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Taste Masking of Enalapril Maleate by the Precipitation Method

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Background: Taste masking of bitter or unpleasant drugs is an important prerequisite to improve patient compliance, especially for children and elderly patients. We aimed at obtaining taste-masked microparticles intended for incorporation into orodispersible tablets (ODTs). We selected the precipitation method using enalapril maleate (ENA) as a model bitter-tasting drug and Eudragit EPO® as a pH sensitive polymer.

Aim: The aim of this study was to obtain microparticles with enalapril maleate by the precipitation method in order to mask the bitter taste of the drug.

Materials and methods: Nine models of enalapril maleate – Eudragit EPO® microparticles were prepared by the precipitation method at varied drug-polymer ratios. The models were characterized in terms of size, shape, production yield, drug content, encapsulation efficiency and moisture content. Fourier-transformed infrared spectroscopy, powder X-ray diffraction and differential scanning calorimetry were used to analyze possible interactions in the complex. In vitro drug release in simulated salivary fluid and in vivo taste evaluation in rats were realized to prove taste masking.

Results: The particle size distribution varied from 266.9 μm to 410.9 μm. The shape of the resulting particles was irregular. The production yield varied from 23.6% to 78.2%. The drug content ranged between 2.3% to 4.8%, encapsulation efficiency increased from 1.6% to 9.0%. In vitro drug release data indicated significant taste masking.

Conclusion: Some of the obtained microparticles by the precipitation method showed satisfactory taste masking efficiency, which proved the taste masking feasibility of this method.

INTRODUCTION

Enalapril maleate, which is an orally active ACE inhibitor, is generally prescribed for the treatment of high blood pressure and heart failure both in elderly patients and in children.[1] Children, as a specific group of patients, have special requirements for oral administration. Enalapril maleate is a bitter-tasting drug; therefore, taste-masking approach is needed in order to make the formulation suitable for pediatric administration. Generally, taste-masking techniques are based on reducing drug solubility in the saliva and achieving drug concentrations below the threshold of taste sensation. This is usually accomplished by applying appropriate methods and using pH-sensitive polymers. In our study, we used Eudragit EPO®, polymethyl methacrylate polymer, insoluble in salivary fluid with pH 6.8 but soluble in gastric fluid of pH = 1.2. Generally, the following methods for masking the bitter taste are applied:[2] microencapsulation,[3-5] single emulsion solvent evaporation[6], usage of ion exchange resins or prodrugs, spray-drying, precipitation[7], preparation of solid dispersion system by melting method, gel formation with subsequent granulation, complexation with dextrins, incorporation into liposomes, formulation of effervescent dosage forms, etc.

AIM

The aim of the present work was to obtain different models of microparticles in the form of drug-polymer complexes using the precipitation method.

MATERIALS AND METHODS

Enalapril maleate was purchased from Alfa Aesar, Germany, Eudragit EPO® was a gift from Evonik, Germany. Ethanol (95% v/v) and NaOH were delivered by Sigma Aldrich, USA. All other reagents (NaCl, HCl, Na_2HPO_4 and KH_2PO_4) were purchased from Sigma Aldrich, USA and were used for the preparation of the simulated salivary fluid (SSF) and simulated gastric fluid (SGF). Wistar male rats, bred in the Medical University Plovdiv vivarium, were used.

Particle preparation

Preparation of the complexes between enalapril maleate and Eudragit EPO® was conducted by the precipitation method. Briefly, saturated solutions of ENA and Eudragit EPO® in ethanol 95% were prepared using magnetic stirrer. The solutions were then mixed in the ratios given in **Table 2** and were added dropwise to 0.1 N sodium hydroxide solution at continuous stirring at 500 rpm. The resultant foam on the top of the solution was removed and allowed to dry at room temperature. The resulting solid mass was triturated in a mortar with a pestle to reduce the particle size. Afterwards, the powder was sifted through a sieve with a mesh size of 600 μm.

Production yield, drug loading and encapsulation efficiency

Production yield was calculated in percentage using equation A, where W1 was the amount of polymer, W2 was the amount of drug, W3 was the mass of the obtained particles. Drug loading was calculated using equation B, where W4 was the quantity of ENA in the models.

$$A)\left(\frac{W3}{W1+W2}\right)*100; \quad B)\left(\frac{W4}{50}\right)*100$$

50 mg of the obtained particles were dissolved in 250 ml of freshly prepared simulated gastric fluid (pH = 1.2, Eur. Ph. IX), filtered using Whatman syringe filter (0.45 μm) and the absorbance was measured at 206 nm by Evolution 300 UV-VIS spectrophotometer (Thermo Fisher Scientific, USA). Encapsulation efficiency (EE %) was calculated as the amount of enalapril included in the obtained particles, relative to the total drug amount used.

