Drug Development and Industrial Pharmacy, 2011; 37(6): 694–701

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI: 10.3109/03639045.2010.535822

informa
healthcare

REVIEW PAPER

Enhanced *in vivo* absorption of CB-1 antagonist in rats via solid solutions prepared by hot-melt extrusion

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Abstract

The aim of the present work was to investigate *in vitro* dissolution properties of three binary solid solutions prepared by a hot-melt extrusion (HME) process with vinyl pirrolidone – vinyl acetate copolymer (Kollidon VA 64), ethyl acrylate, methyl methacrylate polymer (Eudragit E) polyetilenglicol 8000 (PEG 8000) with a cannabinoid type 1 (CB-1) antagonist. Hansen solubility parameters were calculated from the chemical structures of the drug and the individual polymers in order to predict miscibility. Solid state characterizations of drug substance, physical blends and HME formulations were performed with differential scanning calorimetry. The dissolution testing conducted under sink conditions revealed that the dissolution rate of HME formulations improved around 1.8-fold vs drug substance. Supersaturation dissolution study demonstrated that HME formulations composed by Eudragit E and Kollidon VA64 increased drug solubility between 30- and 35-fold, respectively comparing to the drug substance. Physical and chemical stability of formulations were studied at 40°C/75%HR with open dish during 15 days. The formulation composed by the drug and Eudragit E at 10:90 was evaluated for *in vivo* drug absorption in male Wistar–Hannover rats and it was found to increase CB-1 absorption threefold greater than pure drug oral suspension.

Keywords: Hot-melt extrusion, solid dispersion, CB-1 antagonist, dissolution test sink conditions, supersaturation, bioavailability

Introduction

In the recent years an important number of new entities and marketed drugs are products with low aqueous solubility which could be included in biopharmaceutical classification system as a class II substance (Connors and Elder R&D, 2004). The bioavailability of these products that is limited by slower dissolution rate in the gastrointestinal (GI) tract results in low absorption and thus low bioavailability. New technologies and the use of new excipients to enhance and improve drug solubility has become a challenge for scientists and an outstanding goal for pharmaceutical industry (Leuner and Dressman, 2000).

Hot-melt extrusion (HME) is a new platform technology (Repka et al. 2002; Breitenbach et al. 2002; Miller et al. 2007) in which a drug and a carrier are melted together, following the extrudate solidification by cooling. Drug molecules sometimes turn into amorphous state or dissolved in the matrix resulting in solubility and dissolution enhancement (Lloyd et al. 1997; Hülsman et al. 2000; Forster et al. 2001; Rambali et al. 2003; Wang et al. 2005). The advantages of HME (Crowley et al. 2007) involve a continuous production process, short time processing, solvent free, and high flexibility of final dosage design. Also, the extrudates obtained can be milled to get powders, which can be compressed into tablets or filled in capsules. Moreover, the extrudates can be cut into microparticles.

Our drug substance is an antagonist cannabinoid type 1 (CB-1) cannabinoid receptor that targets a novel physiological system. Cannabinoid systems are involved in the central regulation of food intake and in the central nervous system reward like the proposed indications for CB-1 antagonist were; weight management, overweight,

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(Received 08 June 2010; revised 08 September 2010; accepted 25 October 2010)

and obesity. Obesity is a highly chronic and prevalent illness which is frequently associated with numerous and serious diseases such as diabetes, cardiovascular disorders, arthritis, or hypertensional arthrosis. This drug substance is a fine white powder, practically insoluble in water and highly lipophilic with a logP 4.69 and thermostable. Due to these physicochemical and stability properties, CB-1 antagonist was the appropriate candidate for melt extrusion (He et al. 2010).

Materials and methods

Materials

CB-1 antagonist was synthesized at ESTEVE Química Industries from Spain. A summary of the most important physicochemical properties is detailed on Table 1. The polymers selected (Perissutti et al. 2002; Miller-Chou and Koening 2003) were: ethyl acrylate methyl methacrylate polymer (Eudragit E) which was purchased from Evonick Rohm GmbH Pharma, (Darmstadt, Germany) vinyl pirrolidone – vinyl acetate copolymer (Kollidon VA 64) which was supplied by BASF Corporation from (Barcelona, Spain) and polyetilenglicol 8000 (PEG 8000) which was purchased from Comercial Química Masso S.A. (Barcelona, Spain). All the polymers are compendial.

