

# Taste Masking and Characterization of Chlorpheniramine Maleate by Using Enteric Polymers Carrier System

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## ABSTRACT

Chlorpheniramine maleate is a widely used antihistaminic drug but it is very bitter and as yet no mouth dissolving/disintegrating taste-masked preparation that might be useful in pediatric and geriatric patients is available in the market. The aim of this study was to prepare a microsphere formulation in order to mask the bitter taste of chlorpheniramine. Microspheres of chlorpheniramine with pH-dependent polymers (such as Eudragits S100, L100 and L100-55) were prepared by the double emulsion solvent diffusion method. The effect of different polymers and drug-polymer ratios on the taste masking and the characteristics of the microspheres were investigated. At first, the drug dissolved in water and polymer dissolved in an organic solvent that was composed of ethanol (good solvent) and dichloromethane (bridging liquid) with 2:1 ratio. Silica is a good anti-adhesion agent against the viscous characteristic of polymers and disperses into dichloromethane. In the current study formulations with different drug/polymer ratio were prepared and were characterized by drug loading, loading efficiency, yield, particle size, x-ray diffraction (XRD), Fourier transform spectroscopy (FTIR) and differential scanning calorimetry (DSC). The *in vitro* release studies were performed in pH 1.2 and 7.4. The best polymer to drug ratio in microparticles Eudragit L100 and L100-55 were F<sub>3</sub> and F<sub>3</sub>" (7:1) which showed 9.67% and 7.88% of entrapment, loading efficiency 77.34% and 63.08% and mean particle size of 12.484 μm and 10.675 μm, respectively. The drug loading microparticle Eudragit S100 (5:1) showed 9.65% of entrapment, loading efficiency 57.92% and mean particle size of 6.807 μm. The FTIR, XRD and DSC showed the stable character of chlorpheniramine in the drug-loaded microspheres and revealed an amorphous form. The results showed that microparticles prepared with pH-dependent polymers were slower release than the commercial tablet ( $p < 0.05$ ). The results demonstrated that Eudragit S100 was the best for masking the unpleasant taste of chlorpheniramine among the three polymers investigated. The results indicated that the microsphere formulation could be a promising drug carrier for masking the bitter taste of chlorpheniramine.

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## Introduction

The most effective method to achieve maximum taste masking effectiveness is to coat the drug particles, thereby creating a physical barrier around the drug, using microencapsulation techniques such as spray-drying, spray congealing, coacervation and solvent diffusion method <sup>[1]</sup>. Microencapsulation techniques have become more and more popular in the last few decades because they offer significant advantages as far as taste masking is concerned. Furthermore, the materials used to coat the drug particles create a physical barrier and thereby enhance the stability of the particles <sup>[2]</sup>. In order to ensure patient compliance, bitterness masking becomes essential <sup>[3]</sup>. Chlorpheniramine maleate is selected as a suitable candidate for taste masking due to its bitter taste. Taste masking can be done by using flavors, sweeteners and amino acids, also by using various techniques such as lipophilic vehicles, coating, inclusion complexation, ion exchange, effervescent agents, rheological modifications, solid dispersion systems, group alteration and prodrug approach, freeze drying process, wet spherical agglomeration technique and continuous multipurpose melt technology <sup>[3]</sup>. Microencapsulation has a utilitarian value of taste masking, where small drug particles can be coated with polymer. These small, coated particles can be readily formulated into the aforementioned dosage forms. When the dosage form is placed in the mouth as liquid or masticated with the polymer, the coated drug cannot contact the taste buds in the mouth and hence the objectionable taste of bitter drug is eliminated <sup>[4]</sup>.

A novel technique for taste masking of drugs employing multiple emulsions has been prepared by dissolving drug in the inner aqueous phase of water in oil in water (W/O/W) emulsion under conditions of good shelf stability. The formulation is designed to release the drug through the oil phase in the presence of gastrointestinal fluid <sup>[5,6]</sup>.

Multiple emulsions are polydispersed systems where both water in oil and oil in water emulsion exists simultaneously in a single system. Multiple emulsions can be  $W_1/O/W_2$  or  $O_1/W/O_2$  depending on the dispersed phases in dispersion media. In a multiple emulsion system solute has to transverse through the middle immiscible organic phase (liquid membrane) in order to come from inner miscible phase to outer miscible phase, therefore it is also referred to as a liquid membrane system <sup>[7,8]</sup>.

They can be used for the entrapment of both hydrophilic and hydrophobic drugs, protection of the entrapped compound, drug targeting, taste masking and for slow or controlled delivery of drugs.

This method is easy, reproducible and gives a high percentage yield. In this method, an ordinary w/o primary emulsion is first prepared which is then re-emulsified in an excess amount of aqueous phase or oil phase to produce a W/O/W type emulsion <sup>[7,8]</sup>.

Chlorpheniramine is a first-generation alkyl amine antihistamine used in the prevention of the symptoms of allergic conditions such as rhinitis and urticaria. Its sedative effects are relatively weak compared to other first-generation antihistamines. Although not generally approved as an antidepressant or anti-anxiety medication, chlorpheniramine appears to have these properties as well <sup>[9]</sup>.