Size and shape of the particles

Particle size and size distribution were analyzed by laser diffraction using Beckman coulter particle size analyzer (LS 13 320, Beckman Coulter, USA), equipped with a tornado system for powders (Tornado Dry Powder System, DPS). The shape of the particles was visualized using optical microscope Leica DM2000 LED (Leica Microsystems, Germany), equipped with a digital camera (Leica DMC 2900) and software for image processing (Leica Application Suite, LAS).

Moisture content

Moisture content was estimated gravimetrically using moisture analyzer (Kern MLB 09/ 2004, Kern & Sohn Gmbh,Germany).

FTIR spectroscopy

ATR - FTIR spectroscopy was used to analyze the possible mechanism of complexation. Conclusions were made based on peaks number and location in the spectra, about the presence or absence of new chemical bonds and eventual interactions. The study was conducted under the following conditions: 64 scans, 4 mnm resolution, spectral range 4000 – 400 cm^{-1} using FTIR spectrophotometer (Nicolet iS10, Thermo Fisher Scientific, USA), equipped with a diamond ATR accessory. The spectra were analyzed using the OMNIC software package.

Powder X-ray diffractometry

Powder X-ray diffractometry was used to determine the physical state of the drug in the polymer particles. The spectra were obtained on a powder X-ray diffractometer (D2 Phaser Bruker AXS, Cu radiation, 2009) using Ni-filtered Cu - radiation in the range of 4-70° 2-theta at 30 kV and 10 mA.

Thermal analysis

Differential thermal analysis (DTA) and thermogravimetric analysis (TGA) were used to observe temperature changes of the drug and polymer in the particles. The samples were analyzed in a temperature range from 10 to 550°C at a heating rate 10°C min^{-1} under argon atmosphere using a thermal imaging apparatus Stanton Redcroft STA 1500.

Taste evaluation

Taste evaluation was determined by *in vitro* and *in vivo* methods.

In vitro drug release was determined by placing a certain amount of particles, equivalent to 1 mg of enalapril maleate, in 20 ml of freshly prepared simulated salivary fluid (pH 6.8, Eur. Ph. IX) under stirring at 500 rpm for 60 seconds. 2 ml of each sample was filtered through Whatman filter 0.45 μm and then the absorbance of the samples was measured at 206 nm by an UV spectrophotometer and the concentration was calculated from the

calibration curve.

In vivo study was carried out in accordance with the International Council for Laboratory Animal Science Ethical Guideline for Researchers and the relevant institutional and national rules and regulations, and was approved by the Bulgarian Food Safety Agency (license № 87/9.01.2014). The taste was evaluated by investigation of the licking frequency of sample solutions from experimental animals in comparison with water.

Forty male Wistar rats of 170-240 g body weight were used, divided into 5 groups (n=8) **(Table 1)**. The rats were kept under standard laboratory conditions (24±2°C, 50% RH, 12 h light/dark cycle) and provided with food *ad libitum*.

Table 1. Groups of experimental animals used for in vivo taste evaluation

Group	Treatment
1 (control)	Distilled water
2 (test)	ENA solution 13 mg/ml
3 (test)	DPC6
4 (test)	DPC7
5 (test)	DPC9

The rats were deprived of water for 24 h, then, bottles containing distilled water were presented to the animals of all five groups and the number of times every rat licks the bottle for 3 minutes was counted. Thereafter, the animals were housed in the absence of water for 24 h again. Then, the rats were allowed to lick the bottles with the selected models suspended in distilled water according to **Table 1** and licking activity observed in 3 minutes was counted. Percentage of licking frequency was calculated according the formula:

$$\text{Licking frequency (\%)} = \left(\frac{\text{number of licks to test substance or formulation}}{\text{number of licks to water}}\right) \times 100$$

Statistical analysis

All experiments were repeated three times and the results were expressed as means ± SD. The data from *in vivo* taste masking study were presented as means ± standard error of mean (SEM). Statistical analysis was done by One-way analysis of variance (ANOVA) and Bonferroni Multiple Comparison Test of SPSS.17, after verifying the normality of distribution by a Kolmogorov-Smirnov test. Differences were considered statistically significant at $p<0.05$.