Hot-melt extrusion

HME was carried out using a Haake Minilab twin screw extruder (Thermo Electron Corporation, Karlsruhe, Germany). The screws used were co rotated at speed of 75 rpm resulted in a 2–3 min residence time. Hansen solubility parameters of the raw drug substance, Eudragit E, PEG 8000 and Kollidon VA64 were calculated from the chemical structures using Coleman and Painter group contribution method (Coleman and Painter 2006), the values obtained were used to predict miscibility (Greenhalgh et al. 1999). The results of drug and polymers are listed on Table 2. The working ranges of the applied temperature depended on the polymer used, 140° for Eudragit E, (Zheng et al. 2007) 170°C for Kollidon VA 64 and 60°C for PEG 8000. Powder blends of 25 g material with a 10% (w/w) drug were manually fed into the extruder and were processed. Table 3 shows a summary of the formulations composition and process parameters used in hot-melt process. The extrudates obtained from the polymers alone and binary combinations showed a clear appearance. Torque values were comprised between 5 and 25 Ncm. The melt extrudates were milled in a mortar and the particles obtained were comprised between 300 and 500 μm range.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to characterize the morphology of drug substance, physical mixtures, and HME-developed formulations A, other techniques to evaluate the solid state of the drug such as power X-ray diffraction could be used. The equipment used was DSC instruments model 2920; it was used in conventional mode. Ultralight purity nitrogen was used as the purge gas at 150 mL/min flow rate. The samples were weighted by using an approximately 4 mg aluminum pans. Closed pans were used for the analysis (Kit al crucibles 40 μl aluminum) (Mettler-Toledo SAE, Barcelona, Spain). The temperature ramp speed was 10°C/min from 20°C to 200°C for all the tests.

In vitro drug release studies

For all dissolution tests the European Pharmacopoeia 6th edition apparatus II (SR8-Plus dissolution apparatus, Hanson Research, Chatsworth,NJ) was used (paddle method) employing a volume of 1000 mL of dissolution medium at a temperature of 37 ± 0.5°C and a rotational speed of 50 rpm.

Dissolution release (%) was measured with an HP8452A diode array detector (Agilent Technologies, Germany) at wavelength 336 nm for the determination of the drug, on filtrated samples. The flow-cell path length was 1 cm.

In vitro dissolution testing (sink conditions)

The dissolution medium for the study was HCl 0.1N with 0.1% sodium lauril sulfate prepared with demineralized water. Aliquots of 5 mL were collected at 5, 10, 15, 20, 30, 45, and 60 min, replacing the medium removed.

An amount of each tested formulation equivalent to 10 mg of drug was added to each vessel ($n = 4$).

In vitro dissolution testing (non-sink conditions or supersaturation)

Dissolution testing at supersaturated conditions was conducted as stated above but dissolution medium for

Table 1. Physicochemical properties of drug substance (CB-1 antagonist).

Parameter	Results
Thermodynamicsolubility (μg/mL)	1.2–3.6 (pH = 1.2)
pKa	2.8
LogP	4.69
Molecular weight (g/mol)	493.8
Melting point (°C)	143–145
Particle size (μm)	304.4

Table 2. Calculation of the Hansen solubility parameters for drug and polymers and differential values vs raw drug.

Api/polymers	Б(Mpa)$^{1/2}$	Δб(Mpa)$^{1/2}$
Drug	25	—
Eudragit E	19.0	6.0
Kollidon VA 64	22.4	3.6
PEG 8000	18.2	6.8

Table 3. HME formulations and extrusion parameters used.

Drug concentration (w/w) 10%		
Compound	Extrusiontemperature (°C)	Torque(Ncm)
Eudragit E	140	12
Kolllidon VA 64	170	20
PEG 8000	60	5

HME, hot-melt extrusion

the study was 0.1N HCl ($n = 4$). This corresponds to a supersaturation of approximately nine times thermodynamic solubility. Aliquots of 5 mL were collected at 5, 10, 15, 20, 30, 45, and 60 min, replacing the medium removed.