Multiple emulsions of chlorpheniramine, an antihistamine agent, has been prepared by a novel technique called the emulsion solvent diffusion method, which was proposed by Kwashima et al. <sup>[2]</sup>. It is a process in which spherical agglomeration occurs simultaneously during drug crystallization <sup>[10]</sup>. Taste masking can be achieved by incorporating drugs into the inner aqueous phase of W/O/W multiple emulsions, which is surrounded by an oil layer masking the taste. Taste masking of chloroquine and chlorpromazine, an antipsychotic drug, has also been reported by multiple emulsions <sup>[11,12]</sup>. Spherical crystallization technique has been successfully utilized for improvement of masking of the bitter taste. It also enables co-precipitation of drug and the encapsulating polymer in the form of a spherical particle. This technique involves selective formation of agglomerates of crystals held together by liquid bridges <sup>[13]</sup>.

The enteric acrylic acid copolymers including Eudragit S100, Eudragit L100 and Eudragit L100-55 are in widespread use today.

The objective of the work is to develop an efficient method to mask the taste by preparing microparticles of chlorpheniramine maleate by the double-emulsion solvent diffusion technique.

## Materials

Eudragit S100, L100 and L100-55 (Rohm Pharma GMBH, Weiterstadt, Germany), chlorpheniramine (Pingguang Pharmaceutical/China) and poly(vinyl alcohol) (PVA) (Mw 95000-110000 Da) was supplied by Aldrich. Silica, ethanol, dichloromethane, hydrochloric acid, potassium hydrogen phosphate and sodium hydroxide were obtained from Merck (Darmstadt, Germany). All solvents and reagents were of analytical grade.

## Methods

### *Preparation of microspheres*

All microspheres were obtained by the emulsion solvent diffusion method using distilled water as an external phase, in which 1% of PVA was dissolved as an emulsifier. The internal phase consisted of a good solvent and a bridging liquid involving chlorpheniramine maleate, polymer (Eudragit S100, Eudragit L100 and Eudragit L100-55) and silica. In the first step, an organic solution of the polymer (Eudragit S100, Eudragit L100 and Eudragit L100-55) in ethanol (5 ml) was prepared as the external phase of primary emulsion by a magnetic stirrer (45°C). Silica (50 mg) dispersed into the 10 ml dichloromethane (liquid bridge) and was injected into the organic solution (containing the polymer) in a mechanical stirrer. In the second step, aqueous solution (1 ml) of drug (40 mg) used as the internal aqueous phase was emulsified into an organic phase. Two min later, the primary emulsion was poured into 100 ml of 1% PVA aqueous solution in order to obtain a W<sub>1</sub>/O/W<sub>2</sub> double-emulsion (room temperature). After magnetically agitating continuously for 1 hour (400-600 rpm) at room temperature, it was stirred mechanically (600 rpm used for Eudragit S100 and 400 rpm for Eudragit L100 and Eudragit L100-55) and microspheres were allowed to harden. Along with the good solvent diffusing into the poor solvent, the droplets gradually solidified and formed microspheres. Then, the system was filtered to separate the microspheres from the preparation system. The resultant product was washed with distilled water and dried in an oven at 40 °C for 12 h. The whole process was carried out at room temperature.

### *Determination of drug loading and entrapment efficiency*

The drug concentration in polymeric particles was determined spectrophotometrically (UV-160,

Shimadzu, Japan) at 261.4 nm by measuring the amount of non-entrapped chlorpheniramine in the external aqueous solution (indirect method). In the case of microparticles, the external aqueous solution was obtained after centrifugation of the aqueous suspension for 20 min at 8000 rpm. A standard calibration curve was performed with the chlorpheniramine solution (aqueous solution of 1% PVA). Chlorpheniramine entrapment efficiency was expressed as the ratio of the chlorpheniramine amount measured in the supernatant to the total chlorpheniramine amount added <sup>[14]</sup>. Each measurement was repeated three times.

The production yield of the microparticles was determined by calculating accurately the initial weight of the raw materials and the final weight of the polymeric particles obtained. All the experiments were performed in triplicate.

### *Particle size analysis*

The microsphere size analysis was performed by laser light scattering particle size analyzer (SALD-2101, Shimadzu, Japan). Samples were suspended in distilled water contained in a 1 cm cuvette and stirred continuously during the particle size analysis. The particle size distribution of the microspheres for all formulations was determined and the results were the mean of three determinations.

### *X-ray powder diffractometry (X-RPD)*

X-ray diffraction analysis was performed with an apparatus (Siemens D5000, Munich, Germany), using nickel-filtered CuK $\alpha$  radiation (a voltage of 40 KV and a current of 20 mA). The scanning rate was 2°/min over a range of 20-60° and with an interval of 0.02°. Each measurement was repeated three times.

### *Assessment of the bitter taste of the microspheres*

#### *Standard solution for evaluation of the bitter taste threshold of chlorpheniramine maleate*

The bitter taste threshold value of chlorpheniramine maleate was determined based on the bitter taste recognized by six volunteers (three females and three males). A series of chlorpheniramine maleate aqueous solutions were prepared at different concentrations as standard solutions, i.e. 50, 100, 150, 250, 350 and 450  $\mu$ g/ml, respectively. The test was performed as follows: 1ml of each standard

solution was placed on the center of the tongue, it was retained in the mouth for 1 minute, and then the mouth was thoroughly rinsed with distilled water. The threshold value was correspondingly selected from the different chlorpheniramine maleate concentrations as the lowest concentration that had a bitter taste.