RESULTS

Nine models of drug-polymer complexes **(Table 2)** were developed in order to determine the influence

Table 2. Models of drug-polymer complexes (DPC) prepared by the precipitation method

Model	Drug-polymer ratio	Drug, mg	Polymer, mg
DPC1	2.5:1	5	2
DPC2	2:1	4	2
DPC3	1.5:1	3	2
DPC4	1:1	2	2
DPC5	1:1.5	2	3
DPC6	1:2	2	4
DPC7	1:2.5	2	5
DPC8	1:3	2	6
DPC9	1:4	2	8

Table 3. Yield (%), drug loading (%), encapsulation efficiency (%), moisture content (%), medium particle size d50, μm of the obtained drug-polymer complexes

Model	Yield, %	Drug loading, %	Ee, %	Moisture content, %	Medium size d_{50}, μm
DPC1	23.6	4.8±0.4	1.6	4.3	410.9
DPC2	24.7	4.5±0.1	1.7	4.7	266.9
DPC3	37.6	4.2±0.1	2.6	6.9	297.7
DPC4	42.2	4.2±0.2	3.5	5.3	284.3
DPC5	56.4	3.9±0.5	5.5	8.1	315.9
DPC6	66.4	3.6±0.1	7.2	7.1	379.3
DPC7	71.6	3.4±0.2	8.6	4.7	331.2
DPC8	63.6	3.6±0.1	9.0	7.4	333.6
DPC9	78.2	2.3±0.0	9.0	6.3	328.6

of drug-polymer ratio on the physicochemical and biopharmaceutical characteristics of the resulting particles.

The influence of drug-polymer ratio on the yield, drug loading and encapsulation efficiency is presented in **Table 3.**

The yields of the microparticles followed a clear upward trend from DPC1 to DPC9. While in DPC 1 the yield was only 23.6%, it gradually increased to 78.2% in DPC9. The encapsulation efficiency was the lowest in DPC 1 (only 1.6%) and the highest in DPC 8 and DPC 9. DPC 7 also had relatively high encapsulation efficiency (8.6%). The drug loading was not high in the models and ranged from 2.3% in DPC 9 to 4.8% in DPC 1. There was a clear tendency for decreasing the incorporated drug by reducing the amount of drug used during preparation.

The shape of the resulting microparticles was irregular, with pointed tips and edges **(Fig. 1)**.

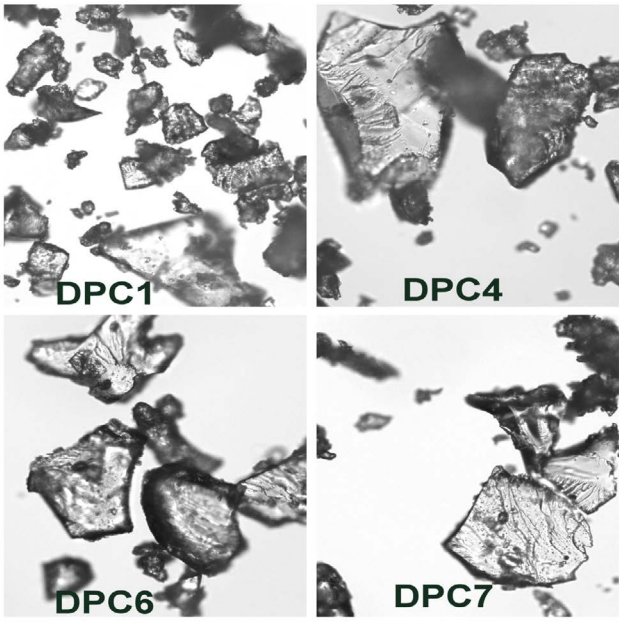

Figure 1. Optical microscopy images of DPC1, DPC4, DPC6 and DPC7.

The average particle size ranged from 266.9 μm (DPC2) to 410.9 μm (DPC1) and provided good bulk characteristics **(Table 3)**. The particle size distribution was monomodal, without presence of aggregates and very fine fractions, which suggested easy further handling of the material **(Fig. 2)**.

The residual moisture after obtaining the particles was not high, ranging from 4.3% up to 8.1%, with lower values in the models with smaller polymer amounts.

FTIR analysis showed changes in the drug and polymer spectra in the obtained models, which was possibly due to an ionic interaction between the polymer and the drug **(Fig. 3)**. The spectra of ENA have a band of C=O (the carboxylic group) which appears at 1750 cm^{-1}. The same band was observed in the physical mixture but was absent in the complexes, which was probably because of a reaction between the acidic groups of enalapril maleate and Eudragit EPO®. This has already been detected by Ramirez-Rigo et al, 2014.[9] The band that belongs to the keto group of Eudragit EPO ®, at 1726 cm^{-1} disappeared. The band at 3210 cm^{-1} which appeared in ENA and in physical mixtures completely disappeared in the complexes. Also, the band at 1646 cm^{-1} that belongs to Enalapril maleate carboxyl stretch was reduced in the complexes and indicated interaction of this group with Eudragit EPO®.

