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ORIGINAL ARTICLE

Evaluation of the Effect of Ethyl Acrylate-Methyl Methacrylate Copolymer in Racecadotril Dispersible Tablet

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ABSTRACT

Objectives: Racecadotril is an anti-diarrheal drug that has the indication to reduce the secretion of water and electrolytes into the intestine. It has an unpleasant taste, when administered orally. The presenting study developed a pharmaceutical racecadotril dispersible tablet, which masked the unpleasant taste using wet granulation method. For this reason, the effect of the number of ethylacrylate-methylmethacrylate copolymers (Eudragit® NE 30D) in taste masking and *in vitro* dissolution of the finished product was investigated.

Materials and Methods: Taste-masked racecadotril granules were prepared using Eudragit® NE 30D and the ratio between the amounts of racecadotril and Eudragit® NE 30D involved in the formulation was optimized. The products obtained in the dispersible tablet dosage form were evaluated in terms of taste and *in vitro* dissolution studies. *In vitro* dissolution profiles of the products obtained in this study were compared with reference product Tiorfan® granules for oral suspension manufactured by Bioprojet Pharma (Paris, France). A method of apparatus II (paddle), 900 mL, pH 4.5 acetate buffer + 1% sodium dodecyl sulfate (SDS) and 100 rpm at 37.0 ± 0.5°C was adopted.

Results: Results of the studies have shown that the formulation should have Eudragit® NE 30D higher than 1% by weight of racecadotril to satisfy the taste-masking ability and the formulation should have Eudragit® NE 30D equal or lower than 10% by weight of racecadotril to have better release characteristic to be compatible with reference product.

Conclusion: Our results demonstrated that a chemically long-term stable racecadotril dispersible tablet product, whose taste is efficiently masked using wet granulation method with an acceptable release profile was obtained with Eudragit® NE 30D ratio higher than 1% and equal or lower than 10% by weight of racecadotril. The developed formulation can increase patient compliance.

Key words: Racecadotril, dispersible tablet, wet granulation, ethyl acrylate-methyl methacrylate copolymers, taste-masking

INTRODUCTION

Racecadotril, which is also known as acetorphan, is a specific inhibitor of enkephalinase for use for treating acute diarrhea.[1-3] Diarrhea, a worldwide critical disease, occurs, when the bowel movements are unable to absorb or actively release fluid, which is loose, watery stools during bowel movements. According to the information released by the World Health Organization, the mortality rate for children under the age of 5 caused by acute diarrhea is estimated at 1.8 million *per* year.[4] Racecadotril active substance reduces excessive secretion of water and electrolytes into the intestinal lumen by preventing the degradation of endogenous opioids (enkephalins).[3,5,6] The efficacy and safety of the specified active substance used orally have been proven in children and adults with acute watery diarrhea.[6] Furthermore, racecadotril has an unpleasant taste, which results in poor patient compliance when administered orally, particularly in the case of children.[2] It is well-known that oral route is commonly used for pediatric patients with solid or liquid dosage forms. Since racecadotril is a hydrophobic active agent, it is difficult to describe in suspension dosage forms. This is why the suspension form is not preferred for formulation development since the active ingredient is water repellent.

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Considering solid dosage forms used in pharmaceutical industry, there are tablets (fast dissolving tablets, dispersible tablets, chewable, immediate release and delayed release), capsules, chewable gums, and powders for oral suspension and granules for oral suspension.