#### **Estimation of the bitter taste of microspheres in vitro**

Microspheres of chlorpheniramine maleate (10 mg) were put into 10 ml distilled water. The mixture was immediately vibrated for 30 s and then filtered. Then the solution was analyzed in a spectrophotometer (UV-160, Shimadzu, Japan) at 227.8 nm to determine the dissolved drug concentration in water, which was then compared with the threshold value [2].

#### **Differential scanning calorimetry (DSC)**

Samples of the microparticle (about 5 mg) were heated (5-300 °C) at a scanning rate of 10 °C/min in crimped sealed aluminum pans under a nitrogen atmosphere. The enthalpy of fusion and melting point was obtained from the thermograms using the instrumental software (DSC 60, Shimadzu, Japan).

#### **Fourier transforms infrared spectroscopy (FT-IR)**

A computerized FT-IR (Bomen, Quebec, Canada) was used to obtain the spectra of various chlorpheniramine maleate samples. The microparticle sample (about 10 mg) in potassium bromide discs (0.5% w/w) was placed on the plate of the machine and the handle was placed on the powder sample to generate enough pressure for compression. The spectrum for each sample showed the wavelength of absorbed light, which is a characteristic of the chemical bonds in the sample. The scanning range was 400-4000 cm<sup>-1</sup> and the resolution was 1 cm<sup>-1</sup>.

#### **In vitro release studies**

The *in vitro* release studies of drug-loaded microspheres were carried out at 37 °C in acidic conditions (pH 1.2) for 2 h followed by 6 h dissolution in phosphate buffer 0.2 M (pH 7.4). Each batch of microspheres containing 200 mg of drug was individually added to 900 mL of dissolution medium in flask. The dissolution media was stirred at 100 rpm according to USP basket method. Three mL of samples were withdrawn at

regular time intervals and the same volume of fresh medium was replaced. After suitable dilution, the drug content of each sample at pH 1.2 and 7.4 was estimated by using a UV spectrophotometer analysis at 295.4 and 276.4 nm, respectively. Each experiment was repeated three times.

In order to have a better comparison between different formulations dissolution efficiency (DE), t<sub>50%</sub> (dissolution time for 50% fraction of drug); and difference factor, f<sub>1</sub> (used to compare multipoint dissolution profiles) were calculated and the results are listed in Table 3 [15]. DE is defined as the area under the dissolution curve up to a certain time, *t*, expressed as a percentage of the area of the rectangle arising from 100% dissolution in the same time. The areas under the curve (AUC) were calculated for each dissolution profile by the trapezoidal rule. DE can be calculated by the following:

$$DE = \int y \frac{dt}{100 t}$$

Where *y* is the drug percent dissolved at time *t*. All dissolution efficiencies were obtained with *t* equal to 1440 min. The *in vitro* release profiles of different microparticle formulations were compared with physical mixture formulation using difference factor (f<sub>1</sub>), as defined by [15]:

$$f_1 = \left\{ \frac{[\sum_{i=1}^n |R_i - T_i|]}{[\sum_{i=1}^n R_i]} \right\} \times 100$$

Where *n* is the number of time points at which % dissolved was determined, *R<sub>i</sub>* is the % dissolved of one formulation at a given time point and *T<sub>i</sub>* is the % dissolved of the formulation to be compared at the same time point. The difference factor fits the result between 0 and 15 when the test and reference profiles are identical, and approaches above 15 as the dissimilarity increases.

Data obtained from *in vitro* release studies were fitted to various kinetic equations to find out the mechanism of drug release from the Eudragits as S100, L100 and L100-55 microparticles. The kinetic models used were:

$$Q_t = k_0 t \text{ (zero-order equation)}$$

$$\ln Q_t = \ln Q_0 - k_1 \cdot t \text{ (first-order equation)}$$

$$Q_t = K \cdot S \cdot t^{0.5} = k_H \cdot t^{0.5} \text{ (Higuchi equation based on Fickian diffusion)}$$

Where, *Q* is the amount of drug release in time *t*, *Q<sub>0</sub>* is the initial amount of drug in the microparticles, *S*

is the surface area of the microparticles and  $k_0$ ,  $k_1$  and  $k_H$  are rate constant of zero order, first order and Higuchi equation, respectively. In addition to these basic release models, the release data was fitted to the Peppas and Korsmeyer equation (power law):

$$M_t/M_\infty = k.t^n$$

Where  $M_t$  is the amount of drug release at time  $t$  and  $M_\infty$  is the amount release at time  $t = \infty$ , thus  $M_t/M_\infty$  is the fraction of drug released at time  $t$ ,  $k$  is the kinetic constant, and  $n$  is the diffusion exponent which can be used to characterize the mechanism of drug release<sup>[16]</sup>.