According to the powder X-ray diffraction, enalapril maleate had crystalline structure as evidenced by characteristic peaks at 5°, 7°, 10°, 13°, 15°, 20°, 25°, and 32° (data not present). The polymer spectrum revealed its amorphous nature. The models diffraction patterns display their amorphous state. Characteristic drug peaks of the crystalline disappeared and an amorphous phase is observed **(Fig. 4)**.

The results of DSC showed that the melting temperature of the drug was 165°C, followed by complete decomposition of the substance. The glass transition temperature of the polymer was around 295°C. The decomposition was a two-stage process, the first effect being in the range of 250-350°C (weight loss was also observed). The thermal behavior of the models resembled that of the polymer. The characteristic peak corresponding to the melting temperature of enalapril maleate at 165°C was not observed in the model complexes. The first melting effect was observed between 250-350°C **(Fig. 5)**. It could be suggested that the polymer had stabilizing effect on the drug in the complexation.

Drug release study in artificial saliva showed 12.5% released amount for DPC7 and 30.5% for DPC9 **(Fig. 6)**. The parameter that defined the rats' preference to the investigated samples was the licking frequency of the model solutions **(Table 1)** as compared to distilled water and ENA solution.[8] The higher the licking frequency, the better the taste of the model. The control group showed

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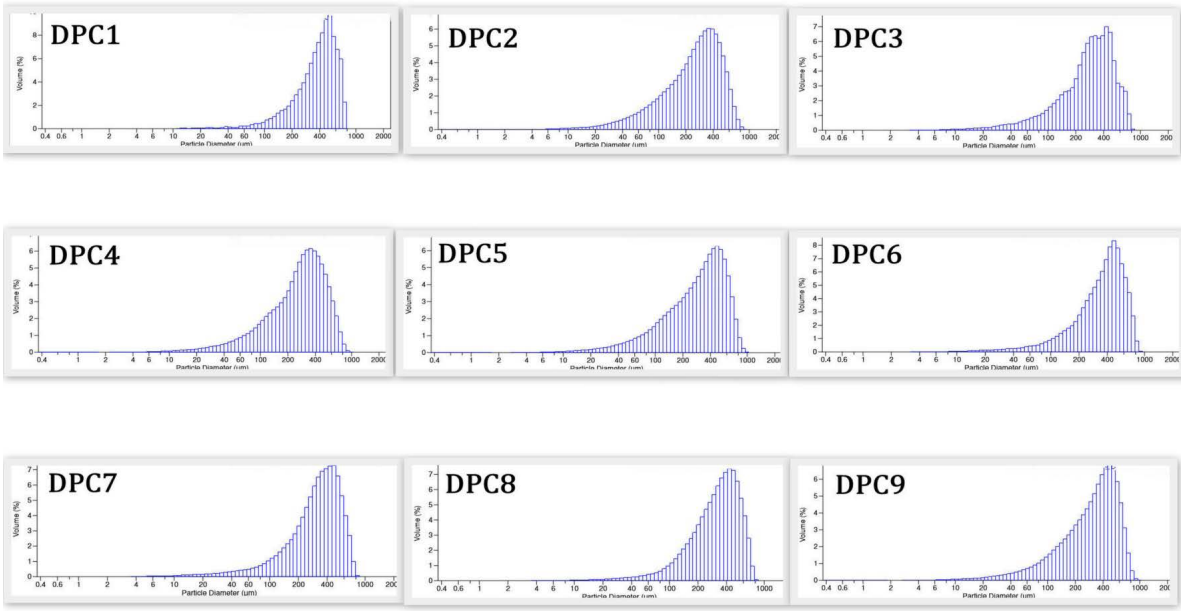

Figure 2. Particle size distribution curves of the drug-polymer complexes.

