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Research paper

# Taste masking of paracetamol by hot-melt extrusion: An *in vitro* and *in vivo* evaluation

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ABSTRACT

The purpose of this study was the *in vitro* and *in vivo* evaluation of the masking efficiency of hot melt extruded paracetamol (PMOL) formulations. Extruded granules containing high PMOL loadings in Eudragit EPO® (EPO) or Kollidon® VA64 (VA64) were prepared by hot-melt extrusion (HME). The taste masking effect of the processed formulation was evaluated *in vivo* by a panel of six healthy human volunteers. In addition, *in vitro* evaluation was carried out by an Astree e-tongue equipped with seven sensors. Taste sensing technology demonstrated taste improvement for both polymers by correlating the data obtained for the placebo polymers and the pure APIs alone. The best masking effect was observed for VA64 at 30% PMOL loading. The e-tongue results were in good agreement with the *in vivo* evaluation. *In vitro* dissolution of the extruded granules showed rapid PMOL releases.



## 1. Introduction

The taste masking of bitter APIs is a major challenge especially for the development of orally disintegrating tablets (ODT) in pharmaceutical industry. Several approaches have been reported which involve fluidized-bed coating, supercritical fluids and coacervation approaches where effective taste masking is achieved by applying polymeric coating layer to create a physical barrier around the drug [1,2]. Other alternatives involve the use of complexing agents (cylcodextrins, ion exchange resins) through the formation of inclusion complexes or resonates [3]. Recently, taste masking approaches have employed taste suppressants molecules by blocking the gap junction channels ad hemichannels and thus suppressing the drugs taste [4,5]. However, there is an enormous need for more robust, cost effective and easy to scale-up taste masking technologies. HME is a continuous, one step process that has been used for the development of solid dispersions of active substances for various applications [6,7].

Hot-melt extrusion (HME) has been employed as a novel technique for the formulation of oral solid dosage forms in pharmaceutical industries in the last decade. It was initially used in food and plastic industry but has attracted significant interest in pharmaceutical manufacturing for the development of robust formulations. HME can be used to develop various formulations such as sustained release matrices [8–11]. It has been also introduced for taste masking purposes of bitter APIs by involving the use of taste masking polymers that create solid dispersions to prevent bitter drugs from coming in contact with the patient's taste buds [12–15].

Taste masking can be achieved through intermolecular forces (e.g., hydrogen bonding) between the active substance and the polymer matrix by processing oppositely charged compounds [1,2]. In addition, solid dispersions in which the drug is molecularly dispersed within the polymer matrix have shown effective for masking of the drug's unpleasant taste. Successful taste masking requires development of HME processing conditions, drug/polymer ratio and selection of the appropriate formulation components (Hansen solubility parameter). HME can be used for the development of robust formulations with increased patient palatability and compliance. Taste masking evaluation of pharmaceutical dosage forms is usually carried out by human taste panels and it can be used for further product optimization. However, the taste assessment is subjected to the individuals leading to significant variations while ethical, safety, and toxicity issues should be also taken in account. Alternatively, electronic taste sensing systems can be employed to predict the taste of pharmaceutical formulations [3,16,17]. Commercially available electronic tongues (Astree e-tongue and Insent taste sensing system) have been well studied and evaluated for taste masking purposes. The Astree e-tongue (AlphaMOS, France) has been systematically used to evaluate the bitterness of pure active substances in comparison to formulated

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products. These e-tongue studies showed very good correlation with human taste panels, reproducibility, low detection limits and high sensitivity [18].

Paracetamol (PMOL) is a white crystalline powder with bitter taste mainly used as analgesic pain reliever and antipyretic. The main uses of paracetamol are the relief of headaches, minor aches and pains. In this study, PMOL was used as a model drug for the purpose of taste masking. At the moment, there are several over-the-counter products of orally disintegrating tablets (ODTs) where the active pharmacological agent is taste masked through various approaches.

In the current study, PMOL extrudates were prepared by optimizing the HME processing [19,20] parameters in order to mask its taste efficiently. The extrudates were evaluated by both *in vivo and in vitro* studies where an electronic tongue analyzer was employed that captures the global taste profile. The electronic tongue can be a valuable tool for the development of pharmaceutical formulations by providing accurate and reliable taste patterns of the desired formulations.

## 2. Materials and methods

### 2.1. Materials

Paracetamol (PMOL) was purchased from Sigma Aldrich (Gillingham, UK). Eudragit EPO polymer was kindly donated from Evonik Pharma Polymers (Darmstadt, Germany). Crosslinked polyvinylpyrrolidone (Kollidon VA64) was also donated from BASF, Germany. The HPLC solvents were of analytical grade and purchased from Fisher Chemicals (UK). All materials were used as received.

### 2.2. Calculation of Hansen solubility parameter

The Hansen solubility parameters of the drug and the polymers were calculated from their chemical structures to check the miscibility of drug/polymer formulations using the Hoftyzer and van Krevelen method [21] according to the following equation:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

where

$$\delta_d = \frac{\Sigma F_{di}}{Vi}, \quad \delta_p = \frac{\sqrt{\Sigma F_{pi}^2}}{Vi}, \quad \delta_h = \sqrt{\frac{\Sigma E_{hi}}{Vi}}$$

$i$ is the structural groups within the molecule; $F_{di}$ is molar attraction constant due to molar dispersion forces; $F_{pi}^2$ is molar attraction constant due to molar polarization forces; $E_{hi}$ is hydrogen bonding energy; $Vi$ is the group contribution to molar volume.

The total solubility parameter ($\delta$) is determined by taking the interactions between dispersion forces ($\delta_d$), hydrogen bonding ($\delta_h$), and polar interactions ($\delta_p$) of the functional groups of the parent molecule into consideration. The average molecular weight was used to determine the solubility parameter of different polymeric excipients.

### 2.3. Hot-melt extrusion (HME) process

PMOL formulations with Kollidon VA64 and Eudragit EPO were mixed properly in 100 g batches for 10 min each. A Turbula TF2 Mixer was used to blend the powder formulations for 10 min. The extrusion of all PMOL blends was performed using a Randcastle single-screw extruder (RCP0625) equipped with a 0.2 mm rod die. The drug/polymers composition consisted of PMOL/EPO and PMOL/VA64 at a ratio of 40/60, 50/50, 60/40 and 30/70, 40/60, 50/50 (% wt/wt), respectively. The temperature profile used for all formulations was 100 °C/113 °C/113 °C/113 °C/115 °C (from feeding zone → Die) with screw speed of 15 rmp (rev/min). The produced extrudates (strands) were milled to obtain granules (<500 μm). Grinding by ball milling carried out with a rotational speed of 400 rpm for 5mins each.

### 2.4. Thermal analysis

For the purposes of the study, differential scanning calorimetry (DSC) and temperature modulated (MTDSC) DSC were performed. The physical state of the pure drug, physical mixtures and extrudates was examined by using a Mettler-Toledo 823e (Greifensee, Switzerland) differential scanning calorimeter. Samples were prepared in sealed aluminum pans (2–5 mg) with a pierced lid. The samples were heated at 10 °C/min under nitrogen atmosphere in a temperature range between 0 and 220 °C. MTDSC experiments were performed from 10 °C to 160 °C temperature range with an underlying heating rate of 1 °C/min to further analyze the samples. The pulse height was adjusted to 1 °C with a temperature pulse width of 15–30 s.