The commercially available product, Tiorfan® granules, for oral suspension with dosage forms of 30 mg and 10 mg produced by Bioprojet Pharma (Paris, France) was used as a reference product to compare *in vitro* dissolution studies of the developed racecadotril dispersible tablets. Characteristic of the formulation is that the racecadotril granulate prepared with a suitable carrier is coated and mixed with a sweetener. Acrylate and methacrylate polymers, especially Eudragit® NE 30D, are stated as coating agents. According to the procedure, firstly, racecadotril granulate is prepared with a little sugar, it is coated with a coating agent; the coated granule is mixed with the remaining sugar, aerosil and sweetener and then filled into a sachet.[7]

Eudragit® NE 30 D is a polymer consisting of methyl methacrylate and ethyl acrylate monomers in a ratio of 2:1, with a low glass transition temperature of -8˚C and a minimum film formation temperature of 5˚C.[8]

Many active substances can be expressed in conventional solid dosage forms, especially capsule and tablet forms, but tablet and capsule forms are not preferred as dosage forms for pediatric patients.[2] Difficulty in swallowing of solid dosage forms in pediatric and geriatric patients can be overcome by developing dispersible tablets that can be dissolved, dispersed or mixed in food, milk or water before administration. These dispersible tablets are suitable dosage form for infants, toddlers, children, and adults. Since dispersible tablets have significant advantages over solid and liquid dosage forms, they are preferable for pediatric usage. Some of the advantages of the solid drugs are listed as being easily portable, providing a range of doses, masking the unpleasent taste, having better adherence. Also, since it remains solid during transportation and storage, the stability of the product is maintained and it turns into a liquid state within a few minutes after dispersion and provides ease of use.[9] It is seen because of these studies that, dispersible tablets improve the efficacy, safety, and compatibility of treatments in infants, toddlers and children.

Solid dispersion technology is a method used to improve the solubility of poor aqueous soluble drugs and hence to achieve an improvement in their bioavailability.[10,11] However, this technology is also known for its ability to mask the taste of bitter-tasting active ingredients. The granules containing the drug substance are obtained by solidification of the molten mixture or evaporation of the solvent. Different methods are also used for the preparation of solid dispersions, such as melting method, solvent method, melting solvent method, melt extrusion method, lyophilization technique, melt agglomeration process, the use of surfactant, electro, spinning, and super critical fluid technology. However, one of the known drawbacks of solid dispersion method is the difficulty in removing the solvent and the cost of preparation of the process compared to other methods.[2,12] In addition to these, the major disadvantage of solid dispersion is related to the degradation that occurs in stability. Exposure to moisture and temperature under stability conditions has a high degrading effect on the products obtained from solid dispersion.[10]

The most important and critical problem in pediatric drugs is the accuracy of the applied dose, which is caused by the unpleasant taste of the product[9] racecadotril can be developed into a dispersible tablet form with taste masking properties in a simple and easy method of wet granulation to overcome the problem of providing a suitable pediatric dosage form that allows for administrating an unpleasant taste drug substance to children. Therefore, taste masking and correct dose with acceptable release are key issues in the current study. The objective of the present study was to develop pharmaceutical compositions comprising racecadotril, whose taste is masked using the wet granulation method, for treating diarrhea.

MATERIALS AND METHODS

Materials

Racecadotril (API grade) was obtained from Symed Labs Limited (India). Eudragit® NE 30D (Evonik, Germany), pregelatinized starch (Colorcon, USA), mannitol (Merch, Germany), aspartame (Vitasweet), kollidon CL (Basf, Germany), acesulfame K (Suzhou, China), strawberry flavor (Firmenich, Switzerland), and sodium stearyl fumarate (JRS Pharma, Germany) were used as inactive ingredients in formulations.

Analytical grades of potassium dihydrogen phosphate (Merck, Germany), phosphoric acid (*ortho*-phosphoric acid 85%, Merck, Germany), and acetonitrile (J.T. Baker, Poland) were used in high performance liquid chromatography (HPLC) analysis. Quantitative stability indicating HPLC test methods were performed on a Shimadzu HPLC System (Shimadzu, Kyoto, Japan) equipped with the separations module and variable wavelength ultraviolet-detector and running with LC solution software. Deionized distilled water was obtained from Millipore water purification system (Millipore Corp., Bedford, MA, USA) and used throughout this study.

Reference product, Tiorfan® granules, for oral suspension produced by Bioprojet Pharma (Paris, France) was purchased.