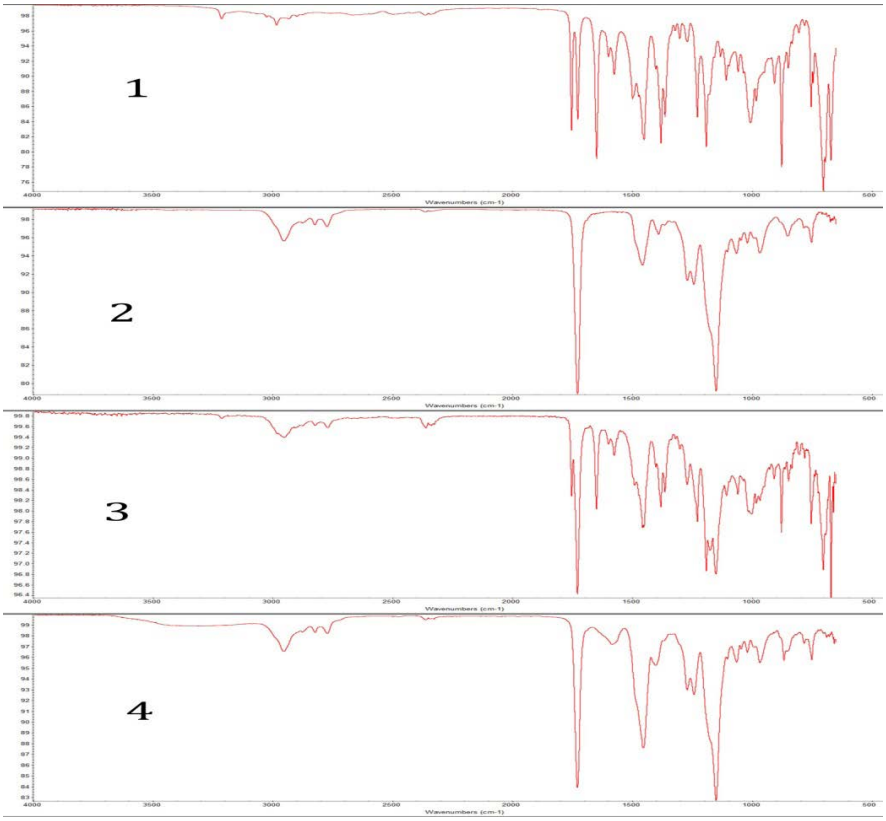

Figure 3. ATR-FTIR spectra; 1-enalapril maleate, 2-eudragit EPO®, 3-physical mixture, 4-model DPC1.

licking frequency of 99.3% **(Fig. 7)**. We estimated a significant decrease in the number of licks for ENA solution (50.1%±11.1 vs. 99.3%±8.4, $p < 0.001$) and DPC6 (60.9% suit the formulation for pediatric administration 2 vs. 99.3%±8.4, $p < 0.01$) compared to the controls. As shown in **Fig. 7**, the formulation DPC7 significantly increased the licking frequency (87.6%±2.7 vs. 50.1%±11.1, $p < 0.01$)

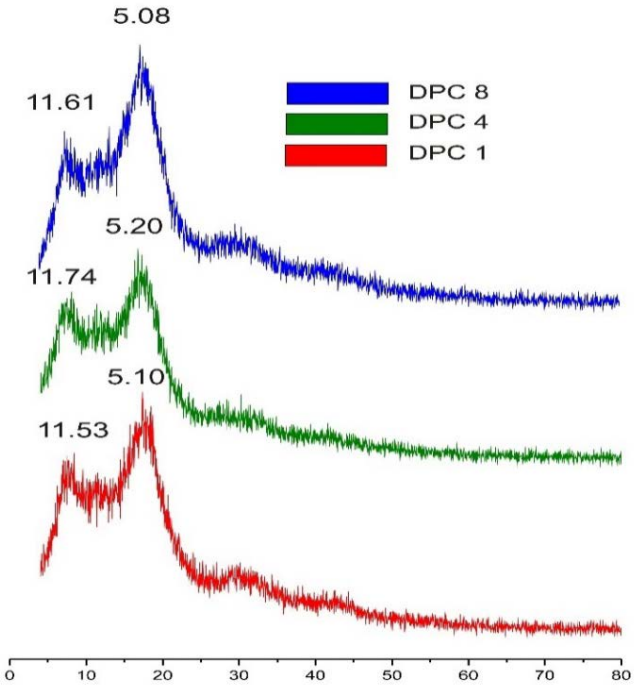

Figure 4. X-ray diffraction patterns of models DPC1, DPC4 and DPC8.