### 2.5. Powder X-ray diffraction

XRPD was used to assess the solid state of the extrudates where samples of pure and loaded PMOL were evaluated using a Bruker D8 Advance in theta–theta mode, Cu anode at 40 kV and 40 mA, parallel beam Goebel mirror, 0.2 mm exit slit, LynxEye Position Sensitive Detector with 3° opening and LynxIris at 6.5 mm, sample rotation at 15 rpm. The sample was scanned from 2 to 40° 2-theta with a step size of 0.02° 2-theta and a counting time of 0.2 s per step; 176 channels active on the PSD making a total counting time of 35.2 s per step.

### 2.6. In vitro drug release studies

*In vitro* drug release studies were carried out in 750 ml of 0.1 M hydrochloric acid for 2 h using a Varian 705 DS dissolution paddle apparatus (Varian Inc., North Carolina, US) at 100 rpm and 37 ± 0.5 °C. After 2 h operation, 250 ml of 0.20 M solution of trisodium phosphate dodecahydrate were added into the vessel (buffer stage, pH 6.8) that has been equilibrated to 37 °C. At predetermined time intervals, samples were withdrawn for HPLC assay. All dissolution studies were performed in triplicate.

### 2.7. HPLC analysis

The release of PMOL was determined by HPLC. An Agilent Technologies system equipped with a HICROM S50DS2, 5 μm × 150 mm × 4 mm column at 276 nm was used for the PMOL HPLC assay. The mobile phase consisted of acetonitrile/water (1% acetic acid) (50:50, v/v). The flow rate was 1.5 ml/min and the retention time of PMOL was 3.6 min. The PMOL calibration curves, at concentrations varying from 10 μg/ml to 50 μg/ml, were used to evaluate all the samples with 20 μl injection volume.

### 2.8. In vivo taste masking evaluation

*In vivo* taste masking evaluation was performed on six healthy human volunteers [22,23] from whom informed consent was first obtained (approved by the Ethics Committee of the University of Greenwich, Ref. No: UG09/10.5.5.12). The study is also in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The healthy volunteers of either sex (3 males and 3 females, age 18–25) were selected, trained and the extruded granules were evaluated (no exclusion criteria). The equivalent of 200 mg of pure PMOL or PMOL extrudates (containing

equal amounts of PMOL) were held in the mouth for 60 s and then spat out. The selection of samples was random and in between of two samples analysis mineral water was used to wash each volunteer's mouth. The bitterness was recorded immediately according to the bitterness intensity scale from 0 to 5 where 0, 1, 2, 3, 4and 5 indicate none, threshold, slight, moderate, bitter and strong bitterness.

### 2.9. In vitro taste masking evaluation (Astree e-tongue)

The assays were realized on Astree e-tongue system equipped with an Alpha M.O.S. sensor set #2 (for pharmaceutical analysis) composed of 7 set of sensors (ZZ, AB, BA, BB, CA, DA, JE) on a 48-positions autosampler using 25 ml-beakers. Acquisition times were fixed at 120 s. All the data generated on Astree system were processed using multidimensional statistics on AlphaSoft V12.3 software. Each sample (granules) was tested on Astree e-tongue at least 4 times with three replicates for each sample for the statistical analysis. The average values between 100 and 120 s were used to build the maps. Astree sensors were cleaned up in deionized water between each sample measurement. Each sample was diluted for 60 s under magnetic stirring in 25 ml of deionized water to reach API concentration corresponding to a final PMOL dose of 200 mg. The mixtures were filtered with Buchner funnel fitted with filter paper of 2.5 μm pore size.

## 3. Results and discussion

### 3.1. Solubility parameters and extrusion process

The PMOL miscibility with EPO and VA64 was investigated prior to extrusion by estimating the Hansen solubility parameter using the method of Hoftyzer and van Krevelen for pure PMOL and both polymers. The prediction of drug/polymers miscibility in solid dispersions has successfully been achieved by the solubility parameters ($\delta$) [24–27]. This miscibility is caused by balancing the energy of mixing released by intermolecular interactions between the components by the energy released by intramolecular interactions within the components [21]. Three-dimensional partial solubility parameters by Hansen [28] calculated by group contributions of dispersion forces, polar forces and hydrogen bonding forces was provided by van Krevelen/Hoftyzer [21] and Fedors [29]. The theoretical approach of the solubility parameter suggests that compounds with similar δ values are likely to be miscible. The reason is that the energy of mixing from intramolecular interactions is balanced with the energy of mixing from intermolecular interactions. It was demonstrated that compounds with $\Delta dt < 7$ MPa$^{1/2}$ were likely to be miscible and compounds with $\Delta dt > 10$ MPa$^{1/2}$ were likely to be immiscible [30]. Thus, solubility parameters provide a simple and generic capability for rational selection of carriers in the preparation of solid dispersions [31]. As it can be seen in Table 1 the difference between the calculated solubility parameters of the polymers and the drug indicate that PMOL is likely miscible with both polymers. By using the VAN Krevelen/Hoftyzer the $\Delta\delta$ values for PMOL and EPO/VA64 are 6.86 and 6.17, respectively.

However, a two-dimensional approach proposed by Bagley et al. [32] was used also to predict drug–polymer miscibility as shown in Table 1. By using the two-dimensional approach Bagley et al. observed that $\delta_p$ and $\delta_d$ have similar thermodynamic effects in contrast to $\delta_h$ and introduced the volume-dependent solubility parameter, $\delta_v$, where

$$\delta_v = \sqrt{\delta_d^2 + d_p^2} \quad (2)$$

This method was further developed by Breitkreutz [33] and Albers [34] and used predicting the duration of intestinal absorption for various drugs. The two-dimensional approach can provide more accurate prediction of the drug–polymer miscibility. The drug/polymer miscibility can be predicted by the distance ($R_{a(v)}$) using the Pythagorean Theorem and the two components are considered miscible when $R_{a(v)} \leqslant 5.6$ MPa$^{1/2}$. In our case, it is obvious from Table 1 that the $\delta_p$ values of the drug–polymer combinations differ significantly indicating an effect on the predicted miscibility.

HME quite often requires the addition of a plasticizer to lower the glass transition temperature of the polymers and thus to conduct the extrusion process at lower temperatures [6,24]. However, plasticizers were not incorporated in our studies as both polymers present low glass transition temperature and samples were processed at low extrusion temperature ranges. The absence of plasticizer did not affect the extrusion process.

### 3.2. Thermal analysis and X-ray solid state characterization studies

DSC studies were performed to investigate the physical state of drug within the polymer matrix. As it can be seen in Fig. 1a the DSC thermogram of pure PMOL (calibrated by the peak onset) showed a sharp melting peak at 169 °C (fusion enthalpy 33.40j/g) with a onset of peak at 168 °C where the amorphous EPO showed an endothermic peak at 48.4 °C (onset 44.1 °C) which corresponds to the glass transition temperature (Tg). Previous studies [35,36] of pure PMOL reported the existence of three crystal forms, the Form III which is highly unstable (melting point at 148 °C), the metastable Form II (melting point at 160 °C) and the stable Form I (melting point at 170 °C) while the amorphous form has a glass transition at 23 °C. The polymorphic form of PMOL that was used in the current study was Form I.

