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Evaluation of the effect of ethyl acrylate-methyl methacrylate copolymer on Racecadotril dispersible tablet

Etil akrilat-metil metakrilat kopolimerin Rasekadotril dağılabilir tablet üzerindeki etkisinin değerlendirilmesi

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ABSTRACT
INTRODUCTION: Racecadotril is an anti-diarrheal drug that has the indication to reduce the secretion of water and electrolytes into the intestine. It is known to have an unpleasant taste when administered orally. The aim of the present study was to develop a pharmaceutical racecadotril dispersible tablet, which masks the bitter taste using the wet granulation method. For this reason, the effect of the amount of ethylacrylate-methylmethacrylate copolymers (Eudragit® NE 30D) on taste masking and in-vitro dissolution of the finished product was investigated.
METHODS: The 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. The in-vitro dissolution profiles of the products obtained from 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: The 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 also 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 the reference product.
DISCUSSION AND CONCLUSION: The obtained results demonstrated that a

chemically long term stable racecadotril dispersible tablet product whose taste is efficiently masked by 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 has the ability to increase patient compliance.
Keywords: Racecadotril, dispersible tablet, wet granulation, ethyl acrylate-methyl methacrylate copolymers, taste-masking

ÖZ

GİRİŞ ve AMAÇ: Rasekadotril, su ve elektrolitlerin bağırsağa salgılanmasını azaltma endikasyonuna sahip ishal önleyici bir ilaçtır. Oral olarak uygulandığında hoş olmayan bir tada sahip olduğu bilinmektedir. Bu çalışmanın amacı, yaş granülasyon yöntemini kullanarak acı tadı maskeleyen farmasötik bir rasekadotril dağılabilir tablet geliştirmektir. Bu nedenle, etil akrilat-metil metakrilat kopolimer (Eudragit® NE 30D) miktarının bitmiş ürünün tat maskelemesi ve in-vitro çözünmesi üzerindeki etkisi araştırılmıştır.

YÖNTEM ve GEREÇLER: Tadı maskelenmiş rasekadotril granüller Eudragit® NE 30D kullanılarak hazırlanmış ve formülasyonda yer alan rasekadotril ve Eudragit® NE 30D miktarları arasındaki oran optimize edilmiştir. Dağılabilir tablet dozaj formunda elde edilen ürünler tat ve in vitro çözünme çalışmaları açısından değerlendirilmiştir. Bu çalışmadan elde edilen ürünlerin in vitro çözünme profilleri, Bioprojet Pharma (Paris, Fransa) tarafından üretilen, Oral Süspansiyon için Tiorfan® Granüller referans ürünü ile karşılaştırılmıştır. Aparat II (pedal), 900 mL, pH 4.5 asetat tamponu + %1 sodyum dodesil sülfat (SDS) ve 37.0 ± 0.5 ° C'de 100 rpm metodu kullanılmıştır.

BULGULAR: Çalışmaların sonuçları, formülasyonda yeterli tat maskelemenin sağlanabilmesi için rasekadotril ağırlığına göre %1'den fazla Eudragit® NE 30D içermesi gerektiğini ve ayrıca referans ürünle uyumlu olacak şekilde daha iyi salım özelliğine sahip olması için formülasyonun rasekadotril ağırlığına göre %10'a eşit veya daha düşük Eudragit® NE 30D içermesi gerektiğini göstermiştir.

TARTIŞMA ve SONUÇ: Elde edilen sonuçlar, racecadotril ağırlığına göre % 1'den fazla ve % 10'a eşit veya daha düşük Eudragit® NE 30D içerecek şekilde yaş granülasyon yöntemi kullanılarak tadı etkili bir şekilde maskelenen kimyasal olarak uzun dönem stabil özelliklere sahip rasekadotril dağılabilir tablet ürününün elde edildiğini göstermiştir. Geliştirilen formülasyon hasta uyumunu arttırma yeteneğine de sahiptir.
Anahtar Kelimeler: Rasekadotril, dağılabilir tablet, yaş granülasyon, etil akrilat-metil metakrilat kopolimeri, tat maskeleme