## Results and Discussion

### Microsphere characterization

Microspheres were formed after a series of steps such as diffusion solvent and addition of liquid bridge and anti-adhesion agent. Each step of microsphere preparation was keenly observed to understand the effect of polymer-to-drug ratio on the particle size, total entrapment and release profiles of the drug-loaded microspheres. The polymer-to-drug ratio was varied by maintaining the amounts of drug, solvent, liquid bridge, and anti-adhesion agent constant in all preparations, while changing the amount of polymer (Table 1).

**Table1.** Chlorpheniramine maleate microparticle formulations prepared by double-emulsion solvent diffusion method (w<sub>1</sub>/o/w<sub>2</sub>)

Formulations	Polymer : Drug ratio	Initial emulsion (W/O <sub>1</sub> )					Secondary phase oil (O <sub>2</sub> )		
		Aqueous phase		Initial organic phase (O <sub>1</sub> )			Silica (mg)	Water (ml)	PVA (%W/V)
		Chlorpheniramine (mg)	Water (ml)	*Polymer (mg)	Ethanol (ml)	Dichloromethane (ml)			
F <sub>1</sub>	3:1	40	1	120	10	5	50	100	1
F <sub>2</sub>	5:1	40	1	200	10	5	50	100	1
F <sub>3</sub>	7:1	40	1	280	10	5	50	100	1

\*Eudragit S100, Eudragit L100 and Eudragit L100-55.

The results of the effect of the polymer-to-drug ratio on production yield, drug loading efficiency and mean particle size are shown in Table 1. Ethanol (good solvent) is an organic solvent which is polar, water miscible and oil immiscible. Dichloromethane is a liquid bridge and silica dispersed in the dichloromethane was used for the preparation of microparticles. Silica has a tremendous surface area, high porosity and unique adsorption properties<sup>[2]</sup>. It is an inorganic material which is insoluble in any organic solvents. During the preparation process of microspheres, silica commixed with the polymer uniformly. The viscosity of the droplets was so reduced, which could prevent conglutination occurring between emulsified droplets. It is good anti-adhesion agent against the viscous characteristic of polymers. What is more, it was considered to be helpful to promote the dispersibility of the drug in the

microspheres. Therefore, it would accelerate the drug release rate.

Important prerequisites for high encapsulation efficiencies by the W/O/W method are: (1) the insolubility of the drug in the external phase from the internal aqueous phase, and (2) the fine dispersion of the aqueous drug solution into the organic polymer solution to form a W/O emulsion<sup>[17]</sup>. Ethanol was used as a good solvent, which can dissolve drug and polymer, and can mix with bridging liquid. In the preparation process of the microspheres, diffusion of the good solvent increased co-precipitation of the drug and the polymer in the droplets, and the residual dichloromethane linked the sediments together to form microspheres. A suitable ratio of dichloromethane to ethanol (1:2 ratio) would affect the preparation process, and the microspheres would not be produced successfully (Table 1). In all of the microspheres prepared by Eudragits, the

amount of drug entrapped in microspheres was lower than the theoretical value. This indicates that some free drug crystals were lost in the process of encapsulation. As the ratio of polymer to drug increases (3:1 to 7:1 ratio) the amount of free drug lost decreases (Table 2), so that at the ratio of polymer to drug of 5:1 (F<sub>2</sub>, Eudragit S100 series) the amount of drug entrapment was 9.65%, which was close to the theoretical value (16.66%). The table also shows the lowest of polymer amount was in F<sub>1</sub>, (ratio of polymer to drug 3:1), however this formulation did not show the highest drug entrapment (19.33%). Increasing the amount of

polymer in the organic phase can increase the viscosity of the external phase of the primary emulsion and this in turn possibly induced highly sticky droplets in the early stages of the preparation process due to the semi-solid polymer, and resulted in the droplets gathering together and hence drug losses to the external phase [2]. This is the main reason for the high drug entrapment and loading efficiency observed for high polymer to drug ratio of all formulations (7:1 ratios). Generally, increasing the polymer amount increased the production yield (Table 2).

**Table 2.** Effect of drug:polymer ratio on the content, production yield and particle size of chlorpheniramine Eudragit microparticles

Formulations	Type of Eudragit	Polymer: Drug ratio	Production Yield (%±SD)	Theoretical drug content (%)	Mean amount of drug Entrapped (%±SD)	Loading efficiency (%±SD)	Mean particle Size (µm±SD)
F <sub>1</sub>	S100	3:1	25.95±2.21	25	4.8±0.56	19.33±1.89	10.80±0.49
F <sub>2</sub>	S100	5:1	24.48±2.15	16.66	9.65±1.13	57.92±4.56	6.81±0.48
F <sub>3</sub>	S100	7:1	26.1±3.22	12.5	4.54±0.62	36.29±2.41	11.20±0.55
F'1	L100	3:1	27.14±3.09	25	10.06±1.47	40.25±4.72	14.52±0.42
F'2	L100	5:1	33.1±4.15	16.66	11.74±1.08	70.45±7.36	9.92±0.45
F'3	L100	7:1	56.48±6.13	12.5	9.67±0.75	77.34±8.31	12.48±0.46
F''1	L100-55	3:1	16.66±1.82	25	4.02±0.91	16.08±2.71	10.12±0.51
F''2	L100-55	5:1	22.41±3.05	16.66	7.4±0.78	44.4±6.73	11.97±0.53
F''3	L100-55	7:1	41.21±5.14	12.5	7.88±0.82	63.08±7.19	10.68±0.51