Analytical method and validation studies

The content of racecadotril for assay studies and *in vitro* dissolution studies were determined spectrophotometrically by an HPLC method at 210 nm using a Shimadzu HPLC System (Shimadzu, Kyoto, Japan). HPLC method with a quaternary pump, autosampler, and diode array detector (DAD) was used during analytical method development and validation for finished product assay and *in vitro* dissolution testing. The separation was achieved using an ODS-3V C18 5 µm column (4.6 mm × 250 mm) using a mobile phase of buffer:acetonitrile (35:65). Buffer was prepared by dissolving 1.0 g of potassium dihydrogen phosphate in a 1 L of deionized water and adjusted to pH 2.5 with phosphoric acid. The granules and tablets to be analyzed were dissolved using the solvent consisting

of buffer:acetonitrile (1:1) mixture. Flow rate was 1.0 mL/min and the signal was monitored at a wavelength of 210 nm. The analytical method of racecadotril was validated for specificity, selectivity, sensitivity, linearity, recovery, accuracy, and precision parameters. Other than statistical evaluation of *f2*, there was no statistical data analysis.

Formulation studies

Due to lack of water solubility of the active ingredient, *i.e.* racecadotril, and inability to press tablets using the direct compression method, it was decided to use the wet granulation production method in a high shear mixer (Pilotmix 150T) for this study.

Granules comprising racecadotril were obtained using wet granulation production method in high shear mixer using Eudragit® NE 30D copolymer. The aim of using Eudragit® NE 30D copolymer was to mask the unpleasent taste of the racecadotril. The granulation process was followed by a drying step with a fluidized bed dryer (HDGC 100) at a maximum of 70˚C temperature. The final blend is obtained by adding other excipients and finally tablet compression is carried out. The unit formula of racecadotril dispersed tablet is given in Table 1.

After the formulation was approximately determined during the pre-formulation, studies were conducted to determine the ratio between Eugragit® NE 30D and racecadotril. To optimize the unit formula of the taste-masked racecadotril granules prepared using wet granulation technique, six formulations (F1-F2-F3-F4-F5-F6) having different weight percent ratios of Eudragit® NE 30D to racecadotril (0.67%, 1%, 2%, 5%, 10%, 12%, respectively) were prepared the following unit formula and prepared as dispersible tablet.

Granules comprising racecadotril, whose taste is masked by being subjected to wet granulation, are used as intermediate products in the preparation of oral pharmaceutical compositions such as tablet, dispersible tablet, and suspension. The granules obtained in this study are blended with the specified excipients and compressed in the form of dispersible tablets. All the dispersible tablet products prepared (F1-F6) were first tested with organoleptic taste properties to determine if the unpleasent taste of racecadotril was masked, and then other quality control tests were performed.

Content uniformity studies

Content uniformity of the final granule mixture

Granules comprising racecadotril are manufactured with wet granulation method and then obtained granules are compressed as tablets. Content uniformity of the final granule mixture was carried out by withdrawing at least 10 random samples taken from different parts like top, center, bottom, and wall locations. Samples selected were dissolved with the solvent in flask and filtered into 0.45 µm polytetrafluoroethylene (PTFE) and transferred to a vial. The prepared vials were tested for racecadotril content using a validated HPLC method mentioned in the analytical methods and validation study section.

Content uniformity of the tablets

Tablets were randomly selected from the beginning, middle, and end of each compression run. Ten tablets were tested for their content uniformity using the validated HPLC method. Each selected tablet is dissolved with the solvent in flask and filtered into 0.45 µm PTFE and transferred to the vial. The prepared vials were tested for racecadotril content using a validated HPLC method mentioned in the analytical methods and validation study section. According to 10 individual assay results, acceptance value (AV) is calculated. Final product content uniformity had to meet European Pharmacopeia (EP) (2.9.40) requirements as the L1 criteria state that 10 samples should be tested and the AV should be equal to or lower than 15.[13]