DISCUSSION

Nine models of drug-polymer complexes were obtained by precipitation method and were characterized in terms of yield, drug loading, encapsulation efficiency, moisture content **(Table 3)** and particle size distribution **(Fig. 2)**. There was a clear tendency towards increased production yields when higher amounts of polymer were used. The highest yield was registered in DPC 9, which could be explained by the largest amount of polymer used in this model. The lower yield of the first models was probably due to the higher amount of drug and the less amount of the polymer used. At higher polymer amounts increased production yields were achieved. When the drug prevailed, the yield was below 40%, so in this method it is advisable to use a larger amount of polymer. By decreasing the amount of enalapril maleate in the models the drug loading in the complexes decreased too, but the encapsulation efficiency increased. The encapsulation efficiency was the greatest in models DPC 7, 8 and 9 with small differences. These models showed satisfactory yield and drug content. For all

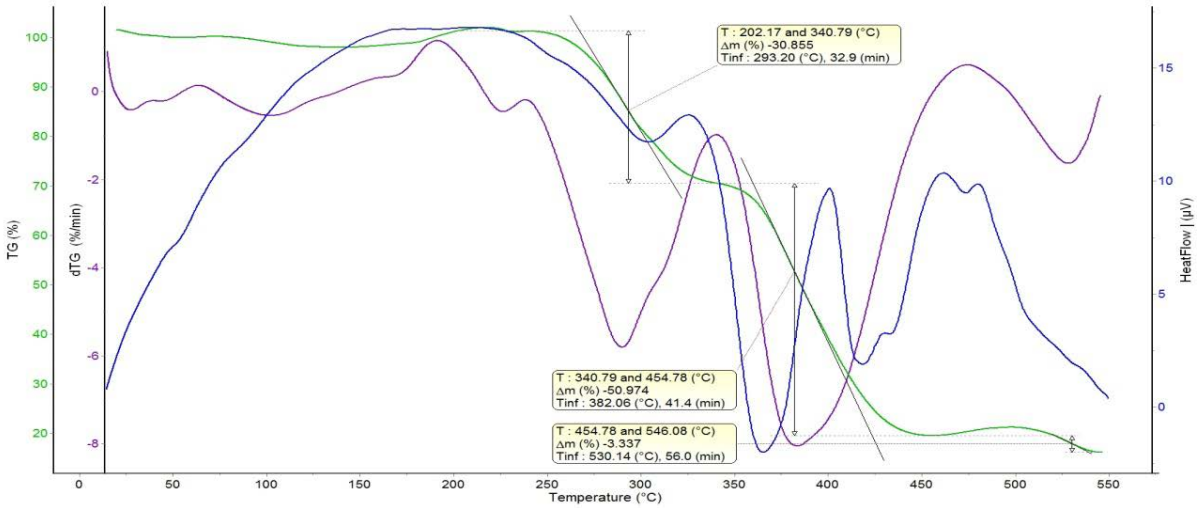

Figure 5. DTA and TGA thermograms of DPC1.

when compared to the enalapril maleate group. Similar results were observed for taste-masked formulations DPC6 (60.9%±2 vs. 50.1%±11.1) and DPC9 (75%±3.6 v/s 50.1%±11.1), but no statistical significance was registered compared to the enalapril maleate group.

the models, one of the steps in the complexation process was drying at room temperature to remove the moisture involved. Therefore, the moisture content was very low, between 4% and 8%, which did not allow particle bonding and formation of larger aggregates. It could be suggested that the higher humidity is due to the larger amount of polymer **(Table 3)**. Moisture content did not cause particle

