum (aqueous 1%)	Vanilla essence	Sodium saccharin	Purified water q.s.
0,2%	8,4%	50 ml	0,4%	0,2%	100 ml

Table 3 reports the formulation for Ora-Sweet® suspension. , 4 g of sodium bicarbonate were added to 50 ml of Ora-Sweet® and were properly mixed (Phase 1). 0,1 g of pure omeprazole were placed in a mortar and a small amount of the alkaline suspension of phase 1 was added and was homogenized. The remaining Ora-Sweet® suspension was added and mixed. Then, it was poured into a beaker and was stirred (IKA Werke EuroStart) for 30 minutes. Finally the necessary amount of Ora-Sweet® was added to reach the final volume of 100ml. The homogeneous suspension should have a pH of 8, 27.

TABLE 3: COMPONENTS OF ORA-SWEET® SUSPENSION

Omeprazole base Fagron	Sodium bicarbonate	Ora-Sweet®
0,1-0,4%	8,4%	100 ml

Extraction of omeprazole from the formulation:

N-hexane was used as extracting solvent. 500 mg of oily suspension were mixed with 70 ml of the solvent for 45 minutes. After decanting the solvent with the extracted omeprazole, the N-hexane solution was recollected and completely removed

by evaporation (rotaevaporator-R Büchi). The precipitated omeprazole was dissolved in sodium phosphate monobasic buffer pH 7,4. Finally samples were analyzed by HPLC. All assays were performed in triplicate. All reagents used in the extraction, dilution and separation of omeprazole were HPLC, or analytical grade.

Quantification technique of omeprazole by HPLC:

To determine the concentration of the drug, an analytical method was developed by High Performance Liquid Chromatography (HPLC), taking as reference the published ones by other authors [10]. The chromatograph used, Hitachi HPLC system manager, consisted of four units: L-7100 isocratic pump, auto sampler L-720, L-7455 spectrophotometer DAD detector of variable wavelength and interface D-7000. The chromatographic system used was constituted by a stainless steel column (Lichrospher 100 RP-8) 250 mm long and 4,6 mm diameter, filled with particles of silicagel bonded with octadecylsilane particles of 5 µm diameter. Quantification of omeprazole was carried out at the wavelength of maximum absorbance, at about 259 nm. Mobile phase was a mixture of acetonitrile and sodium phosphate monobasic (0,01 M) (45:55 v/v), and it was adjusted to pH 7,5 with sodium hydroxide solution. The flow rate was set to 1 ml/min. With these conditions, adequate separation between the peaks of omeprazole and other interference that could appear in the samples was ensured.

It was prepared a stock solution of 0,4 mg/ml concentration, dissolving 400 mg of omeprazole in 100 ml of mobile phase. All other solutions were prepared with concentrations of omeprazole 0,1-0,0005 mg/ml. Calibration standards were prepared using the mobile phase to dilute the stock solution of omeprazole.

Characterization of the oily suspension:

Appearance and organoleptic characteristics: pleasant organoleptic characteristics, such as a suitable and coordinated taste, smell and color are essential in this type of formulation aimed at Pediatrics, in order to reach optimal acceptability by patients, and therefore, the recommended dosing for children. The taste was determined trying different essences like citrus fruits, chocolate, among others, until it was discovered that the better tasting were vanilla and caramel. 2 ml of the formulated test were given to 15 healthy volunteers aged between 19 and 41. The smell was enhanced since the first lots started to develop. Various components were progressively eliminated, such as soybean oil and soy lecithin, which gave the formula some undesirable organoleptic characteristics. The suspension color was pale yellow (vanilla taste is always associated with yellow color). From the beginning it was always thought that the formula should have a sweet taste, it was believed it would be really accepted by the pediatric population, instead of acid or bitter taste. Therefore, to achieve a desired sweetness, besides flavoring, the needed amounts of sweeteners were added.