For instance, as the ratio of polymer to drug was increased from 3:1 to 7:1, the production yield was significantly increased ( $p < 0.05$ ) from 16.66 to 56.48%. The reason for this increase in high polymer: drug ratio could be due to a reduction in the diffusion rate of solvent from concentrated solutions (organic phase) into the external phase of primary emulsion. The particle analysis of microspheres prepared by three Eudragits is shown in Table 2. The table shows that an increase in polymer to drug ratio from 3:1 to 7:1 did not result in a significant effect on the mean particle size of microspheres. The analysis of data showed that all obtained microcapsules followed an arithmetic-probability distribution. The microsphere size depended on the rate of polymer solidification. Since the polymer deposition within the droplets

occurs through the removal of the polymer solvent (ethanol), the partitioning rate of ethanol and dichloromethane from primary emulsion to external phase could be the main factor controlling the deposition rate of the polymer.

In contrast to other studies, as the ratio of drug to polymer increases, the size of microsphere slightly decreases (Eudragit L100 formulation) ( $p > 0.05$ ). This could be due to poor solubility of chlorpheniramine in ethanol and dichloromethane, which is not able to increase the viscosity of the internal phase significantly. Also, these formulations showed high drug entrapment and loading efficiency. Therefore the amount of solvent is not enough for dissolution of the drug and polymer together. If chlorpheniramine was soluble

in ethanol, then an increase in the ratio of polymer to drug would increase the viscosity of the external phase. This increase in the viscosity of the external phase (with increasing of polymer amount) does not prevent the rate and extent of ethanol partitioning into the external phase of second emulsion (with high affinity of ethanol to water) which leads to rapid solidification of polymer, hence a decrease in microsphere particle size. As the size of the microsphere almost remained the same, this indicates that the ratio of

polymer to drug had no significant effect on the rate of solidification of polymer (Table 2) in Eudragit microsphere<sup>[18]</sup>. Once the dichloromethane evaporated completely, the partitioning rate of ethanol became similar to that for the three series of Eudragit microspheres. Table 2 also shows that the increasing of polymer increased the production yield ( $p < 0.05$ ). The reason for the increased production yield at high ratio of polymer could be due to increased diffusion rate of solvent from the concentrated solutions into the external phase. In all of the microspheres produced by Eudragits, however, an increase in the amount of polymer improved drug-loading efficiency. The best polymer to drug ratio in microparticles Eudragit L100 and L100-55 were F<sub>3</sub> and F<sub>3</sub> (7:1) which showed 9.67% and 7.88% of

entrapment, loading efficiency 77.34% and 63.08% and mean particle size 12.484  $\mu\text{m}$  and 10.675  $\mu\text{m}$ , respectively.

### The bitter taste studies

Bitter taste masking can be achieved by various techniques, but in the microencapsulation technique particles of the bitter drug are entrapped in the polymers, thereby offering a barrier between the drug and the taste receptors of the tongue. As a result the drug cannot bind with the taste receptor and therefore the taste is not sensed<sup>[19,20]</sup>.

### Determination of bitter threshold recognition threshold of chlorpheniramine

All eight volunteers could not recognize the bitter taste of chlorpheniramine at 50  $\mu\text{g/ml}$ . Five out of eight volunteers could perceive the bitter taste at 100  $\mu\text{g/ml}$ , whereas all eight volunteers reported that the solutions of 100 and 150  $\mu\text{g/ml}$  were bitter. Thus, the threshold bitterness value lies in between 100 and 150  $\mu\text{g/ml}$ . Therefore, the chlorpheniramine solutions of 50, 100, 150, 250, 350 and 450  $\mu\text{g/ml}$  concentrations were prepared, and the same procedure was repeated. From Table 3, the bitter taste threshold value of chlorpheniramine is 100  $\mu\text{g/ml}$ .

**Table3.** Taste recognition threshold determination

No. of Volunteers rating the solution as	Concentration ( $\mu\text{g/ml}$ )					
	50	100	150	250	350	450
1	-	-	+	++	+++	+++++
2	-	+	++	+++	++++	+++++
3	-	+	++	++++	+++++	+++++
4	-	+	++	+++	+++	+++++
5	-	±	++	+++	++++	+++++
6	-	+	++	++++	++++	+++++
7	-	±	+	++	++++	+++++
8	-	+	++	++	++++	+++++

\* - = good, ± = tasteless, + = slightly bitter, ++ = moderate bitter, +++ = bitter, ++++ = very bitter, +++++ = awful.

***In vitro* evaluation of bitter taste of microspheres**

The microspheres were prepared with different polymer to drug ratios. The drug release of

microparticles in water was studied to evaluate taste masking (Table 4).