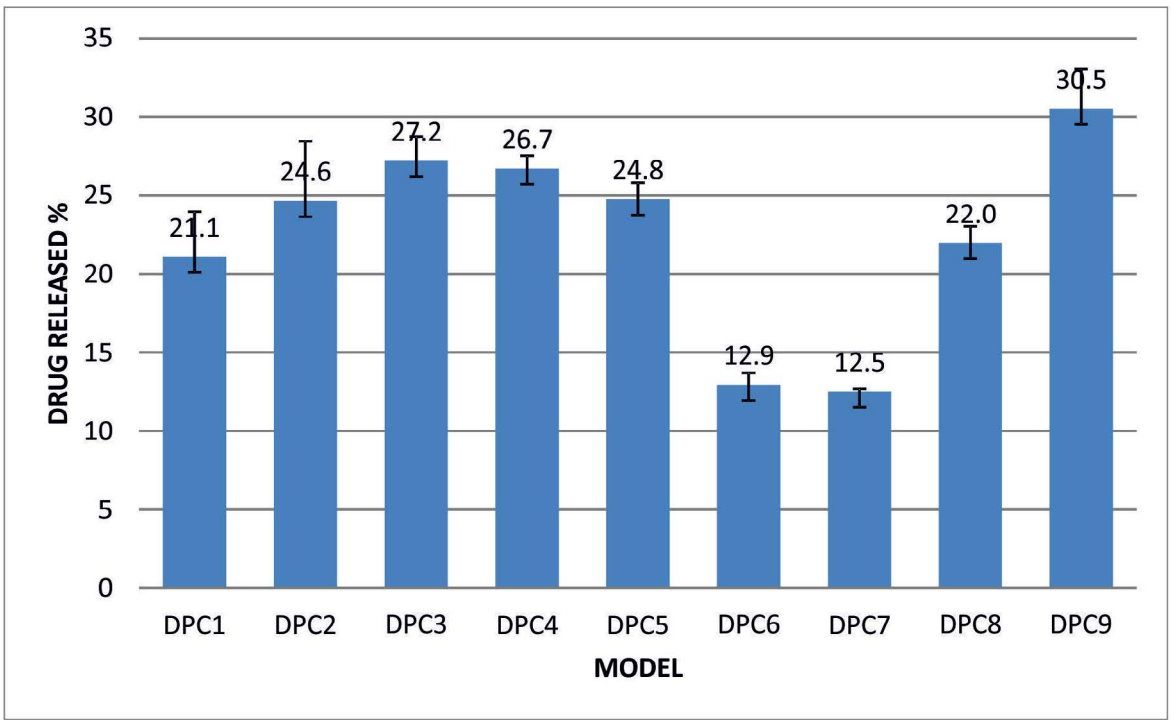

Figure 6. In vitro drug release of ENA from experimental models in simulated salivary fluid pH 6.8.

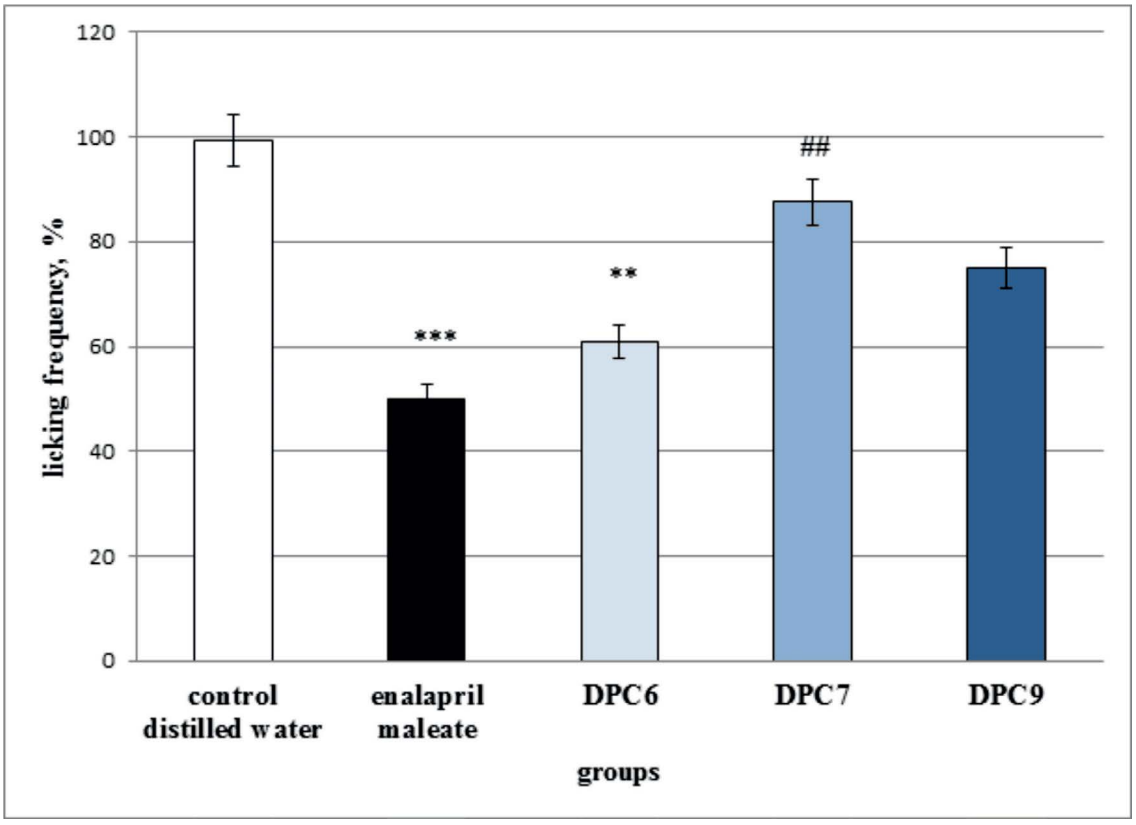

Figure 7. Licking frequency by rats. ***p < 0.001 vs control; **p < 0.01 vs control; ##p < 0.01 vs enalapril maleate (One-way analysis of variance ANOVA); n=8

aggregation, as evidenced by the monomodal particle size distribution. The medium particle size varied within narrow ranges and the particle size was until 410 μm, achieved only by trituration in a mortar with a pestle. The distribution of the particle size was bell-shaped, resembling the ideal case **(Fig. 2)**.