Disintegration time testing

Disintegration testing was performed in accordance with EP monograph for tablet disintegration. This test is provided to determine, whether tablets or capsules disintegrate within the prescribed time, when placed in a liquid medium at the experimental conditions. Six tablets were tested for each batch and the mean result was reported. Disintegration time testing

Table 1. Unit formulas of racecadotril 30 mg dispersible tablet used in the study

Ingredients	F1	F2	F3	F4	F5	F6
	(mg)					
Racecadotril	30.0	30.0	30.0	30.0	30.0	30.0
Eudragit® NE 30D	0.2	0.3	0.6	1.5	3.0	3.6
Aspartam	10.0	10.0	10.0	10.0	10.0	10.0
Kollidon CL	30.0	30.0	30.0	30.0	30.0	30.0
Mannitol	126.0	125.9	125.6	124.7	123.2	122.6
Acesulfame K	4.0	4.0	4.0	4.0	4.0	4.0
Pregelatinized starch	26.0	26.0	26.0	26.0	26.0	26.0
Strawberry flavor	9.0	9.0	9.0	9.0	9.0	9.0
Sodium stearyl fumarate	4.8	4.8	4.8	4.8	4.8	4.8
Total	**240.0**	**240.0**	**240.0**	**240.0**	**240.0**	**240.0**

was performed by adding a tablet to a beaker of water at 37 ± 0.5°C and recording the time for the tablet to become fully disintegrated.

In vitro dissolution studies

Comparative dissolution studies in three different dissolution media were conducted to demonstrate *in vitro* dissolution behavior between reference product of Tiorfan® 30 mg granules for oral suspension (produced by Bioprojet Pharma, Paris/France) and test products of racecadotril dispersible tablet (F1-F6). The dissolution tests were carried out with a Distek Evolution 6300 dissolution tester. Since there is not any available *in vitro* dissolution method specified by the Food and Drug Administration (FDA) or pharmacopeias for racecadotril, *in vitro* dissolution method was developed using in-house method. The used dissolution method is Apparatus II (Paddle), a volume of 900 mL, pH 4.5 acetate buffer + 1% sodium dodecyl sulfate (SDS) and 100 rpm at 37.0 ± 0.5°C. In addition to pH 4.5 media, dissolution studies were conducted at two other dissolution mediums (0.1 N HCl + 1% SDS and pH 6.8 phosphate buffer + 1% SDS). Racecadotril has poor water solubility, which is measured as 28.98 µg/mL.[14] In addition to water solubility, the solubility of racecadotril was reported as 327.7 µg/mL in pH 4.5 acetate buffer, 61.75 µg/mL in 0.1 N, HCl and 50.86 µg/mL in pH 6.8 phosphate buffer. Furthermore, the solubility of racecadotril is 587.8 µg/mL in phosphate buffer pH 6.8 with 0.75% SLS.[2] Surfactants play an important role in the dissolution preparations, and the solubility studies carried out mediums of pH 4.5, pH 6.8 and 0.1 N HCl with 1% SDS provide sink conditions for used mediums. At pre-determined time intervals (10, 15, 20, 30, 45, 60 min), 2 mL of the release medium is withdrawn and an equal volume of medium is added instead. The sample withdrawn from the medium is filtered and analyzed using a validated HPLC method at 210 nm to determine the amount of dissolved racecadotril.

To achieve effective bioavailability and provide *in vitro-in vivo* correlation, it is expected that at least about 80% of the total amount of racecadotril have dissolved after 45 minutes of measurement and at least about 90% of the total amount of racecadotril after 60 min of measurement at given pH 4.5 acetate buffer + 1% SDS dissolution medium.