**Table 4.** Taste masking ability of various polymers

Formulation code	Type of Eudragit	Drug:polymer ratio	Taste	Concentration (µg/ml)
F <sub>1</sub>	S100	1:3	Good	15.6
F <sub>2</sub>	S100	1:5	Good	8.3
F <sub>3</sub>	S100	1:7	Good	11
F' <sub>1</sub>	L100	1:3	Bitter	49.7
F' <sub>2</sub>	L100	1:5	Good	25.7
F' <sub>3</sub>	L100	1:7	Good	22.7
F'' <sub>1</sub>	L100-55	1:3	Bitter	51.5
F'' <sub>2</sub>	L100-55	1:5	Good	13.4
F'' <sub>3</sub>	L100-55	1:7	Good	8.5

Composition of Eudragit S100 polymer and drug in the ratios of 3:1, 5:1 and 7:1 (F<sub>1</sub>, F<sub>2</sub> and F<sub>3</sub>) was less than the threshold bitterness value, i.e. 100 µg/ml, and completely masked the bitter taste of the drug more successfully than both polymers (Eudragits L100 and L100-55). Eudragits L100 and L100-55 exhibited taste masking at polymer-drug ratios 5:1 and 7:1 (not 3:1). Eudragit (as L100 and L100-55) is insoluble in acidic solutions at pHs under 5 (Table 4). This may be because of incomplete film formation by the Eudragit L100 and L100-55, which fail to release chlorpheniramine at salivary pH.

The drug was dispersed in a crystalline or amorphous form or dissolved in the polymeric matrix during formulation of the microparticles. Any abrupt or drastic change in the thermal behavior of either the drug or polymer may indicate a possible drug-polymer interaction. The DSC curve of the chlorpheniramine is seen in Figure 1, endothermic peaks at 134.78 and 207°C (melting point), respectively. However in the thermogram of the microparticles there was no endothermic peak of the drug melting, suggesting the amorphous state of the drug in the microparticles.



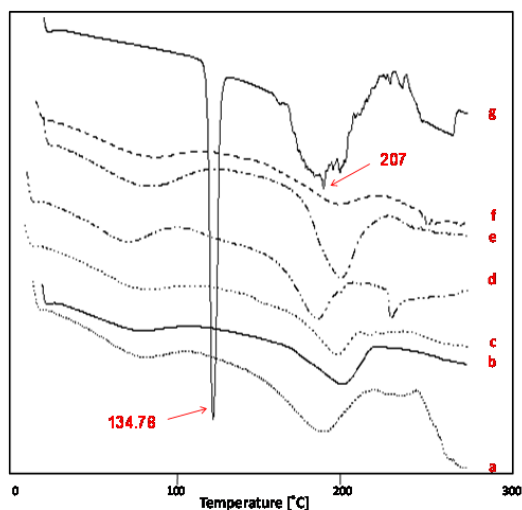


Fig. 1. DSC thermogram of chlorpheniramine (a); Eudragit S100 (b); F<sub>2</sub> (c); Eudragit L100 (d), F'<sub>3</sub> (e); Eudragit L100-55 (f); F''<sub>3</sub> (g).

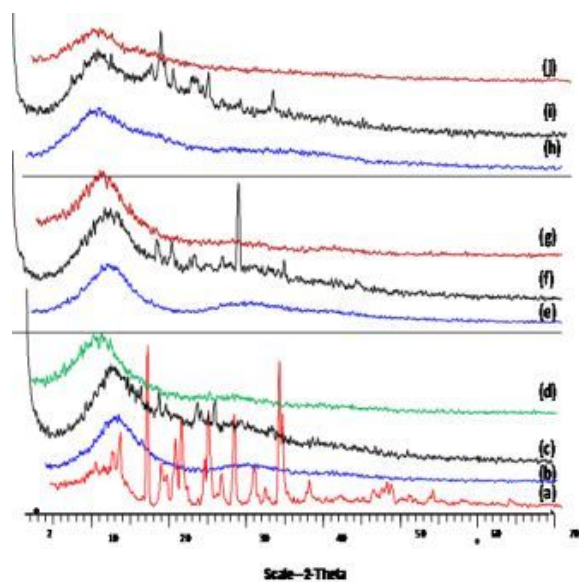
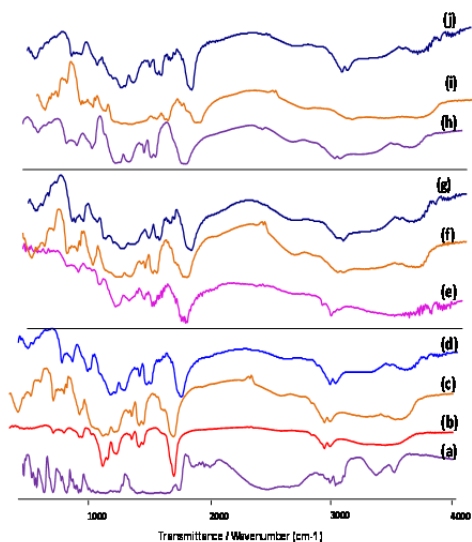


Fig. 2. X-ray diffraction of chlorpheniramine (a); Eudragit S100 (b); Physical Mixture F<sub>2</sub> (c), F<sub>2</sub> (d); Eudragit L100 (e), Physical Mixture F'<sub>3</sub> (f); F'<sub>3</sub> (g); Eudragit L100-55 (h); Physical Mixture F''<sub>3</sub> (i); F''<sub>3</sub> (j).