The DSC scans of the PMOL/EPO extrudates (Fig. 1b) showed melting endotherms at 143.3 °C, 148.5 °C, and 151.5 °C, respectively, that correspond to 40%, 50%, and 60% PMOL loadings. The observed melting peaks are shifted to lower temperatures and the peak shapes are broader compared with those of pure PMOL suggesting the presence of crystalline PMOL. The observed melting peak of PMOL between 143 and 152 °C indicates the presence of Form I paracetamol in the polymer matrix. However, the shifts of the melting endothermic peaks can also be attributed to possible PMOL–EPO interactions without any changes in the crystal modifications. The presence of Form I was confirmed by the X-ray characterization studies as described below. If the PMLO/EPO components are miscible the Tg of the extruded samples can be derived by the Gordon–Taylor equation [37] and it will show a single Tg that varies between the Tg of the pure components. The EPO glass transition temperatures for the PMOL loaded samples

**Table 1**
Calculated solubility parameters of drug/polymers.

| Sample | $\delta_d$ (MPa$^{1/2}$) | $\delta_p$ (MPa$^{1/2}$) | $\delta_v$ (MPa$^{1/2}$) | $\delta_h$ (MPa$^{1/2}$) | $\delta_t$ (MPa$^{1/2}$) | $\Delta\delta$ | Distance $R_{a(v)}$ |
|---|---|---|---|---|---|---|---|
| PMOL | 19.43 | 9.71 | 29.14 | 13.88 | 25.77 | – | – |
| EPO | 17.89 | 0.65 | 18.54 | 6.08 | 18.91 | 6.86 | 13.16 |
| VA64 | 18.0 | 0.64 | 18.64 | 7.73 | 19.60 | 6.17 | 12.17 |

$R_{a(v)} = \sqrt{(\delta_{v2} - \delta_{v1})^2 + (\delta_{h2} - \delta_{h1})^2}$.

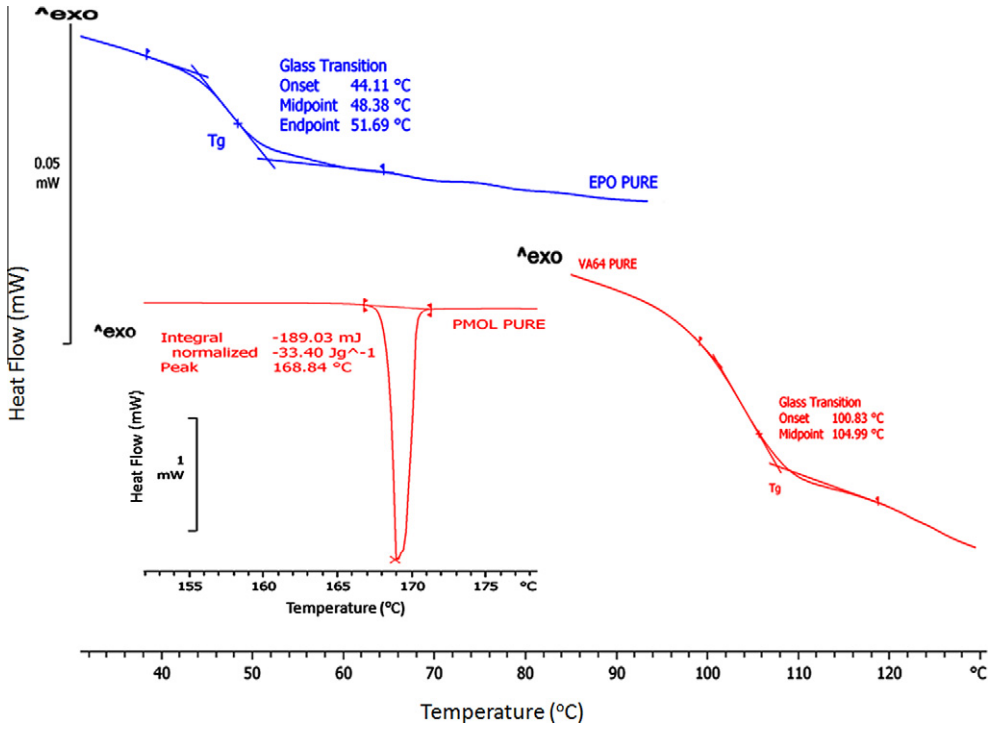


**Fig. 1a.** MTDSC thermograms of pure PMOL (inset) and Eudragit EPO, Kollidon VA64. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

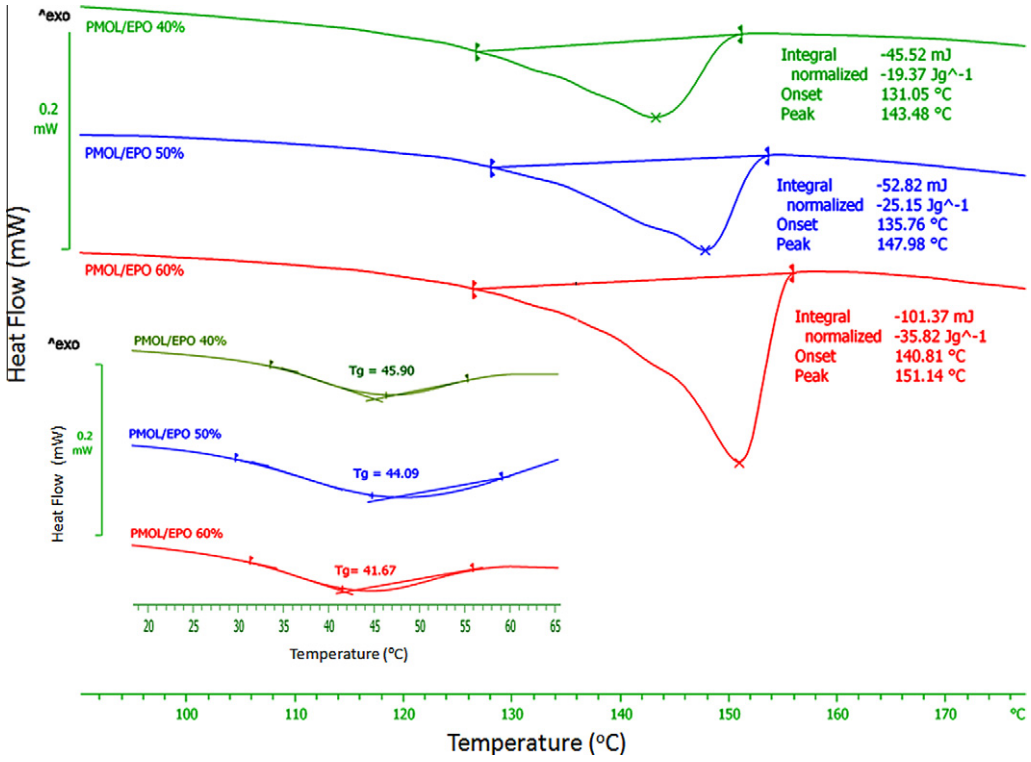


**Fig. 1b.** MTDSC thermograms of PMOL/EPO extrudates at different PMOL loadings. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(30–60%) are shifted at lower temperatures (45.9 °C, 44.1 °C, 41.7 °C) and are slightly different from the estimated Gordon–Taylor theoretical values at 36.0 °C, 33.7 °C, 31.6 °C, respectively. In addition, only a single Tg was observed for all PMOL/EPO ratios, while the Tgs decreased with increase in PMOL concentrations showing partial drug–polymer miscibility and PMOL plasticization effect. In total, the shifts of the melting PMOL peaks and EPO glass transition temperatures suggest the co-existence of molecularly dispersed and crystalline PMOL within the polymer matrix. Similar observations were reported by [38] for PMOL/EPO extrudates