Content uniformity test: the test for Content Uniformity was applied to ensure that the active ingredient was uniformly distributed in the preparation according to European Pharmacopoeia rules. Five aliquots of the final formulation between 495 and 507 mg were taken. After that, samples of omeprazole of weights between 1,092 and 1,209 mg were correctly extracted from the oily product and then those samples were analyzed by HPLC to get the percentage recovery. Each assay was performed in triplicate.

Viscosity: In order to determine whether the storage period at 4°C affected the viscosity of the oily suspension, the viscosities of the samples were measured using a rotational viscometer (Brookfield DV-II+Pro). Viscosity measurements were made on a volume of 60 ml of sample. They were performed immediately after the sample was prepared and also after a storage period of 1 to 7 days. The samples were subjected to a sheer force of 110 N for 120 s to 4°C.

Formulation Stability:

Once the formula was developed, it was essential to have a wide margin of stability that could allow us to maintain adequate stock to meet the needs of patients. The formulas were given in the bibliography; they generally had a relatively short period of stability, which hindered its use in daily practice. Moreover, the stability of omeprazole

solutions could be affected by many factors, among which the pH is one of them. Firstly, omeprazole stability in the formulation was determined by HPLC. The drug was subjected to forced degradation in acidic medium. An omeprazole solution 1,2 mg/ml was prepared. Each one of the samples was made in triplicate. 100µL aliquots were extracted and the omeprazole content was determined at time zero. 140µL of a solution of 12 N HCl were added to the remaining contents (1,9 ml) in each tube, and after their incubation in different solutions for 15 and 30 minutes at 25°C, then 100µL aliquots were taken. All aliquots were finally analyzed by HPLC. In order to ensure the stability of omeprazole in the prepared suspension, samples of approximately 1 ml of product were extracted after preparation and during storage. The studies were carried out in the short and long term. For preparations stored for one week, aliquots were removed at 6, 12, 24, 48, and 168 hours (7 days), while the long term samples were taken at 7, 14, 21 and 28 days for stability studies. Formulations were discarded if the loss of an active pharmaceutical ingredient was more than 0,05 from the initial value. In addition, samples were stored in darkness and in the presence of ambient light, as showed in **Table 4.**

TABLE 4: CONDITIONS OF STORAGE OF SAMPLES OF OMEPRAZOLE FOR THE STABILITY STUDY

Studies	Conditions	Time
1	4°C, darkness	6, 12, 24, 48 y 168 hours
2	25°C, light	6, 12, 24, 48 y 168 hours
3	4°C, darkness	7, 14, 21 y 28 days

Study of dissolution rate and kinetic fit:

The dissolution rate studies were performed according to the technique employed in USP 35-NF 30 using a Sotax CH-4123 Allschwil / Basel system, Switzerland, equipped with blades.

The dissolution medium simulated a gastric medium, the rotation speed was 50rpm and temperature of 37±0,5°C. The amount of sample tested was 12 mg of omeprazole, using equivalent amounts of omeprazole for the rest of suspensions assessed. Aliquot samples (5ml) were taken from the dissolution medium during the previously established time interval for further assessment. All assays were performed in triplicate. After representing the release profiles of all the systems under study, model-independent parameters were obtained as dissolution efficacy at 60 minutes (ED 60) and specific empirical parameters as t10% and t20% [11-14]. In the same way adjustment profiles were performed with respect to the most appropriate dissolution kinetics [15-17].

RESULTS AND DISCUSSION:

Final formula designed:

Different batches (1-32) were prepared (1-32), changing the concentration of some components depending on the characteristics of the product, as shown in **Table 5.**

Sensory evaluation in food quality control is a scientific method used to evoke, measure, analyze and interpret those responses to products as perceived through the senses of sight, smell, touch, taste, and hearing and it is not usual, it uses Instruments [18].