An amount of each tested formulation equivalent to 20 mg of drug was added to each vessel ($n = 4$).

Statistical analysis

Statistical differences of dissolution test were determined using one way analysis of variance using JMP statistical software 7.0.1 (SAS Institute, Cary, NC). A statistically significant difference was considered when ($P < 0.05$).

In vivo evaluation of HME formulation prepared with Eudragit E

The formulation composed by the drug substance and Eudragit EPO at 10:90 proportion and the drug substance alone were selected for an *in vivo* test. (Zheng et al. 2007.)

In vivo pharmacokinetics in male fasted rats (20 mg/kg of drug substance) was done with the oral formulation and compared to non-formulated drug substance administered orally (20 mg/kg) and intravenously (1 mg/kg).

Wistar–Hannover rats weighing 175–200 g were supplied by Harlan Italia (Harlan ZI Azzida UD, Italy). Manipulations and experimental procedure were conformed to the current norms of animal welfare.

Blood samples collected in ethylenediaminetetraacetic acid-K3 were obtained at the following time points: predose, 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h y 24 h ($n = 5$ per time point).

After centrifugation, 100 µl of the resulting plasma samples were purified by protein precipitation with 600 µl of acetonitrile followed by centrifugation. Supernatants were diluted with 0.1% formic acid in water and analyzed using a validated a by tandem liquid chromatography-mass spectrometry method with a Chiralcel OJRH column and 0.05% acetic acid in water/acetonitrile (40:60, v:v) as mobile phase at a flow rate of 0.8 mL/min.

The pharmacokinetic parameters were calculated from the mean plasma level curves by means of non-compartmental kinetics using the program WinNonlin Professional version 5.0.1 (Pharsight Corporation, Mountain View, CA.

The peak plasma concentration values (C_{max}) and the time to reach this concentration (t_{max}) were obtained directly from the experimental data. The elimination constant (k_{el}) and elimination half-life ($t_{1/2}$) were calculated by linear regression of the last phase of the curve (log concentration vs time). The area under the curve of plasma levels vs time from zero to the last time determined [area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_{0-t})] was calculated be means of the trapezoidal method. The area under the curve of plasma levels vs time from zero to infinity ($AUC_{0-\infty}$) was calculated with the expression: $AUC_{0-\infty} = AUC_{0-t} + C_{last}/k_{el}$, wherein C_{last} is the plasma concentration at the last time measured. The normalized area under the curve (AUC/D) was also calculated by dividing the $AUC_{0-\infty}$ value by the administered dose. The clearance (Cl, Cl/F for extravascular routes) was calculated with the expression $Cl = D/AUC_{0-\infty}$. The volume of distribution based on the terminal phase (V_d, V_d/F for extravascular routes) was calculated $V_d = D/k_{el} \cdot AUC_{0-\infty}$. The bioavailability ($F$) was calculated as follows: $F = (AUC_{0-\infty(po)} \cdot D_{(iv)}/AUC_{0-\infty(iv)} D_{(po)}) \times 100$.

Statistical comparison of C_{max} and AUC was done by means of Bailer test of contrasts, assuming equal variance at each time point (Bailer 1988).

Stability studies

The samples were placed in opened dish conditions and stored in a chamber equilibrated at 40°C/75%HR during 15 days. After 15 days were checked: assay, degradation products, moisture and *in vitro* dissolution profiles at non-sink conditions (supersaturated conditions) which is more representative of *in vivo* performance test.

Results and discussion

Calculated solubility parameters

Solubility parameters have been used to predict the miscibility of the drug together with the excipients and the polymers in solid dispersions.

Table 2, shows the calculated solubility parameters for the drug substance (CB-1 antagonist), PEG 8000, Kollidon VA64. and Eudragit E. The difference between the calculated solubility parameters of the drug and the polymers predicts that all combinations would be likely miscible as observed on the DSC thermograms of HME formulations which supported this approach A. Kollidon VA 64 and drug substance showed the most similar values in Hansen solubility parameters.