**Table 2**
Crystalline/amorphous degree percentage of the extruded PMOL formulations.

| Formulation | Amorphous (%) | Crystalline (%) | Tg (°C) | Tm (°C) |
|---|---|---|---|---|
| PMOL/EPO 40% | 79.5 | 20.5 | 45.9 | 143.3 |
| PMOL/EPO 50% | 75.5 | 24.5 | 44.1 | 148.5 |
| PMOL/EPO 60% | 52.0 | 48.0 | 41.7 | 151.5 |
| PMOL/VA64 30% | 100.0 | – | 85.8 | – |
| PMOL/VA64 40% | 100.0 | – | 95.2 | – |
| PMOL/VA64 50% | 100.0 | – | 93.5 | – |

Tg: polymer glass transition, Tm: PMOL melting point.

where PMOL was presented in two physical forms simultaneously. The calculated amorphous/crystallinity degrees [39] of the extruded formulations are shown in Table 2. It is obvious that the presence of crystalline PMOL is increased with the PMOL loading in each formulation.

In contrast, the PMOL/VA64 extrudates showed two Tg peaks, one close to the Tg of bulk VA64 (105 °C) and the other between 27 and 42 °C depending on the PMOL loadings. Pure VA64 showed a baseline shift at 105 °C which is reported as Tg and there is another endothermic peak visible at about 200 °C which correspond to decomposition of the polymer. As Fig. 1c shows the low temperature Tg is related to the PMOL loading with descending order of PMOL (30%) > PMOL(40%) > PMOL(50%) → (41.1 °C, 37.7 °C, 27.6 °C) and are elevated at higher temperature in comparison with amorphous PMOL Tg (25 °C). The transformation of PMOL from Form I to amorphous is supported by the disappearance of the melting endothermic peak at 169 °C. As a result, we could rule out the presence of molecularly dispersed PMOL within the VA64 matrix which can be recognized by the presence of one single mixed-phase Tg. In our case, the two consecutive glass transitions indicate the presence of amorphous mixtures and an amorphous/amorphous phase separation. This observation is not unusual as similar results have been observed for itraconazole/EPO100 solid dispersions [40].

XRPD was employed to investigate the crystalline state of PMOL within the polymer matrices. The standard XRPD patterns of pure PMOL, physical mixtures with Eudragit EPO, and extrudates are depicted in Fig. 2a. Crystalline PMOL has distinct crystalline peaks at $2\theta$ angles of 12.11, 13.82, 15.52, 18.20, 20.42, 23.51, 24.39, and 26.59° and a series of smaller peaks at different $2\theta$ angles ranging from 26.78 to 38.45°. The diffraction patterns of the physical mixtures of drug and polymers in three different ratios presented identical crystalline peaks to those of pure PMOL but at a lower intensity. The XRD patterns of extruded formulations showed increased amorphous trends compared with the pure PMOL due to the dispersion of the drug into the polymer matrix. Furthermore, the diffractions patterns of the all PMOL–EPO extrudates confirmed the presence of Form I within the polymer matrices as no new distinct crystalline peaks at different $2\theta$ could be observed [35].

The PMOL intensity peaks supported the DSC investigations where crystalline drug was detected in the binary mixtures. In contrast, for the PMOL–VA64 extrudates, no distinct peaks were observed suggesting the presence of amorphous PMOL as shown in Fig. 2b. The absence of crystalline PMOL was detected for all drug loadings even at 50% PMOL. The combined DSC and X-ray characterization studies revealed different PMOL crystalline states mainly depend on the polymeric carrier and its miscibility with the active substance. Finally, no PMOL degradation was observed in all extruded batches as it was confirmed by solid state NMR studies (data not shown).

### 3.3. In vivo and in vitro taste masking evaluation

The masking efficiency of the developed granules was evaluated *in vivo* with the assistance of six healthy human volunteers (age 18–25). The *in vivo* statistical data collected for the pure active substance, bulk polymers and the extruded formulations are summarized in Table 3. The data analysis showed significant suppression of the bitter taste for PMOL and strong influence of the polymeric

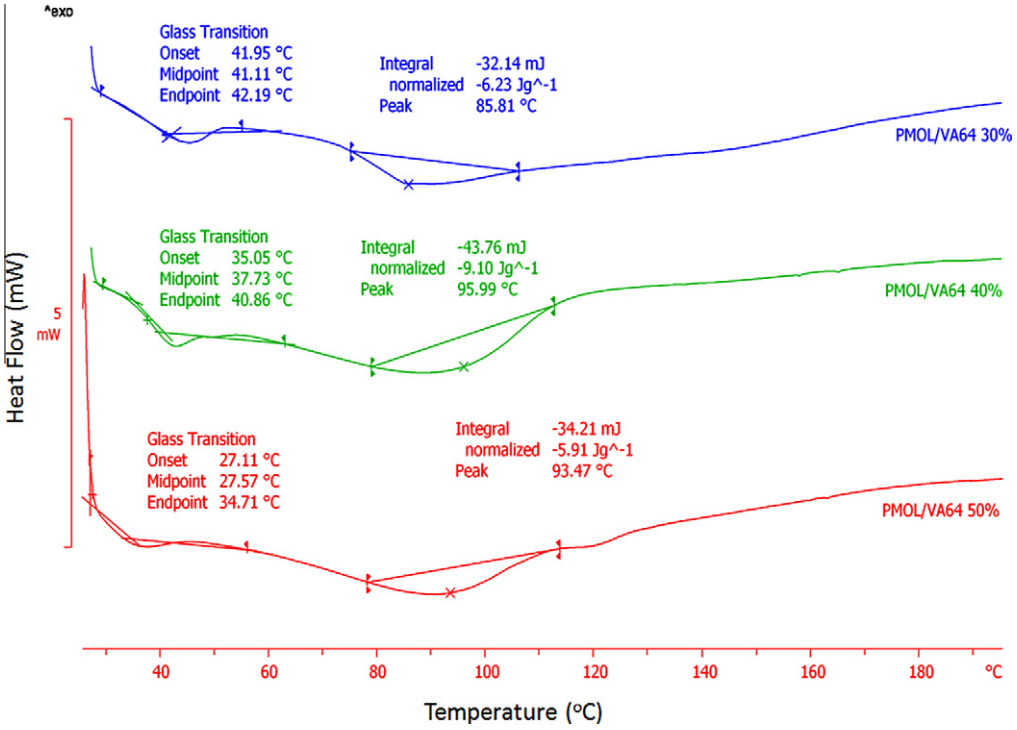


**Fig. 1c.** MTDSC thermograms of PMOL/VA64 extrudates at different PMOL loadings. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