TABLE 5: PERCENTAGE COMPOSITION OF TEST BATCHES

Lots	Omeprazole	Soybean oil	Sesame oil	Labrafac®	Compritol®	Calcium carbonate	Soy lecithin	Aspartame	Flavor
1			65		10	16,5	8	0,1	0,4
2			65		10	16,5	8	0,1	0,4
3			67		8	16,4	8	0,1	0,5
4			70		5	16,4	8	0,1	0,5
5			49,9	20	5	16,5	8	0,1	0,5
6		36	36		3	16,4	8	0,1	0,5
7		73,1	0		2	16,3	8	0,1	0,5
8		36,5	36,5		2	16,4	8	0,1	0,5

9		73		2	16,4	8	0,1	0,5
10		36,5	36,5	2	16,4	8	0,1	0,5
11		36,5	36,5	2	16,4	8	0,1	0,5
12		36,5	36,5	2	16,4	8	0,1	0,5
13		36,5	36,9	2	16,3	8	0,1	0,2
14		36	35	2	16,0	10,7	0,1	0,2
15		36,5	36,9	2	16,3	8	0,1	0,2
16		37	36,9	2	16,0	8	0,1	0
17		36,5	37	2	16,4	8	0,1	0
18		39	39	2	11,9	8	0,1	0
19		37	37	2	15,7	8	0,1	0,2
20		37	37	2	15,7	8	0,1	0,2
21		37	38	1	15,9	8	0,1	0
22		37	37	1,5	16,2	8	0,1	0,2
23		37	37	1,5	16,2	8	0,1	0,2
24		37	39	1,5	16,2	6	0,1	0,2
25		37	41	1,5	16,2	4	0,1	0,2
26		37	41	1,5	16,2	4	0,1	0,2
27		38	42	1,5	14,2	4	0,1	0,2
28		38	42	1,5	14,2	4	0,1	0,2
29	0,2	37,5	42	1,5	14,5	4	0,1	0,2
30	0,2	37,5	42	1,5	14,5	4	0,1	0,2
31	0,2	37,5	42	1,5	14,5	4	0,1	0,2
32	0,2	37,5	42	1,5	14,5	4	0,1	0,2

After the realization of different lots, we have come to obtain an oily suspension with optimum organoleptic properties: beige color, pleasant scent with vanilla and caramel aromas, sweet flavor and creamy texture. This gives rise to a thin product with very good palatability for administration to children.

Extraction of omeprazole from the formulation:

TABLE 6: MEAN RECOVERIES VALUES OF OMEPRAZOLE OBTAINED IN DIFFERENT ALIQUOTS OF THE PREPARED FORMULATION

Aliquot	Aliquot weight (mg)	Theoretical average: content in omeprazole (mg)	Actual content in omeprazole (mg)	% recovery
1	495	1,188	1,092	91,92
2	502	1,205	1,199	99,50
3	498	1,195	1,175	98,33
4	490	1,176	1,186	100,85
5	507	1,217	1,209	99,34

As shown in **Table 6**, samples tested in recent batches showed a content of active principle comprised between 91, 92 and 100, 85%, being the remaining values very close to 100%, therefore confirming the drug, once resuspended by agitation of the preparation, remains evenly distributed during dosing.

Stability of oily suspension:

Oily suspension was maintained at 4°C and in darkness did not show an appreciable degradation during storage in short-term. Samples were stored for a period of one week showed a loss less than 0,02 of active omeprazole. In contrast to other results obtained, for formulations were stored in light environment and at room temperature (25°C), the drug experienced a loss of stability of 12,5% after 7 days in preparation containing 2,4% of omeprazole and 15,6% in the formulation containing 4,8% of the active principle, as observed in **Table 7** [19].

TABLE 7: RESULTS OF THE STUDY OF STABILITY FOR A WEEK

Storage Conditions	Omeprazole (mg/ml)	6 h	12 h	24 h	48 h	168 h
	1,2	99,5±3,6	102,0±4,3	101,3±6,4	101,2±5,1	98,9±5,3
4ºC	2,4	98,6±1,1	98,8±0,4	99,3±0,4	99,3±0,1	98,9±0,7
Darkness	4,8	99,9±0,3	100,9±0,9	99,5±2,7	98,9±1,8	99,8±4,3
	1,2	98,3±4,2	99,3±3,9	98,8±5,3	97,2±7,6	98,1±4,0
25ºC	2,4	100,9±1,2	100,3±1,5	98,1±1,8	94,8±2,3	87,5±2,8
Light	4,8	97,0±1,6	99,4±1,2	96,3±0,6	91,1±0,9	84,4±0,2

From the results above, it could be deduced that the most suitable storage conditions of these formulations should be at a temperature of 4°C, and packed in topaz coloured glass bottles to isolate light. Therefore, samples were stored for 28 days; presented losses of between 2% and 4% in the analysis of three different formulations (**Table 8**), therefore it was indicative of formulations were stable under these storage conditions.