The dissolution profiles were compared; the dissolution profiles obtained were evaluated using the similarity factor (*f2*).[15] According to the Eurpean Medicines Evaluation Agengy (EMEA) and FDA Guidelines; dissolution similarity may be determined using the *f*2 statistic as follows:

$$f2 = 50.\log\left[\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{t=n}\left[\overline{R}(t)-\overline{T}(t)\right]2}{n}}}\right] \quad \text{equation (1)}$$

In this equation [equation (1)] *f*2 is the similarity factor, n is the number of time points, R(t) is the mean percent reference drug dissolved at time t after initiation of the study; T(t) is the mean percent of test drug dissolved at time t after initiation of the study. For both reference and test formulations, percentage dissolution should be determined. An *f2* value between 50 and 100 suggests that the two dissolution profiles are similar.[15]

Stability studies

The selected formulation with proper taste and *in vitro* dissolution results was investigated according to the requirements of ICH stability guidelines.[16] For this purpose, tablets were packed with ALU-ALU blister primary packaging and stored in stability cabinets for 6 months at 40 ± 2°C/75% ± 5% relative humidity (RH) (accelerated conditions) and for 24 months at 25 ± 2°C/60% ± 5% RH (long term conditions). At determined time intervals, the test products were evaluated from the specifications such as assay, related substances, and dissolution tests with using validated HPLC method.

RESULTS

Validation studies of analytical method

The analytical method to determine content (assay) of racecadotril in quantification tests and *in vitro* dissolution tests was developed and validated using HPLC system. The assay and *in vitro* dissolution test method of the finished product validations were completed successfully as to specificity, linearity, stress, precision, accuracy, recovery, and robustness. Calibration curve for racecadotril ranged from 0.0067 mg/mL to 0.04 mg/mL and linearity determination coefficients between concentrations and areas were higher than 0.99 (r^2 >0.99) for both assay and *in vitro* dissolution analysis. Also, the recovery of racecadotril was 99.5 ± 1.15% for assay and 98.9 ± 0.90% for dissolution tests; both are in 95% confidence interval. The methods specified according to the method validation test results were shown to be specific for racecadotril and meet all the requirements for validation.

Formulation

In this study, unpleasent taste of racecadotril was masked by wet granulation method with six formulations prepared using Eudragit® NE 30D in different concentrations. Content uniformity test was applied to the prepared granules. Then, dispersible tablets were compressed from these granules and content uniformity test was also applied to these tablets.

Critical process parameters were evaluated in this study, considering into account the known critical steps during granule preparation using the wet granulation process. Two different critical process parameters were determined as 5 min of granulation time with adjusted to the solution delivery rate. First critical parameter is drying temperature and air flow during drying. The drying process was accomplished in two studies; at 50°C and 80 m^3/h and at 70°C and 120 m^3/h drying temperature and air flow. Proper results could not be obtained because the desired moisture content of 2.0% could not be achieved in the study where the drying temperature and air flow rate was low (50°C and 80 m^3/h); and the dissolution profile was obtained lower than reference product in the dissolution studies carried

out in pH 4.5 + 1% SDS medium. The desired moisture content of below 2.0% was obtained with the granules dried at 70°C and the desired particle size of granules was obtained at 120 m^3/h air flow rate. In dissolution studies conducted in pH 4.5 + 1% SDS medium, it was observed that the dissolution profile showed a similar profile to reference product. Second critical parameters are sieving and sieve opening. Sieves with 0.8 mm and 1.5 mm sieve openings were used to reveal the difference in the obtained product. The small sieve opening and sufficient sieving speed enabled the particle size to be reduced to the desired size and in this case, a similar dissolution profile was obtained with reference product for the dissolution studies carried out in pH 4.5 + 1% SDS medium.

After tablet pressing, tests such as appearance, tablet dimensions, friability, disintegration time, hardness, average weight, and weight distribution were applied and all results were found in accordance with the specifications. pH of the water-dispersed tablet was tested and found to be 7.3, which is similar to reference product.

Content uniformity results of racecadotril at final granules and tablet are given in Table 2. According to the results of the content uniformity of the granules and tablets, both of them met the content uniformity specifications. The contents of racecadotril in the granules and tablets tested were found to be in the range of 97.0 - 103.0% with having L1 values lower than 15, as shown in Table 2.