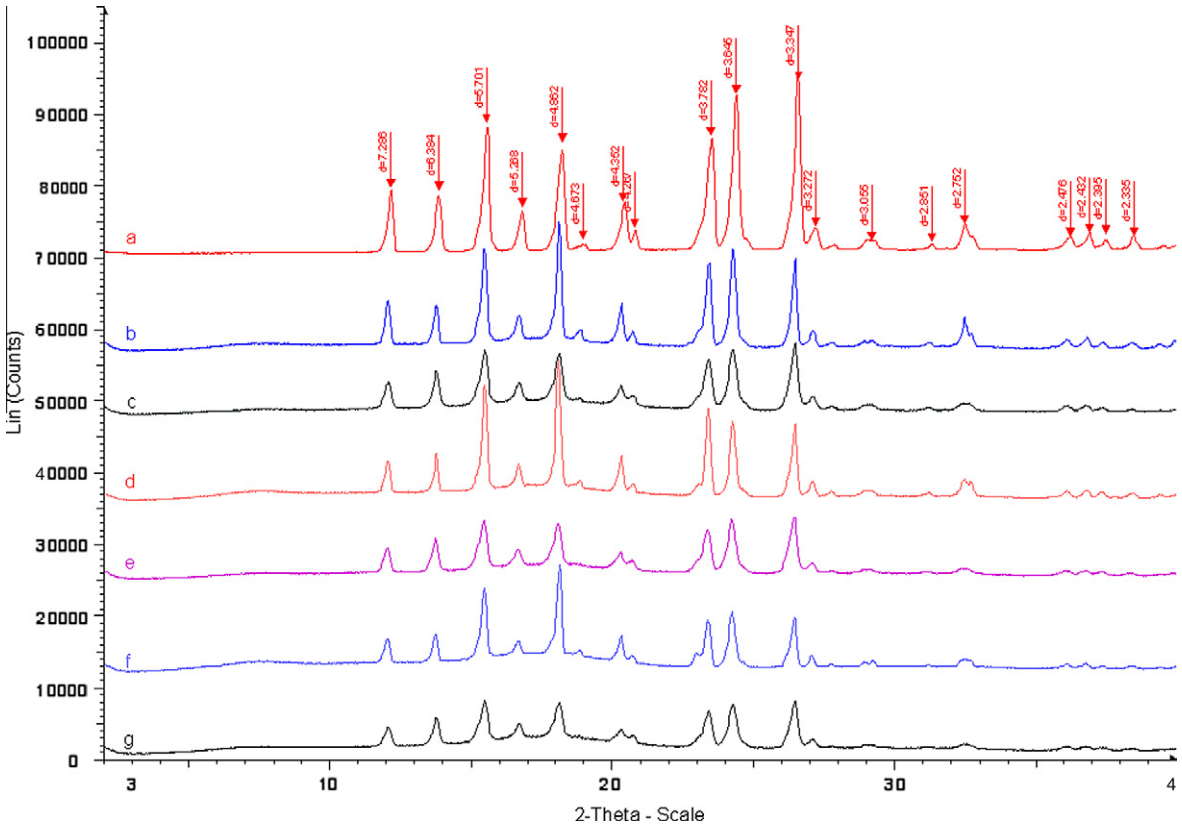


**Fig. 2a.** Powder XRPD patterns of PMOL/EPO solid dispersion (SD) and physical mixtures (PM) systems: (a) PMOL (b) PMOL/EPO 60% PM (c) PMOL/EPO 60% Ext. (d) PMOL/EPO 50% PM (e) PMOL/EPO 50% Ext. 50% (f) PMOL/EPO 40% PM (g) PMOL/EPO 40% Ext. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

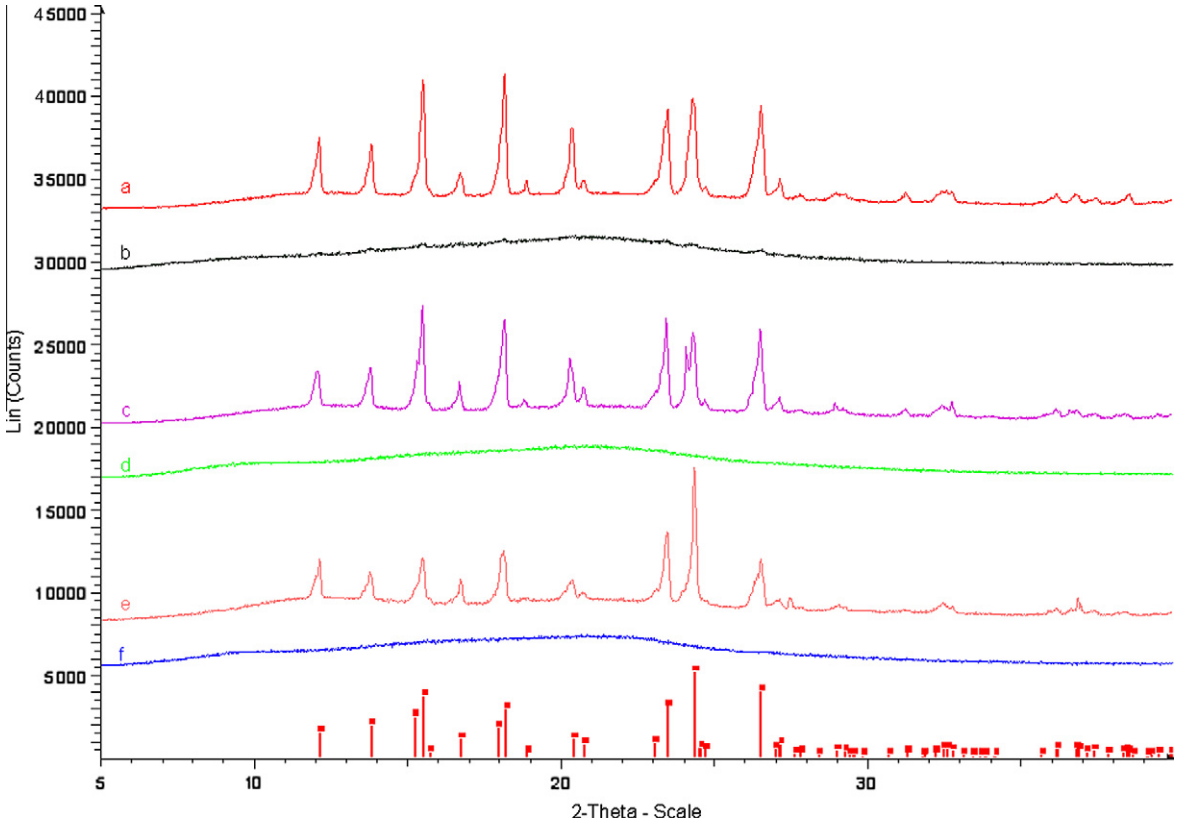


**Fig. 2b.** Powder XRPD patterns of PMOL/VA64 extruded (Ext) and physical mixtures (PM)samples: (a) PMOL/VA64 50% PM (b) PMOL/VA64 50% Ext (c) PMOL/VA64 40% PM (d) PMOL/VA64 40% Ext (e) PMOL/VA64 30% PM and (f) PMOL/VA64 30% Ext. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 3**
Sensory scores for polymers and PMOL extruded samples.