1. Introduction

Racecadotril which is also known as acetorphan is a specific inhibitor of enkephalinase for use in the treatment of acute diarrhea. [1-3] Diarrhea, a worldwide critical disease, occurs when the bowel movements are unable to absorb or actively releases fluid, which is loose, watery stools during bowel movements. According to the information released by the World Health Organization (WHO), 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 has been proven in children and adults with acute watery diarrhea. [6] Furthermore, racecadotril has unpleasant taste which results poor patient compliance when administered orally, especially in the case of children. [2] It is well-known that, oral route is used commonly for pediatric patients with solid or liquid dosage forms. Since racecadotril is a hydrophobic active agent, it is difficult to formulate in suspension dosage forms. This is why the suspension form is not preferred for formulation development since the active ingredient is water repellent. Considering solid dosage forms used in the pharmaceutical industry, it is known that there are tablets (fast dissolving tablets, dispersible tablets, chewable, immediate release and delayed release), capsules, and chewable gums, 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 reference product to compare in-vitro dissolution studies of the developed Racecadotril Dispersible Tablets. The 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, first, 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 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 (Tg) of -8°C and a minimum film formation temperature of 5°C. [8]

Many active substances can be formulated 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 more preferable for pediatric usage. Some of the advantages of the solid drugs are listed as being easily portable, providing range of doses, masking the bitter 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 as a result of the 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] On the other hand, 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 preparation of solid dispersions such as melting method, solvent method, melting solvent method, melt extrusion method, lyophilisation technique, melt agglomeration process, the use of surfactant, electro spinning and super critical fluid technology However, one of the known drawback 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 with the degradation that occurs in stability. Exposure to moisture and temperature under stability conditions have a high degrading effect on the products obtained by 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] It has been found that racecadotril can be formulated 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 the administration of 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 is to develop pharmaceutical compositions comprising racecadotril whose taste is masked by using wet granulation method, for the treatment of diarrhea.

2. Materials and methods

2.1. 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 HPLC analysis. Quantitative stability indicating HPLC test methods were performed on Shimatzu HPLC System (Shimatzu, Kyoto, Japan) equipped with the Separations Module and variable wavelength UV-Detector and ran with Lc Solution Software. Deionized distilled water was obtained from a Millipore water purification system (Millipore Corp., Bedford, MA, USA) and used throughout this study.

The reference product Tiorfan® Granules for oral suspension produced by Bioprojet Pharma (Paris, France) was purchased.

2.2. 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 Shimatzu HPLC System (Shimatzu, Kyoto, Japan). A high performance liquid chromatography (HPLC) method with a quaternary pump, autosampler and diode array detector was used during analytical method development and validation for finished product assay and in vitro dissolution testing. Separation was achieved by using a 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 liter of deionized water and adjusted to pH 2.5 with phosphoric acid. The granules and tablets to be analyzed were dissolved using a solvent consisting of buffer : acetonitrile (1:1) mixture. The 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.

2.3. Formulation Studies

Due to the lack of water solubility of the active ingredient, racecadotril, and the inability to press tablets by direct compression method, it was decided to use the wet granulation production method in a high shear mixer (Pilotmix 150T) for the present 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 bitter taste of the racecadotril. The granulation process was followed by a drying step with 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. Unit formula of racecadotril dispersed tablet is given at Table 1.

After the formulation was approximately determined during the preformulation, studies were conducted to determine the ratio between Eugragit® NE 30D and racecadotril. In order to optimize the unit formula of the taste-masked racecadotril granules prepared by 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 with 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 product 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 see if the bitter taste of racecadotril was masked, and then other quality control tests were performed.

2.4. Content Uniformity Studies

2.4.1 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 the 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 Analytical Method and Validation Studies section.

2.4.2 Content Uniformity of the Tablets

Tablets were randomly selected from the beginning, middle and end of each compression run. 10 tablets were tested for their content uniformity using the validated HPLC method. Each of the selected tablets is dissolved with the solvent in the 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 Analytical Method and Validation Studies section. According to 10 individual assay results, the acceptance value (AV) is calculated. Final product content uniformity had to meet EP (2.9.40) requirements as the L1 criteria states that 10 samples should be tested and the AV should be equal or lower than 15 [13].

2.5. Disintegration time testing

Disintegration testing was performed in accordance with the European Pharmacopeia 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 was performed by adding a tablet to a beaker of water at 37°C ± 0.5°C and recording the time for the tablet to become fully disintegrated.