TABLE 8: PERCENTAGE OF OMEPRAZOLE REMAINING IN THE CONDITIONS LISTED IN TABLE

Omeprazole(mg/ml)	7 days	14 days	21 days	28 days
1,2	98,3±0,7	98,9±2,6	98,5±0,9	96,2±3,9
2,4	101,3±0,9	99,5±3,1	100,2±1,4	100,8±1,4
4,8	99,6±1,8	101,1±1,2	102,0±1,2	101,5±1,2

Moreover, omeprazole in refrigerated samples stored did not have a significant degradation process, for a period of one month, regardless of the concentration used. All formulations showed a percentage of degradation less than or equal to 2% during the first week to initiate the stability study and a percentage between 2 and 4% after a month.

Studies of release:

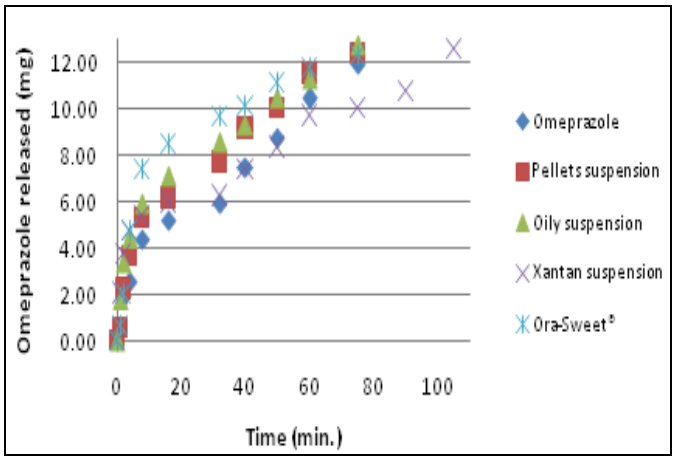

FIG.1: DISSOLUTION RATE PROFILES OF OMEPRAZOLE, PELLETS SUSPENSION, OILY SUSPENSION, XANTHAN SUSPENSION AND ORA-SWEET® SUSPENSION

Fig. 1 shows dissolution profiles of omeprazole, pellets suspension, oily suspension, xanthan suspension and Ora-Sweet®suspension [20-21]. All assays were performed in triplicate with an equivalent amount of 12 mg of omeprazole for each sample, using as dissolution an artificial gastric medium. In **Table 9** parameters such as ED60 and the TMD are listed.

TABLE 9: PARAMETERS OF DISSOLUTION OF OMEPRAZOLE, PELLETS SUSPENSION, OILY SUSPENSION, XANTHAN SUSPENSION, ORA –SWEET® SUSPENSION

	ED60 (%)	TMD (minutes)
Omeprazole	52,3	60,0
Pellets suspension	62,9	59,7
Oily suspension	67,7	61,0
Xantan suspension	55,3	63,0
Ora-Sweet®suspension	75,0	43,0

Analyzing all the parameters together, we can conclude that the oily suspension and Ora-Sweet®suspension [20-21] are those with better release profiles. To understand the results of these studies release profiles kinetics were necessary.