Differential scanning calorimetry

All the HME formulations were processed at 200°C (10°C/min) which is above the melting point of drug. It is expected that HME formulations at 10% of drug loading completely turn into amorphous compositions. The results of the DSC analysis of drug substance A, their physical mixtures and HME formulations are shown on Figure 1 and Figure 2.

DSC thermograms demonstrated that the drug was in amorphous state for HME formulations as indicated by the absence of the melting endoderm for the crystalline drug at approximately 143°C as observed with the drug and the physical mixtures.

In vitro drug release studies

Results of dissolution testing obtained from the milled powders at sink conditions with the drug and HME formulations are shown on Figure 3. The formulation containing the polymer Eudragit E released the drug quickly at 10 min is delivered 100%. The formulation

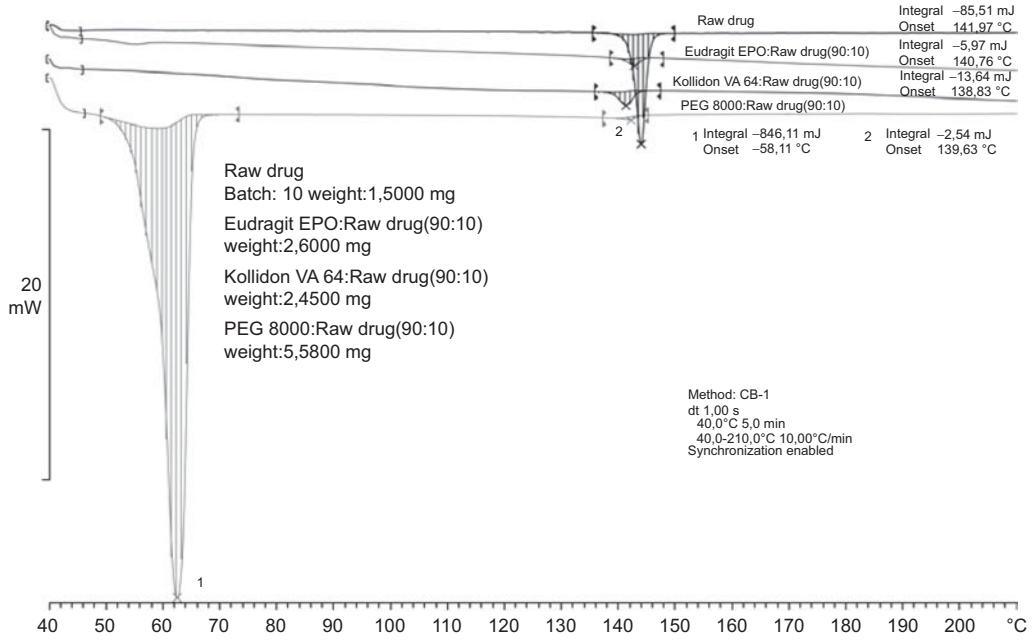

Figure 1. Differential scanning calorimetry analysis of the drug, the physical mixtures of raw drug and polymer, proportion (10:90), Eudragit E: raw drug, Kollidon VA64: raw drug, PEG 8000:raw drug.