The x-ray diffraction patterns of pure drug show that the pure drug is crystalline in nature (Figure 2). However, when it was incorporated into the polymer matrix, the principal peaks of the drug disappeared. This could be ascribed to the

amorphous state of the drug in the microparticles. This confirms the results obtained from DSC experiments.



**Fig. 3.** FTIR spectrum of chlorpheniramine (a); Eudragit S100 (b); Physical Mixture F<sub>2</sub> (c), F<sub>2</sub> (d); Eudragit L100 (e), Physical Mixture F'<sub>3</sub> (f); F'<sub>3</sub> (g); Eudragit L100-55 (h); Physical Mixture F''<sub>3</sub> (i); F''<sub>3</sub> (j).

The FT-IR spectra of pure chlorpheniramine (Figure 3) depicts three characteristic bands at 1580 cm<sup>-1</sup>, 1476 cm<sup>-1</sup> and 1352 cm<sup>-1</sup> due to C=C stretching, C-H stretching and C-H bending respectively. Another two sharp bands can be seen at 864 cm<sup>-1</sup> and 702 cm<sup>-1</sup>, which are due to C-C and C-Cl stretching vibration.

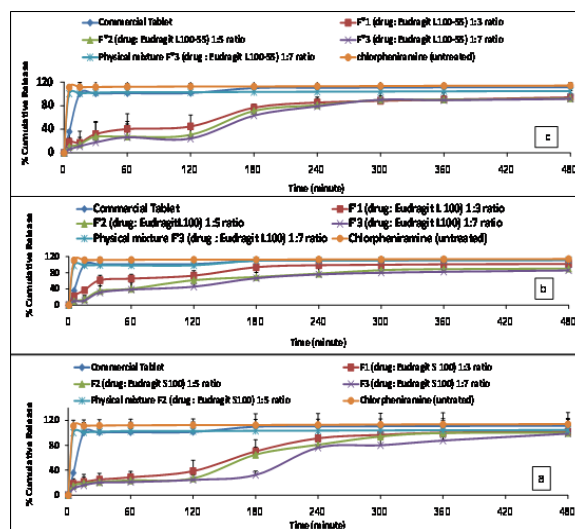
In the spectrum of Eudragits (Figure 3), an intense peak at 3438 cm<sup>-1</sup> was evident due to the O-H stretching vibration. The C=O vibration band of the carboxylic groups presents as a shoulder at 1705 cm<sup>-1</sup>, while the peak at 1730 cm<sup>-1</sup> is attributed to the esterified carboxyl groups.

The Eudragit microspheres exhibited the characteristic peaks of C=O stretching bands at 1730, 1733 and 1735 cm<sup>-1</sup>, respectively (Figure 3). The characteristic OH stretching, NH stretching, C-H stretching and C=O stretching of pure drug was changed in the spectra of the microspheres. The results suggest that the drug maintained its chemical instability during the encapsulation process. In summary, the FT-IR, DSC and x-ray diffraction data indicated signs of major chemical interaction between the drug and the polymer and showed that although the crystallinity of the drug is reduced in the microsphere, the chlorpheniramine inside the microsphere was mainly changed.

### *In vitro release studies*

The release profiles for all microspheres are illustrated in Figure 4. In order to have better comparison between the dissolution profiles, dissolution efficiency,  $t_{50\%}$ ,  $Q_5$  and  $Q_{180}$  were calculated and the results showed that microspheres with high loading efficiency or high drug entrapment showed faster dissolution rate. This could be due to higher level of polymer corresponding to lower level of the drug in the formulation, which resulted in a decrease in the drug release rate. As more drugs are released from the microspheres, more channels are probably produced, contributing to faster drug release rates. Figure 4 and Table 5 show that the initial drug releases for some of the microsphere formulations are slightly high. F<sub>3</sub>, F'<sub>3</sub> and F''<sub>3</sub> (7:1, polymer to drug ratio) formulations showed lower burst release and F''<sub>3</sub> resulted in the lowest burst release (9.51%) in comparison with other microsphere formulations and the percentage of burst release reduced as the increasing of polymer to drug ratio. F'<sub>3</sub> showed the highest production yield (56.48%) and loading efficiency (77.34%). The reason for the burst release could be due to the presence of some chlorpheniramine particles close to the surface of the microspheres. When particles are prepared by the W/O/W method, water-soluble drugs have a tendency to migrate to the polar medium, thereby

concentrating at the surface of the microspheres and inducing the burst effect <sup>[21]</sup>.



**Fig. 4.** Cumulative percent release of chlorpheniramine from microspheres prepared with different polymer-to-drug ratios, physical mixture and commercial <sup>®</sup> tablet.