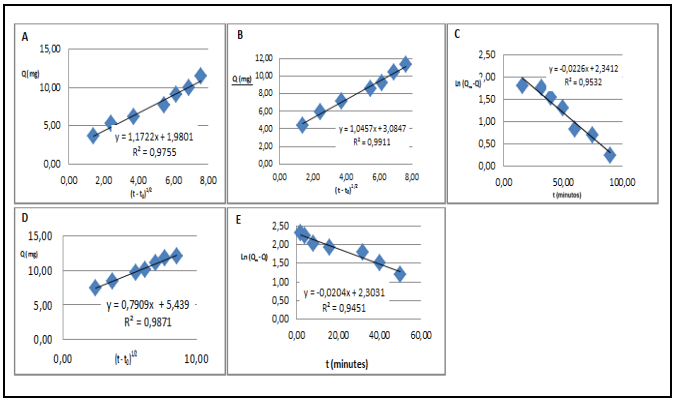

FIG.2: RESULTS OF RELEASE ASSAYS COMPARING THE KINETIC PROFILES OF OMEPRAZOLE AND DIFFERENT SUSPENSIONS. A: OMEPRAZOLE, B: PELLET SUSPENSION, C: OILY SUSPENSION, D: XANTHAN SUSPENSION, E: ORA-SWEET®SUSPENSION

Fig. 2 illustrates the release profiles of omeprazole and different suspensions. After obtaining the release profiles for both the pure omeprazole and for different suspensions under test, we proceeded to adjust the curves of the release kinetics (**Table 10**).

TABLE 10: BIOPHARMACEUTICAL PARAMETERS DERIVED FROM KINETIC OMEPRAZOLE AND DIFFERENT SUSPENSIONS. A: OMEPRAZOLE, B: PELLET SUSPENSION, C: OILY SUSPENSION, D: XANTHAN SUSPENSION, E: ORA-SWEET®SUSPENSION

A	**Zero order**	**First order**	**Cube root**	**Higuchi**	**Weibull distribution**
Slope	0,13	-0,02	0,01	1,10	0,54
Intercept	2,44	2,30	0,06	1,05	-1,86
R	0,9646	0,9722	0,9860	0,9657	0,9441
r^2	0,9305	0,9451	0,9370	0,9325	0,8913
Kd	0,13	0,02	0,01	1,10	
β					0,54
Td (min)					32,05
B	**Zero order**	**First order**	**Cube root**	**Higuchi**	**Weibull distribution**
Slope	0,14	-0,03	0,02	1,17	0,55
Intercept	3,17	2,26	0,19	1,98	-1,55
r	0,9675	0,9867	0,9864	0,9877	0,9352
r^2	0,9361	0,9736	0,9729	0,9755	0,8746
Kd	0,14	0,03	0,02	1,17	
β					0,55
Td (min)					16,53
C	**Zero order**	**First order**	**Cube root**	**Higuchi**	**Weibull distribution**
Slope	0,11	-0,04	0,02	1,05	0,48
Intercept	4,74	2,23	0,28	3,08	-1,24
r	0,9850	0,9706	0,9887	0,9955	0,9592
r^2	0,9703	0,9421	0,9776	0,9911	0,9201
Kd	0,11	0,04	0,02	1,05	
β					0,55
Td (min)					12,87
D	**Zero order**	**First order**	**Cube root**	**Higuchi**	**Weibull distribution**
Slope	0,07	-0,02	0,01	0,95	0,69
Intercept	4,59	2,34	0,19	1,81	-2,41
r	0,9706	0,9763	0,9762	0,9647	0,9311
r^2	0,9421	0,9532	0,9529	0,9306	0,8669
Kd	0,07	0,02	0,01	0,95	
β					0,69
Td (min)					31,01
E	**Zero order**	**First order**	**Cube root**	**Higuchi**	**Weibull distribution**
Slope	0,11	-0,05	0,02	0,79	0,52
Intercept	5,86	2,20	0,36	5,44	-1,08
r	0,9401	0,9491	0,9772	0,9935	0,9598
r^2	0,8838	0,9008	0,9550	0,9871	0,9212
Kd	0,11	0,05	0,02	0,79	
β					0,52
Td (min)					7,99