| Formulations | *In vivo* | | *In vitro* | |
|---|---|---|---|---|
| | Average | RSD (%) | Average | RSD (%) |
| PMOL | 3.0 | 0.3 | 3.0 | 0.9 |
| PMOL/VA64 30% | 1.5 | 0.3 | 1.5 | 3.1 |
| PMOL/VA64 40% | 2.0 | 0.0 | 2.1 | 5.1 |
| PMOL/VA64 50% | 2.5 | 0.3 | 2.2 | 1.1 |
| PMOL/EPO 40% | 2.0 | 0.3 | 2.2 | 1.9 |
| PMOL/EPO 50% | 2.5 | 0.0 | 2.4 | 1.6 |
| PMOL/EPO 60% | 3.0 | 0.3 | 2.9 | 1.9 |

carriers indicating the importance of drug loading in the final formulation.

Both polymers showed improved taste masking capacity for certain formulations with descending order VA64 > EPO. The PMOL/EPO extrudates presented masking effect for active concentrations up to 50% with panelists' scores showing slight bitterness. In Fig. 3, it can be seen that PMOL/EPO extrudates showed better taste suppression at 40% loading, while at 60%, no masking effect was observed. The PMOL/VA64 extrudates demonstrated similar masking effect where for PMOL loadings from 40% to 50% the recorded scores suggested slight bitterness. The PMOL/VA64 (30%) extrudates showed improved masking effect with panelists' scores indicating threshold values.

Interestingly, no difference was observed in the *in vivo* taste scores for both polymers at the same PMOL loadings. For example, at 40% PMOL loading, the average panelists' score was identical for EPO and VA64 extrudates respectively.

A novel *in vitro* approach to evaluate the taste masking efficiency of various pharmaceutical dosage forms and avoid problems related to human panelists is the use of electronic sensor arrays [18,41,42,43] known as electronic tongues (e-tongue). Similar studies were performed by other researchers where a principal component analysis (PCA) of active formulations against the placebo was presented through PCA maps in order to determine the taste masking potency of various components [44–46]. For the purposes of the study pure PMOL, bulk polymers and extruded

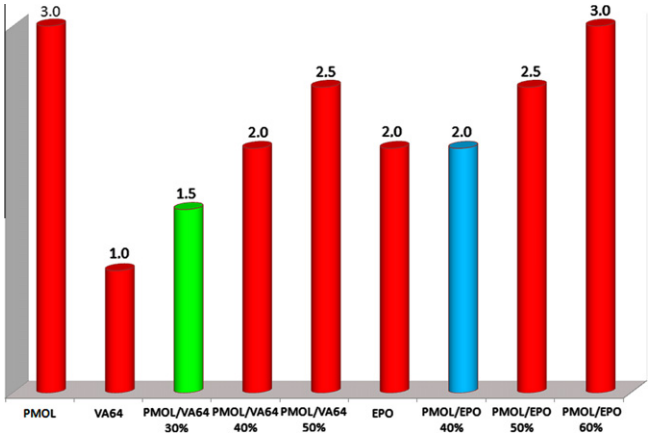


**Fig. 3.** Schematic representation of the taste scores of pure API, bulk polymers and the extruded formulations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

granules were processed as described in the previous section. The signal of the different formulations was represented on taste maps based on a projection obtained by PCA as depicted in Figs. 4a and 4b. These maps showed the relative repartition and proximity of bitterness for each formulation. According to Fig. 4a, the active sample (100% PMOL) and placebo polymer (VA64) are well separated indicating a big distance and taste differences. Also, the taste map indicates significant discrimination between the placebo and the active extruded formulations. All three drug–polymer extruded samples are close to each other while relatively far from PMOL. This means a significant taste evolution and a masking improvement toward pure PMOL. Similar to Kollidon VA64 samples, the same conclusions are observed for EPO polymer, despite a lowest distance from pure active to placebo formulation (Fig. 4b).

The distance between active and polymer formulations are indicative of the taste potency of each polymer. The closer the formulation is located to the placebo and the larger the distances to the pure unpleasant PMOL are, the better the taste masking is

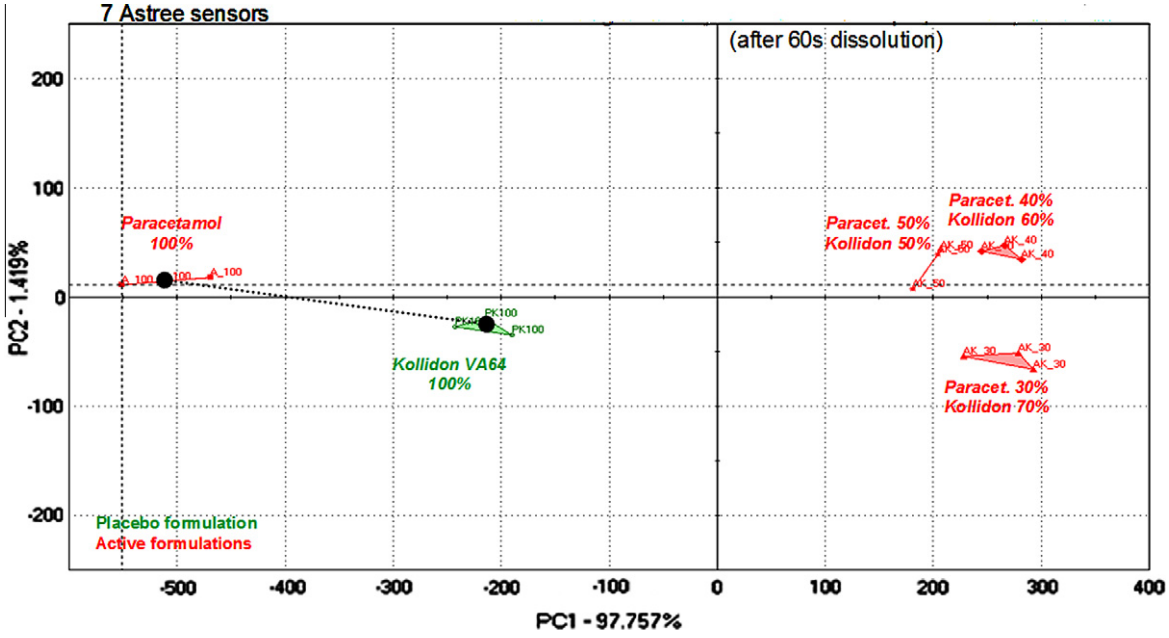


**Fig. 4a.** Electronic tongue "taste map": Global signal comparison (PCA analysis of the electrode responses) between pure PMOL and extruded formulations with VA64 polymer after dissolution for 60 s. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