2.6. In-vitro Dissolution Studies

Comparative dissolution studies at three different dissolution media were performed to demonstrate in vitro dissolution behaviors between the 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 in FDA or pharmacopeias for racecadotril, in-vitro dissolution method was developed by 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 carried out at two other dissolution mediums (0.1 N HCl + 1% SDS & pH 6.8 phosphate buffer + 1% SDS). Racecadotril has poor water solubility which is measured as 28.98 µg/mL [14]. Addition to water solubility, the solubilities of racecadotril were 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 [15]. It is known that surfactants play an important role in the dissolution of 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 condition for used mediums. At predetermined time intervals (10, 15, 20, 30, 45, 60 minutes), 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 by a validated HPLC method at 210 nm to determine the amount of dissolved racecadotril.

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

The dissolution profiles were compared; the dissolution profiles obtained were evaluated by similarity factor (*f2*) [16]. According to the EMEA and FDA Guidelines; Dissolution similarity may be determined using the *f*2 statistic as follows:

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

In this equation (Eq.(1)) *f2* 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 test drug dissolved at time t after initiation of the study. For both the reference and test formulations, percent dissolution should be determined. An *f2* value between 50 and 100 suggests that the two dissolution profiles are similar. [16]

2.7. Stability Studies

The selected formulation having proper taste and in-vitro dissolution results was investigated according to the requirements of the ICH stability guideline [17]. For this

purpose, tablets were packed with ALU-ALU blister primary packaging and stored in stability cabinets for 6 months at 40°C ± 2°C / 75% ± 5% Relative Humidity (RH) (accelerated conditions) and for 24 months at 25°C ± 2°C/ 60% ± 5% RH (long term conditions). At determined time intervals the test products were evaluated from the specifications such as assay, related substance and dissolution tests with using validated HPLC method.

3. Results

3.1 Validation Studies of Analytical Method

The analytical method to determine the content (assay) of racecadotril in quantification tests and in-vitro dissolution tests was developed and validated using High Peerformance Liquid Chromatography (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 have shown to be specific for racecadotril and meet all the requirements for validation.

3.2. Formulation

In this study, the bitter 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 the present study, taking into account the known critical steps during granule preparation using the wet granulation process. Two different critical process parameters were determined as 5 minutes of granulation time with adjusted to solution delivery rate. First critical parameter is drying temperature & air flow during drying. Drying process was accomplished in two studies; at 50ºC & 80m3/h and at 70ºC & 120m^3/h drying temperature and air flow. Proper results could not be obtained due to the fact that the desired moisture content of 2.0% could not be achieved in the study where the drying temperature and air flow rate were low (50ºC & 80m^3/h); and also the dissolution profile was obtained lower than the reference product in the dissolution studies carried out in pH 4.5 + 1% SDS medium. The desired moisture content of below 2.0% were obtained with the granules dried at 70ºC and the desired particle size of granules were obtained with 120 m^3/h air flow rate. In dissolution studies performed in pH 4.5+1% SDS medium, it was observed that the dissolution profile showed similar profile with the reference product. Second critical parameter is sieving & 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 the 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, weight distribution were applied and all

results were found in accordance with the specifications. The pH of the water dispersed tablet was tested and found to be 7.3, which is similar to the reference product.
Content uniformity results of racecadotril at final granules and tablet are given at Table 2. According to the results of the content uniformity of the granules and tablets, both of them meet the content uniformity specifications. The contents of racecadotril in all 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.

3.3 Taste-masking Studies

In the present 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 of this problem is the main purpose of this study.
According to human taste test performed on all the products prepared (F1-F6), it was observed that the taste of the products prepared with 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 by 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.

3.4. In-vitro Dissolution Studies

The in-vitro dissolution behavior of formulations (F2 - F6) prepared with different concentrations of Eudragit® NE 30D by using wet granulation method were 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 below and in similarity factors (f_2) calculated for three mediums are given in Table 3 by comparison with the reference product Tiorfan® 30 mg Granules for oral suspension.
In comparison with the formulations prepared in this study, the F4 formulation appears to have lower and slower release, and only about 80% of the drug dissolved within 60 minutes. According to in-vitro dissolution results, when the percent ratio between Eudragit® NE 30D copolymer and racecadotril is higher than 10% (F6), total amount dissolved after 45 minutes is under 80% (76.3%) and total amount dissolved after 60 minutes is arount 80% which means dissolution does not complete.
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 the reference product and the test products having percent 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 in order to achieve desired dissolution profile and related to achieve an effective bioavailability; the percent ratio between Eudragit® NE 30D copolymer and racecadotril should be lower than 10%.
According to taste and in-vitro dissolution results, the percent 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.