Fig.2 (A) shows the release kinetics of omeprazole dissolution curve. The kinetic parameters obtained are summarized in **Table 10 (A).** Based on the values of different correlation coefficients for each one of the kinetics valued, we could conclude that the release profile of omeprazole was adjusted to a first order reaction kinetics. **Fig. 2 (B)** shows the release kinetics of omeprazole from omeprazole

pellets suspension dissolution curve. The kinetic parameters obtained are summarized in **Table 10 (B).** Observing the correlation coefficients for each one of the kinetics valued, we could conclude that the release profile of pellets suspension was adjusted to Higuchi kinetics. **Fig. 2 (C)** shows the release kinetics of omeprazole from oily suspension dissolution curve. The kinetic parameters obtained are summarized in **Table 10 (C).** The results suggested Higuchi kinetics. **Fig. 2 (D)** shows curve of the release kinetics of omeprazole from xanthan suspension which is a first order reaction kinetics. The kinetic parameters obtained are summarized in **Table 10 (D**). Observing correlation coefficients for each kinetic, we could conclude that xanthan suspension followed first order reaction kinetics, because its value of the correlation coefficient is closer to one (r = 0, 9763). Similar studies were found in evaluation of dissolution behavior of paracetamol suspensions [22]. **Fig. 2 (E)** shows curve of the release kinetics of omeprazole from Ora-Sweet® suspension. The kinetic parameters obtained are summarized in **Table 10 (E).**

The results suggested Higuchi kinetics because the value of the correlation coefficient is closer to one (r= 0,9935). Similar studies were found in comparative study for *in vitro* release of metformin of two immediate-release multisource products, marketed in Colombia and Kinetic study in vitro release biomaterial formed by HAP- 200 / POVIAC / CaCO3 [23-24]. **Table 11** shows the main parameters calculated for each one of the systems using the different release kinetics.

TABLE 11: EVALUATED RELEASE KINETICS AND MOST REPRESENTATIVE PARAMETERS OF OMEPRAZOLE AND THE SUSPENSIONS EVALUATED

	Release Kinetics	k_d	t10%(min)	t20% (min)	r
Omeprazole	First order	0,02 min^{-1}	5,5	11,0	0,9722
Pellets suspension	Higuchi	1,17 $mg/min^{1/2}$	1,05	4,20	0,9877
Oily suspension	Higuchi	1,05 $mg/min^{1/2}$	1,30	5,22	0,9955
Xantan suspension	First order	0,02 min^{-1}	5,5	11,0	0,9763
Ora-Sweet®suspension	Higuchi	0,79 $mg/min^{1/2}$	2,30	9,22	0,9935

After this study, our suspension showed smaller t10% and t20%, meaning that omeprazole was released sooner than in the other two suspensions, ensuring the faster therapeutic effect, which was a great advantage in the resulting pharmaceutical suspension [25].

CONCLUSIONS:

1. Quantification of omeprazole by HPLC is linear in the concentration range studied.
2. The final formula was an oily suspension with optimum organoleptic properties: beige color, pleasant scent with vanilla and caramel aromas, sweet flavor and creamy texture. This gives rise to a thin product with very good palatability for administration to children.
3. The content uniformity test for omeprazole ensured that the drug, once resuspended by agitating the preparation, remained evenly distributed during dosing, with the recovery percentages within the limits established in bibliography.
4. Stability studies were performed on different formulations of omeprazole in the same storage conditions. As a conclusion, refrigerated and protected from light, samples showed lower percentage degradation than the other ones.
5. Release studies showed that the oily and Ora-Sweet® suspensions presented the best release profiles. The entire dose was dissolved in less time under all test conditions (*in vitro*).
6. The oily suspension that we have developed was the one with better parameters, t10% and t20%, based on kinetic adjustments and the value of its dissociation constant, compared with other current marketed suspensions.
7. After these studies, the following composition for pediatric use was proposed: 0,2% omeprazole, 37,5%sesame oil, 42% Labrafac®, 1,54%Compritol®, 14,5% calcium carbonate, 4% soy lecithin, 0,1%

aspartame, 0,11% vanilla flavor and 0,05% caramel flavor.

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