Table 2. Content uniformity results of racecadotril at final granule mixture and tablet (n: 10)

	Final granules					
Sample	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	101.5	101.2	100.3	102.3	100.6	100.4
2	100.9	98.5	101.1	100.4	101.6	102.6
3	99.6	97.6	99.5	98.8	99.5	98.4
4	98.4	102.5	98.6	100.4	97.9	100.5
5	97.6	101.6	97.9	101.5	99.1	102.6
6	99.1	99.5	100.6	103.6	100.6	101.5
7	100.8	99.4	101.5	99.5	101.5	100.6
8	101.1	98.5	98.6	100.4	98.4	98.7
9	99.5	101.5	101.6	101.6	99.4	99.5
10	102.3	102.1	100.9	99.8	98.1	100.4
Average	**100.1**	**100.2**	**100.1**	**100.8**	**99.7**	**100.5**
SD[a]	**1.48**	**1.74**	**1.33**	**1.43**	**1.35**	**1.43**
RSD[b] %	**1.48**	**1.73**	**1.33**	**1.42**	**1.36**	**1.43**
	Tablet					
Sample	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	101.5	99.8	99.7	99.3	102.3	99.6
2	103.5	101.6	100.5	101.4	100.5	100.5
3	98.5	100.4	102.6	100.6	100.6	101.6
4	99.5	102.3	101.2	102.7	98.5	102.6
5	99.4	100.5	98.6	103.6	100.1	98.6
6	100.5	99.1	98.4	98.5	99.5	99.5
7	101.6	98.3	101.5	101.6	98.6	97.6
8	97.5	102.3	100.5	102.4	98.4	100.5
9	98.9	99.6	98.1	100.5	100.5	102.5
10	100.6	102.5	97.6	100.4	101.6	100.4
Average	**100.2**	**100.6**	**99.9**	**101.1**	**100.1**	**100.3**
SD[a]	**1.76**	**1.48**	**1.66**	**1.56**	**1.32**	**1.61**
RSD[b] %	**1.75**	**1.47**	**1.66**	**1.54**	**1.32**	**1.60**

[a]SD: Standard deviation, [b]RSD: Relative standard deviation

Taste-masking studies

In this study, six formulations with variable concentrations of Eudragit® NE 30D were subjected to human taste tests to mask the unpleasant taste of racecadotril using the wet granulation method. Since taste is an important issue in the administration of drugs containing bitter active substances in the oral administration system, the solution to this problem is the main purpose of this study.

According to human taste test performed on all products prepared (F1-F6), it was observed that the taste of the products prepared with the F1 formulation was still bitter. In other words, racecadotril could not be masked at a sufficient level. As a consequence, the bitter taste of the racecadotril compound is not masked, if the percentage ratio between Eudragit® NE 30D and racecadotril is below 1%.

The products obtained from the F2-F6 formulations developed have confirmed the acceptability of the bitter taste of racecadotril by taste masking by human taste test. According to the taste evaluation results, it was shown that an effective taste mask formulation was achieved using Eudragit® NE 30D higher than 1% by weight of racecadotril.

Since the product is a dispersible tablet and is intended for pediatric patients, the most important step is efficient taste masking. For this reason, if the necessary coating process is not sufficient to mask the bitter taste of racecadotril, then, the issues in patient compliance occur.

In vitro dissolution studies

In vitro dissolution behavior of formulations (F2-F6) prepared with different concentrations of Eudragit® NE 30D by using wet granulation method was examined in pH 4.5 acetate buffer + 1% SDS buffer, 0.1 N HCl + 1% SDS and pH 6.8 phosphate buffer + 1% SDS mediums. The corresponding profiles at pH 4.5 acetate buffer + 1% SDS buffer are shown in Figure 1 and the similarity factors (f_2) calculated for three mediums are given in Table 3 by comparison with reference product Tiorfan® 30 mg granules for oral suspension.