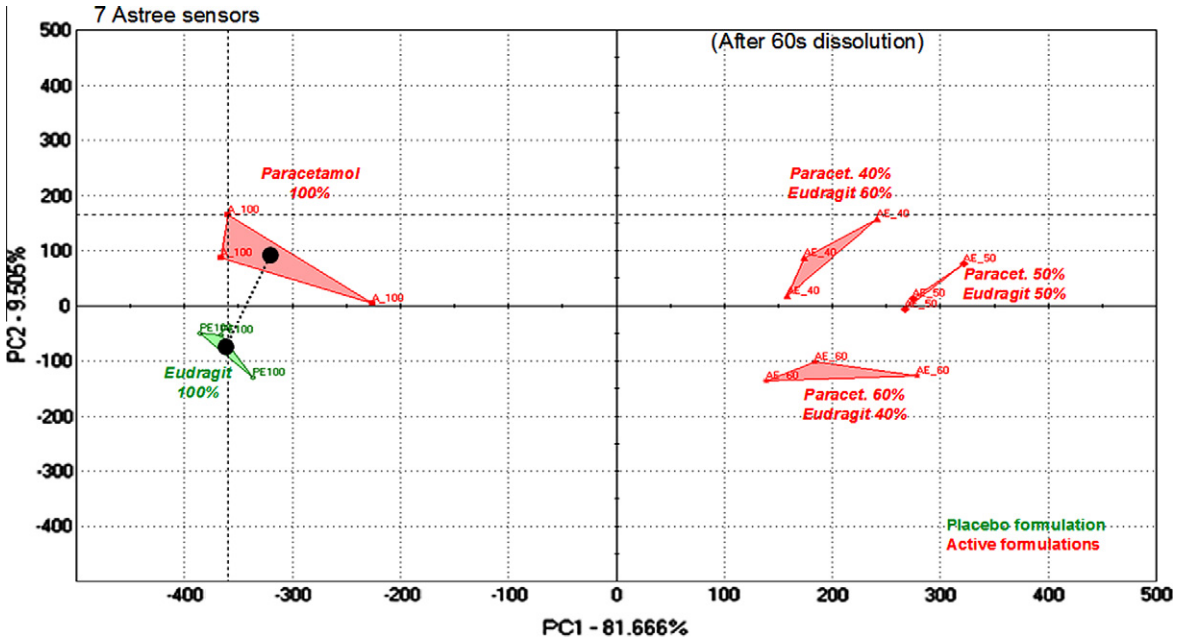


**Fig. 4b.** Electronic tongue "taste map": Global signal comparison (PCA analysis of the electrode responses) between pure and exrtuded formulations with EPO polymer after dissolution for 60 s. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[47]. A taste improved effect is thus observed for each of the three PMOL-VA64 extrudates compared to polymer alone (DI > 80%). As shown in Fig. 6, a taste improvement is perceptible with VA64 with the highest average distance obtained for PMOL/VA64 at 30/70%.

In Fig. 5, it can also be seen that the PMOL/EPO extrudates showed closer distances and lower DI to pure API. However, these distances suggest improved masking effect with the best result achieved for PMOL loading at 50%. This last result is slightly different than the panelists' scores. Furthermore, a sensory correlated model based on Partial Least Square (PLS) was built to evaluate the correlation with sensory scores as depicted in Fig. 6. The correlation model is valid ($R^2$ < 0.8) despite dispersion and low discrimination between formulations ($p$ value > 0).

The *in vitro* e-tongue evaluation was in good agreement with the *in vivo* tests and it was able to identify the optimum taste masked formulations. The e-tongue can be proved an efficient approach to develop palatable and pleasant-tasting products by replacing taste panelists.

### 3.4. Dissolution studies

Dissolution profiles of PMOL from PMOL/EPO 40–60% and PMOL/VA64 30–50% are shown in Figs. 7a and 7b. The dissolution rates of PMOL for both EPO and VA64 extrudates were rapid and approximately 80% PMOL was released in 15 min while more than 92% was released in 30 min. Only a slightly lower release rate was observed for the PMOL/EPO at 50–60% loadings which can be attributed to the higher crystalline matter of PMOL in the extrudates. As a result each of the extruded formulations can be applied for fast onset action dosage forms. Furthermore, PMOL release

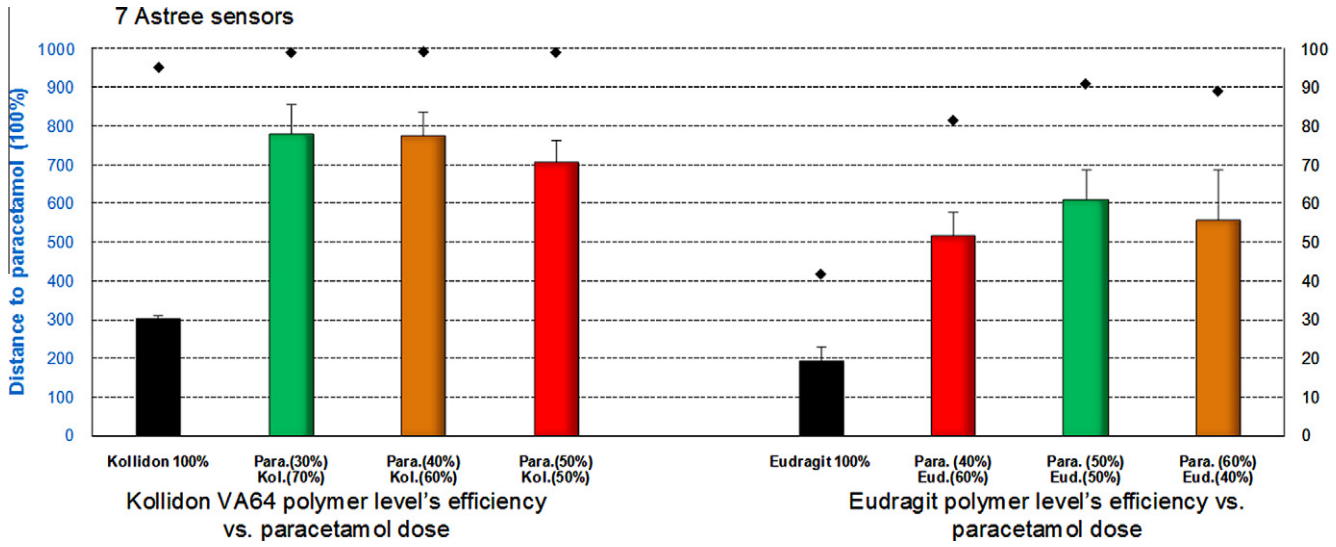


**Fig. 5.** Distance and discrimination comparison between signal of 100% PMOL formulation and each polymer's formulation on Astree e-tongue (after 60 s). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