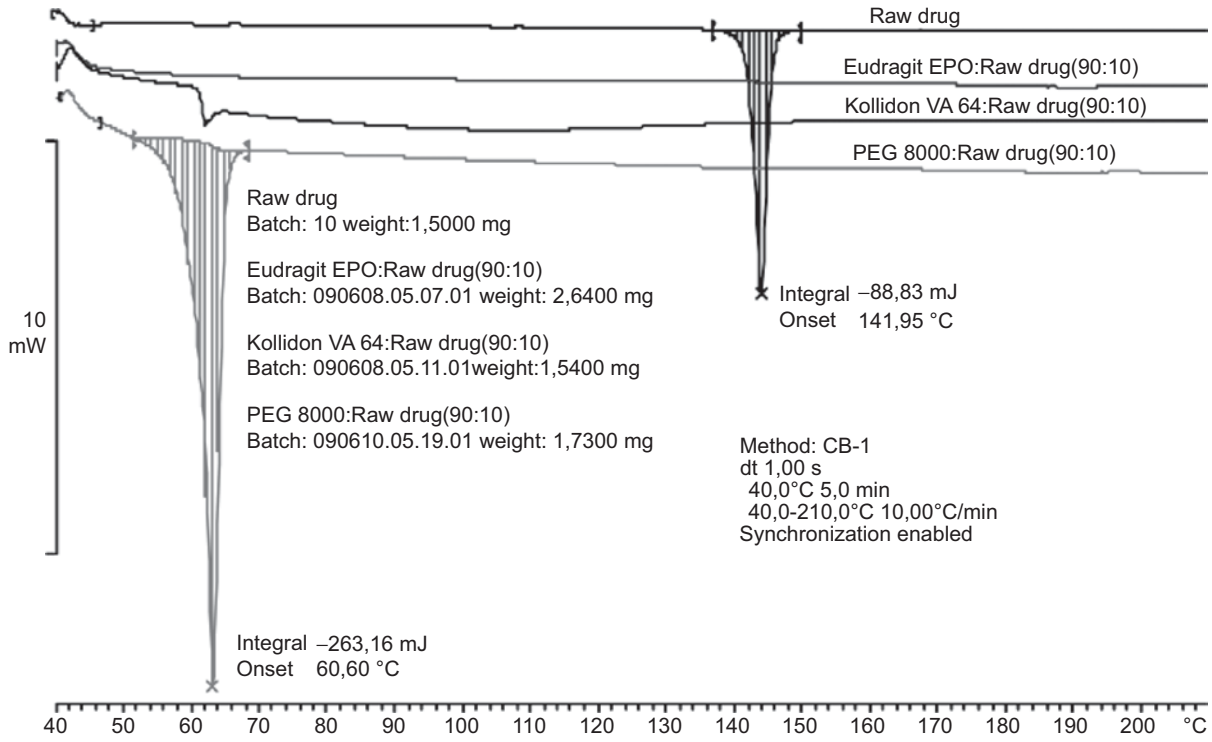

Figure 2. Differential scanning calorimetry analysis of drug and hot-melt extrusion formulations, proportion (10:90): Eudragit E: raw drug, KollidonVA64: raw drug and PEG 8000: raw drug.

composed by PEG 8000 showed an intermediate drug release rate, while kollidon VA 64 only released approximately 50% of drug after 10 min. The drug substance powder showed a slow dissolution rate with 53% of the drug released at 60 min. The HME formulations improved 1.7–1.8-fold the drug release rate of drug at 60 min.

The solubility of drug in acidic medium is very low (1.5–3.6 μg/mL), therefore is reasonable to suppose that an oral formulation must supersaturate the dissolving medium in GI tract in order to produce sufficient dissolved drug in GI fluids to be absorbed. In order to evaluate and mimic the *in vivo* conditions, the performance of supersaturated conditions was checked.

The results of the dissolution testing from milled powders at supersaturated and non-sink conditions with the drug and the HME formulations are shown on Figure 4.

The formulation containing the polymer Kollidon VA64 and Eudragit E exhibited rapid drug release; more than 80% is delivered during the first 10 min following the 100% of the drug release at 60 min. The formulation composed by PEG 8000 delivered 43% of the drug at 60 min.

The drug substance showed a slow dissolution rate approximately 3% of the drug was dissolved at 60 min. The HME formulations improved drug release rate from 14-fold for the PEG 8000 formulation to 35-folds drug solubility of drug at 60 min for the formulations composed by Kollidon VA64 and Eudragit E

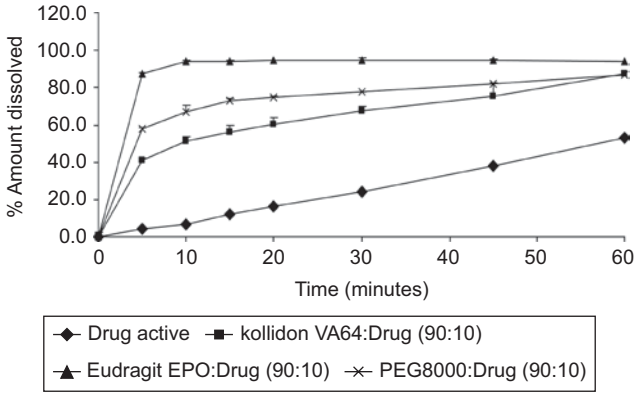

Figure 3. Dissolution profiles of drug and hot-melt extrusion formulations in HCl 0.1N 0.1% sodium lauril sulfate. 1000 mL volume, 50 rpm speed. (Media of $n = 4$.)