3.5. 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 as well as at long term storage conditions for periods of several months. Experiments can be performed at different temperatures and humidity. The oral pharmaceutical compositions of the present invention which are prepared according to Test product F2 were subjected to accelerated stability studies at 40°C ± 2°C / 75% ± 5 RH (accelerated conditions) and 25°C ± 2°C / 60% ± 5% RH (long term conditions). The stability results are given at Table 4.

4. Discussion

The objective of this study was 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. Analytical HPLC Method has been validated successfully; with the results obtained the method has been used in in-vitro dissolution tests and other stability tests. In this study, six formulations with variable concentration 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%, the bitter taste of the racecadotril compound is not masked. Since the product is dispersible tablet and developed for pediatric patients, effective taste masking is critical process. Due to bitter taste of racecadotril, if the coating process is not sufficient then problems in patient compliance may occur.
The 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 minutes 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 & 75% ± 5% RH conditions for 6 months and at 25°C ± 2°C & 60% ± 5% RH conditions for 24 months.
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.

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TABLES

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

Ingredients	**F1 (mg)**	**F2**	**F3**	**F4**	**F5**	**F6**
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**

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

	Final Granule					
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] Standard deviation.

[b] Relative 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	f2: 74	f2: 66	f2: 68
F3 vs Reference Product	f2: 63	f2: 57	f2: 56
F4 vs Reference Product	f2: 56	f2: 52	f2: 53
F5 vs Reference Product	f2: 51	f2: 52	f2: 51
F6 vs Reference Product	f2: 39	f2: 45	f2: 41

Table 4. Stability results for test product F2 initially and after 6 months at 40°C ± 2°C & 75% ± 5% RH storage condition and 24 months at 25°C ± 2°C & 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), 900mL, pH 4.5 acetate buffer + 1% Sodium dodecyl sulfate (SDS) and 100 rpm at 37.0±0.5°C.
****** Dispersed in one glass of water

FIGURE

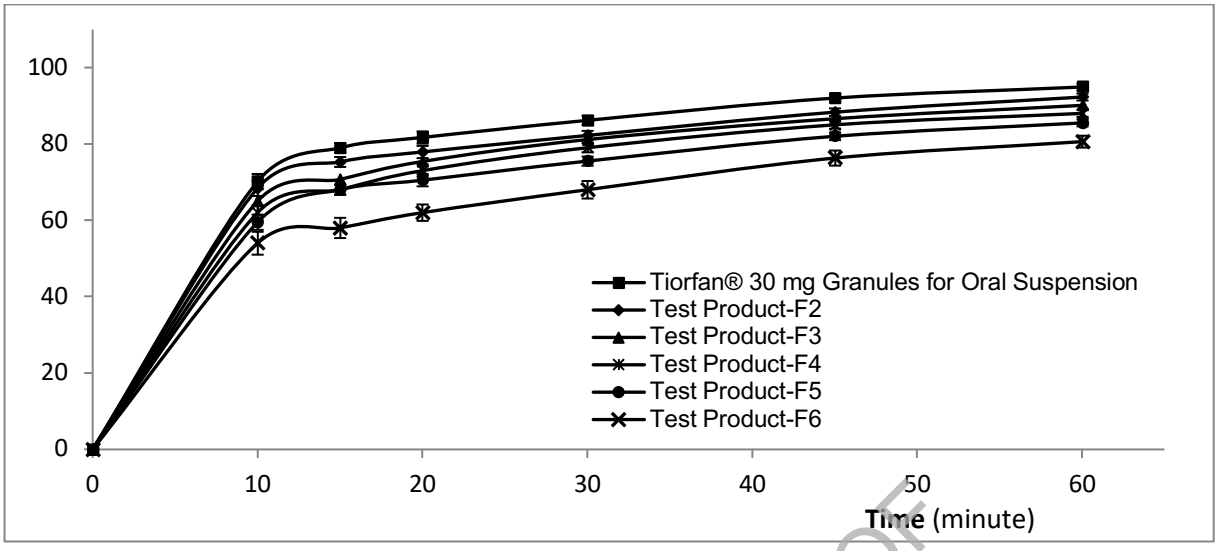

Figure In-vitro % released racecadotril vs. time profiles from the test products (F2 - F6) and reference product of Tiorfan® 30 mg granules for oral suspension (SXE1159) in pH 4.5 acetate buffer + 1% SDS medium (mean ± SD, n = 12).