In comparison with the formulations prepared in this study, F4 formulation appears to have lower and slower release, and only about 80% of the drug dissolved within 60 min. According to *in vitro* dissolution results, when the percentage ratio between Eudragit® NE 30D copolymer and racecadotril is higher than 10% (F6), total amount dissolved after 45 min is under 80% (76.3%) and total amount dissolved after 60 min is around 80%, which means dissolution does not complete.

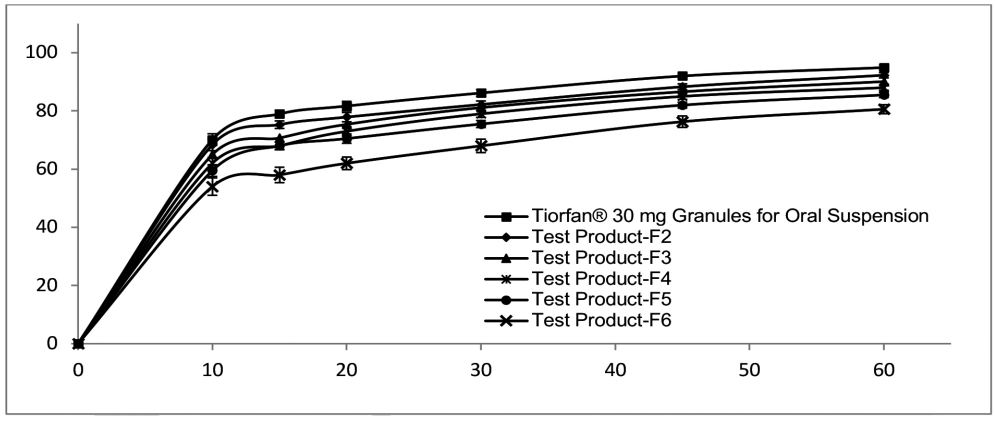

Figure 1. *In vitro* % released racecadotril *vs.* time profiles from the test products (F2-F6) and reference product of Tiorfan® 30 mg granules for oral suspension (SXE1159) in pH 4.5 acetate buffer + 1% SDS medium (mean ± SD, n: 12)

SDS: Sodium dodecyl sulfate, SD: Standard deviation

Table 3. The summary of similarity factor (f_2). test products (F2-F6) *vs.* reference product-Tiorfan® 30 mg granules for oral suspension (Bioprojet Pharma, Paris/France)

f_2 (similarity factor)			
Products	**pH 4.5 acetate + 1% SDS**	**0.1 N HCl + 1% SDS**	**pH 6.8 phosphate buffer + 1% SDS**
F2 *vs.* reference product	f_2: 74	f_2: 66	f_2: 68
F3 *vs.* reference product	f_2: 63	f_2: 57	f_2: 56
F4 *vs.* reference product	f_2: 56	f_2: 52	f_2: 53
F5 *vs.* reference product	f_2: 51	f_2: 52	f_2: 51
F6 *vs.* reference product	f_2: 39	f_2: 45	f_2: 41

SDS: Sodium dodecyl sulfate

Table 4. Stability results for test product F2 initially and after 6 months at 40 ± 2˚C and 75% ± 5% RH storage condition and 24 months at 25 ± 2˚C and 60 ± 5% storage condition (mean ± SD, n: 6)

		Time point		
Initially		**After 6 months at 40˚C**	**After 24 months at 25˚C**	
Taste		Complies	Complies	Complies
Disintegration time (at 37˚C water)		Lower than 3 minutes	Lower than 3 minutes	Lower than 4 minutes
Assay	**Racecadotril**	99.6 ± 0.78%	96.2 ± 1.3%	98.5 ± 0.60%
Related substance	**Total imp.**	0.09%	0.46%	0.37%
Dissolution*	**After 45 minutes**	88 ± 1.6%	82 ± 3.1%	81 ± 2.4%
pH**		7.27	7.30	7.33

*Apparatus II (Paddle), 900 mL, pH 4.5 acetate buffer + 1% sodium dodecyl sulfate and 100 rpm at 37.0 ± 0.5˚C. **Dispersed in one glass of water. RH: Relative humidity, SD: Standard deviation

The results obtained confirmed that there were acceptable similarities between the test products (F2-F5) and reference products for various dissolution mediums under comparison; as a result, *f2* values of all dissolution media are higher than 50 (Table 3). The comparative dissolution rate profiles show that reference product and the test products having a percentage ratio of Eudragit® NE 30D to racecadotril lower than 10% gave similar dissolution profiles.