**Table 5.** Comparison of various release characteristics of chlorpheniramine from different microsphere formulations, physical mixture and commercial <sup>®</sup> tablet

Formulations	Type of Eudragit	Rel <sub>5</sub> <sup>a</sup> (%)	<sup>b</sup> Rel <sub>180</sub> (%)	DE <sup>c</sup>	<sup>d</sup> t <sub>50%</sub> (min)	<sup>e</sup> F <sub>1</sub>
F <sub>1</sub>	S100	18.59	70.11	72.94	160	40.29
F <sub>2</sub>	S100	14.91	64.85	68.08	180	45.06
F <sub>3</sub>	S100	10.55	32.30	58.56	220	52.91
Physical mixture F <sub>2</sub>	S100	100.297	110.068	101.85	5	10.39
F' <sub>1</sub>	L100	22.44	93.85	87.55	45	24.06
F' <sub>2</sub>	L100	10.01	69.46	70.78	110	42.17
F' <sub>3</sub>	L100	9.51	66.72	65.29	130	46.90
Physical mixture F' <sub>3</sub>	L100	97.93	104.614	105.36	5	7.32
F'' <sub>1</sub>	L100-55	18.60	76.73	71.59	150	40.84
F'' <sub>2</sub>	L100-55	10.01	71.11	66.84	155	46.23
F'' <sub>3</sub>	L100-55	5.67	63.15	63.90	160	49.85
Physical mixture F'' <sub>3</sub>	L100-55	94.92	106.866	102.54	5	8.92

Moreover, the burst release could also be explained by the imperfect encapsulation of the drug inside microparticles, as a result of the unstable nature of the emulsion droplets during the solvent removal step. This potential instability may cause a part of the loaded drug to relocate at the microparticle surface, thereby being rapidly released<sup>[22]</sup>. Figure 4 also shows that in most cases a biphasic dissolution pattern was observed. This is the point where the pH of the dissolution medium was altered from 1.2 to 7.4. It can be supposed that the first portion of the curves is due to chlorpheniramine dissolution, which starts immediately after the beginning of the test for the portion of drug very close to the surface of microspheres. After such a phase, two phenomena can combine to enhance the diffusion of the remaining dispersed drug into the bulk phase as well as the formation of pores within the matrix due to the initial drug dissolution which enhances the permeability of the polymer to the drug<sup>[23]</sup>. Comparing the drug release from microspheres prepared by the different pH-dependent polymers shows that the release of drug from microspheres prepared using Eudragit L100 is faster ( $t_{50\%} = 45-130$  min) than the release of drug from microspheres prepared by using Eudragit L100 and L100-55. However, a significant difference was observed between the percentages of drug released at 180 min ( $Q_{180}$ ) between microspheres prepared by the three Eudragits ( $p > 0.05$ ). The highest drug release at 180<sup>th</sup> min (pH 7.4) with Eudragit L100 microspheres  $F_1$  (93.85%) compared to other

microspheres (Eudragit S100 and L100-55) may be due to the higher permeability of the Eudragit L100 microspheres. It can be seen from Figure 4 that different chlorpheniramine microspheres showed different dissolution profiles. In order to see which release profiles is suitable for oral administration, the release data were compared with the release data of commercial chlorpheniramine release formulations. Our chlorpheniramine microspheres can be embedded into soft gelatin capsules and, according to US pharmacopoeia, more than 80% of chlorpheniramine should be released within 8 h. The difference factor test showed that microsphere formulation does not match the release profile of commercial formulations and there was a significant difference between these dissolution profiles. Physical mixtures of microspheres ( $F_2$ ,  $F_3$  and  $F_3$ ) exactly match the release profile of the tablet ( $f_2 = 10.39, 7.32$  and  $8.92\%$ , respectively). A high correlation was observed between the Peppas and first order model (Table 6). The data obtained were also put in the Korsmeyer-Peppas model in order to find out the  $n$  value, which describes the drug release mechanism<sup>[24]</sup>. The  $n$  value of Eudragit microparticles of different polymer to drug ratios was between  $0 < n < 0.5$ , indicating that the mechanism of the drug release was diffusion controlled (Table 6). The  $n$  value of the commercial tablet was not calculated because the primary release percentage was more than 60%<sup>[25]</sup>.

**Table 6.** Fitting parameters of the in vitro release data to various release kinetics models

Zero $f=kt$	K RSQ D(SS)%	0.0021 0.8886 500.9489	0.0017 0.8515 555.7405	0.0021 0.8822 407.4953	0.0005 0.1325 913.3543
First $\ln(1-f)=kt$	k RSQ D(SS)%	0.0248 0.7982 565.8150	0.0042 0.9528 292.6418	0.0059 0.9282 223.4863	0.0039 0.0516 554.4722
Weibull $\ln[-\ln(1-f)]=blnk+blnt$	b k RSQ D(SS)%	0.9078 0.0125 0.7723 317.0520	0.7108 0.0059 0.9657 119.1287	0.8759 0.0055 0.9271 192.9283	0.4503 0.4164 0.3251 160.3292
Peppas $\ln f = \ln k + blnt$	b k RSQ D(SS)%	0.2228 0.1217 0.9390 30.2129	0.5592 0.0350 0.8834 100.4498	0.5860 0.0224 0.9170 93.8543	- - - -
Higuchi $f=kt^{0.5}$	k RSQ D(SS)%	0.0509 0.9264 180.1419	0.0426 0.9567 137.8060	0.0512 0.9254 466.5415	0.0152 0.2166 803.2798

### Conflict of interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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