The shape of the particles was irregular, which is common for structures obtained via the precipitation technique and the method of comminution - by trituration in a mortar with a pestle **(Fig. 1)**. Moreover, the drug molecules distribution throughout the polymer matrix was probably nonuniform. Since the mechanism of complexation is not fully elucidated, we supposed that certain amounts of ENA were probably incorporated inside the particle structure whereas others were located on the surface. Our suggestions were supported by the drug release study data. The high values of released ENA in some of the models suggests high dissolution rates from the particles' surface. The results from drug loading study suggest that the polymer has limited capacity for complexation of drug molecules. When higher amounts of ENA were used, higher dissolution rate was registered. That confirmed the thesis that the polymer incorporated a limited amount of drug molecules inside the matrix while the excess drug was deposited on the surface. The results from this investigation outlined DPC6 and DPC7 as optimal models, with drug-polymer ratios respectively 1:2 and 1:2.5. Drug release was the most important indicator that outlined the most optimal model. Taste-masked models were considered those with minimum or no drug release in simulated salivary fluid. The released drug from these models in artificial saliva was about 12% **(Fig. 6)**. In terms of FTIR spectroscopy **(Fig. 3)**, there was a clear indication for interaction between enalapril maleate and the polymer. The spectrum of the selected model resembled that of the polymer, and the characteristic peaks of enalapril maleate disappeared, which evidenced a full interaction between the drug and the polymer. That was also evidenced by the thermogravimetric analysis.

The data from *in vivo* and *in vitro* taste evaluation demonstrated that successful taste-masking was accomplished with model DPC7 which was prepared at a drug-polymer ratio of 1:2.5 and demonstrated 12.5% drug release in artificial saliva, 8.6% encapsulation efficiency and 3.4% drug loading. The production yield was 71.6% with a low moisture content of 4.7% and an average particle size of 331.2 μm. The rats' licking frequency was the highest, which signified high acceptance rate to this model. Therefore, this model is suitable for further investigations as a constituent of solid dosage forms.

CONCLUSION

In the present study, the precipitation technique was applied for the preparation of structures with masked bitter taste of enalapril maleate. After the characterization of all the models, DPC7 was selected due to its reliable results in terms of yield, drug loading, encapsulation efficiency, *in vitro* and *in vivo* taste evaluation. It could be concluded that the precipitation method is a suitable method for masking the bitter taste of enalapril maleate and affirms its potential for incorporation into solid dosage forms.

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Коррекция вкуса эналаприла малеата методом осаждения

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Введение: Коррекция вкуса горьких или неприятных лекарств является важной предпосылкой для улучшения соблюдения пациентом предписанной терапии, особенно у детей и пожилых пациентов. Мы стремились получить корректирующие вкус микрочастицы, предназначенные для соединения с диспергируемыми во рту таблетками. В качестве модели лекарственного средства с горьким вкусом мы выбрали метод осаждения эналаприла малеата (ЭНА) и Eudragit EPO® - в качестве pH-чувствительного полимера.

Цель: Целью настоящего исследования было получение микрочастиц эналаприла малеата методом осаждения для коррекции вкуса горького лекарственного средства.

Материалы и методы: Девять моделей микрочастиц эналаприла малеата - Eudragit EPO® были получены методом осаждения в различных пропорциях лекарственного средства и полимера. Модели были описаны с точки зрения размера, формы, объёма производства, содержания лекарственного средства, эффективности инкапсуляции и содержания влаги. Для анализа возможных взаимодействий в комплексе были использованы инфракрасная спектроскопия с Фурье-преобразованием, порошковая рентгеновская дифракция, дифференциальная сканирующая калориметрия. Введение препарата in vitro в искусственную слюнную жидкость и оценку вкуса in vivo у крыс проводили для доказательства коррекции вкуса.

Результаты: : Гранулометрия варьировалась от 266,9 μm до 410,9 μm. Форма полученных частиц была неправильной. Объемы производства варьировались от 23,6% до 78,2%. Содержание препарата составляло от 2,3% до 4,8%, эффективность инкапсуляции увеличилась с 1,6% до 9,0%. Данные по введению препарата in vitro свидетельствуют о значительной коррекции вкуса.

Заключение: Некоторые из полученных методом осаждения микрочастиц показали значительную эффективность коррекции вкуса, что доказало применимость коррекции вкуса этим методом.