As *in vitro* dissolution is related to the *in vivo* properties of the product, the bioavailability will be lower in products due to lower values in their dissolution profiles. Primarily to achieve desired dissolution profile and related to achieve effective bioavailability; the percentage ratio between Eudragit® NE 30D copolymer and racecadotril should be lower than 10%.

According to taste and *in vitro* dissolution results, the percentage ratio range of Eudragit® NE 30D copolymer should be higher than 1% and equal or lower than 10% by weight of the amount of racecadotril.

Test product F2 was found to be the most suitable in all formulations in the taste masking and *in vitro* dissolution studies; therefore, stability studies continued with this formulation.

Stability studies

Test product F2 (the best formulation among the others) was further studied with stability studies. In a further aspect of the invention, the unit dosage form of formulation according to the invention is physically and chemically stable. Stability of the tablets can be measured at accelerated and at long term storage conditions for periods of several months. Experiments can be performed at different temperatures and humidity. The oral pharmaceutical compositions of this invention, which are prepared according to Test product F2, were subjected to accelerated stability studies at 40 ± 2˚C/75% ± 5 RH (accelerated conditions) and 25 ± 2˚C/60% ± 5% RH (long term conditions). The stability results are given in Table 4.

DISCUSSION

This study aimed to demonstrate the effect of Eudragit® NE 30D concentrations in the dispersible tablet formulation on taste-masking and on the *in vitro* dissolution profile of racecadotril by using wet granulation technique. The analytical HPLC method was validated successfully; with results obtained the method has been used in *in vitro* dissolution tests and other stability tests. In this study, six formulations with variable concentrations of Eudragit® NE 30D were prepared by wet granulation method and evaluated for taste and *in vitro* drug release. The results of the taste assessment showed that by providing a minimum ethyl acrylate-methyl methacrylate copolymer ratio of 1% by weight of racecadotril quantity, an appropriate taste-masked formulation, was achieved. If the ratio between ethyl acrylate-methyl methacrylate copolymer and racecadotril is under 1%, bitter taste of the racecadotril compound is not masked. Since the product is a dispersible tablet and developed for pediatric patients, effective taste masking is a critical process. Due to bitter taste of racecadotril, if the coating process is not sufficient, problems in patient compliance may occur.

Maximum ratio of ethyl acrylate-methyl methacrylate copolymer to racecadotril should be 10% by weight so that the amount of dissolved racecadotril resulting from an *in vitro* dissolution study in 45 min is at least about 80% of the total amount of active ingredient. According to stability test results, racecadoril dispersible tablets were found to be stable in terms of assay, impurity, and dissolution results at 40 ± 2˚C and 75 ± 5% RH conditions for 6 months and at 25 ± 2˚C and 60 ± 5% RH conditions for 24 months.

CONCLUSION

This study confirms the feasibility of developing a racecadotril dispersible tablet formulation using wet granulation method and shows the effect of Eudragit® NE 30D on the taste and dissolution properties of the drug product.

Ethics

Ethics Committee Approval: Not necessary.

Informed Consent: Not necessary.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: O.P., B.B., G.P.G., N.A., A.A., Design: O.P., B.B., G.P.G., N.A., A.A., Data Collection or Processing: O.P., B.B., G.P.G., N.A., A.A., Analysis or Interpretation: O.P., B.B., G.P.G., N.A., A.A., N.S., Literature Search: O.P., B.B., G.P.G., N.A., A.A., N.S., Writing: N.S., O.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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