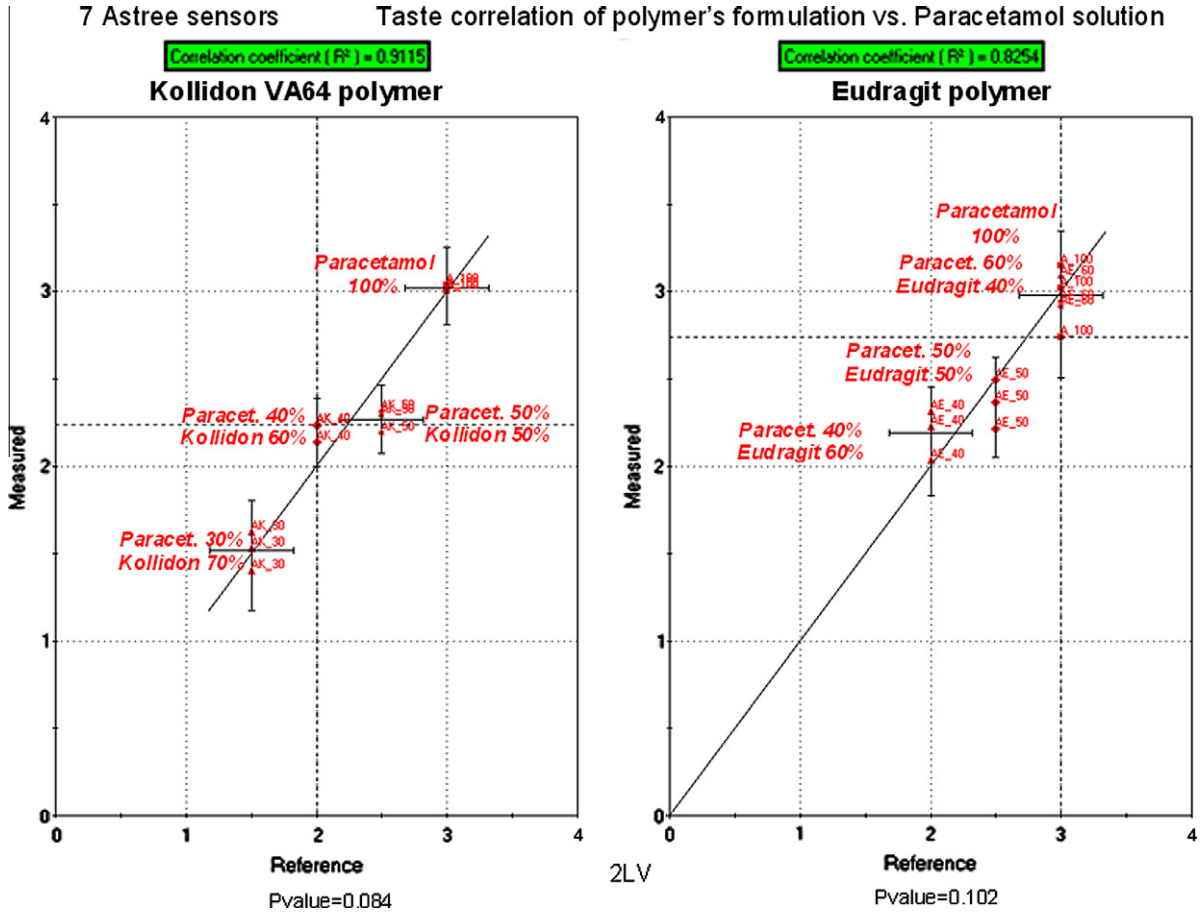


**Fig. 6.** Correlation of human sensory data "Reference" with Astree Electronic tongue measurements ("Measured"). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

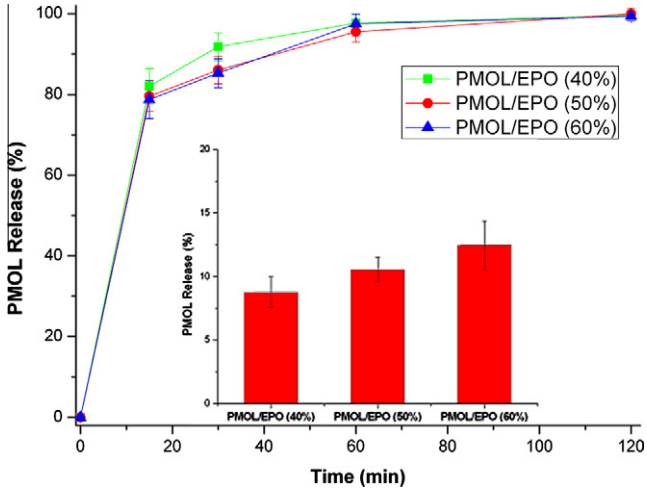


**Fig. 7a.** (a) Dissolution profiles of PMOL in PMOL/EPO extrudates ($n = 3$) and (b) dissolution profiles at 60 s (inset, $n = 3$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

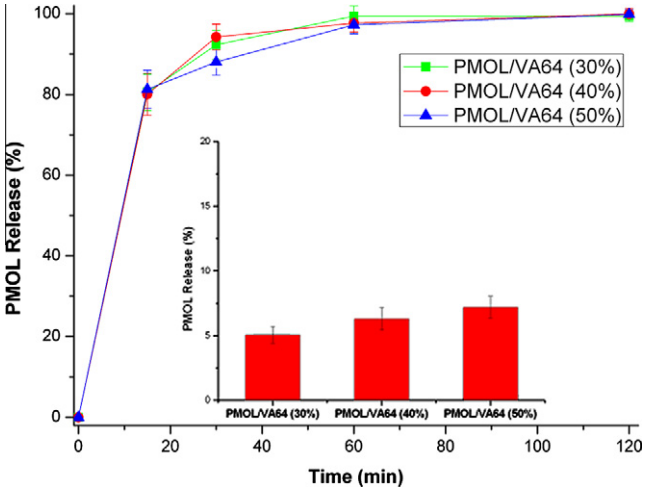


**Fig. 7b.** (a) Dissolution profiles of PMOL in PMOL/VA64 extrudates ($n = 3$) and (b) dissolution profiles at 60 s (inset, $n = 3$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

patterns for the first 60 s were investigated to determine the actual drug amount released during the *in vitro* taste masking evaluation as shown in Figs. 7a and 7b (insets). The PMOL release was found to be dependant on the polymer grade and the actual drug loading. In the case of PMOL/EPO extrudates, the release varied between ~9% and 14% and the released drug amounts increased with increase in the drug loading. Similarly, the PMOL/VA64 exhibited the same trends but slower PMOL release patterns which varied from ~5% to 7%. The study of the onset PMOL release is important in order to verify the ability of both polymers to be used as masking agents.

## 4. Conclusions

In the current study, hot-melt extrusion was employed as a processing technique to manufacture taste masked PMOL formulation by embedding the active substance either in Eudragit EPO or Kollidon VA64 polymer carriers. PMOL was found to be in crystalline or amorphous state depending on the polymer used for extrusion. The optimized formulations were evaluated in terms of taste masking efficiency both by *in vivo* human panellists and an electronic tongue. The extruded formulations of VA64 demonstrated better taste masking compared with those of EPO, while the e-tongue was found to be a valuable tool for taste masking assessments and formulation development.

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