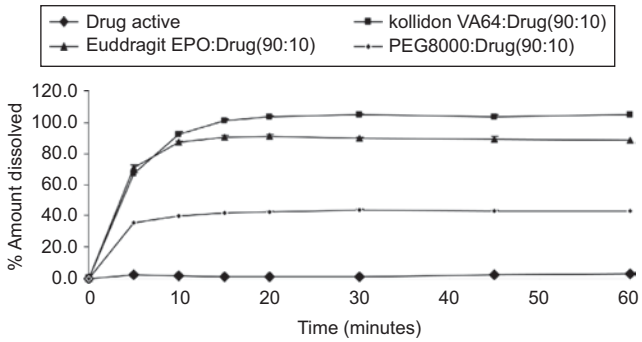

Figure 4. Dissolution profiles at supersaturated conditions of drug and hot-melt extrusion formulations in HCl 0.1N. 1000 mL volume, 50 rpm speed. (Media of $n = 4$.)

The enhanced dissolution performance in both sink and non-sink conditions achieved by polymers such Eudragit E and Kollidon VA64 vs drug can be attributed to the solubilization effect of the carrier and the improved wettability of drug from the carrier. All these characteristics make HME process be a promising platform to enhance absorption of poorly soluble drugs.

Oral pharmacokinetics in rat of Eudragit E formulation

The results obtained after the oral administration of the HME formulation prepared with Eudragit E (10:90) compared with oral and intravenous administration of the drug substance are shown on Table 4 and Figure 5. Faster and higher exposure rate in terms of t_{max} and C_{max}, respectively, were observed for HME formulation. Moreover, a significant increase of about three times in the total exposure extent (AUC_{0-t}) was observed, when HME formulation of Eudragit E was administered ($P = 0.05$). Similarly, a bioavailability increase from 3.5 to 12 was found when comparing the suspension and the HME formulation to the intravenous route.

Stability studies

The extrudate powders remained in the original shape and integrity without noticing any visual changes. The moisture absorption showed that the K*F*% was important for Kollidon VA64 which increased from 0.5 to 3.75% and limited for Eudragit E and PEG 8000 with individual K*F* values < 1%. DSC thermograms obtained from HME formulations did not show any recrystalization of the drug. However, in the thermogram of the HME powder composed by PEG 8000 is detected an increase of the melting energy for the polymer PEG 8000 initially 133 j/g and after accelerated storage 166 j/g. This data might indicate that a fraction of PEG 8000 is recrystallizing and there is less amount of polymer available to enhance drug dissolution also it s decreasing the mobility of drug molecules inside the polymer network. High-performance liquid chromatography analysis method of the extrudate powders was performed after 15 days stored at the aforementioned conditions. The drug content remaining in the powders is maintained constant without changes see Figure 6, and there was not a significant increase in degradation products in the extrudate powders results see Figure 7, due to the high thermal stability

Table 4. Pharmacokinetic data from the *in vivo* absorption study of HME formulation and pure drug substance.

				Pharmacokinetic parameters							
				$t_{1/2}$	t_{max}	C_{max} [a]	AUC_{0-t}	$AUC_{0-\infty}$	V_d [b]	Cl[c]	F[d]
Route	Sex	Dose (mg/kg)	Formulation	(h)	(h)	(ng/mL)	(ngh/mL)	(ngh/mL)	(l/kg)	(l/h/kg)	(%)
po	Male	20	Suspension	NC	6	102.8	374.2	NC	NC	NC	3.5
po	Male	20	HME	5.3	4	289.4	1276.8	1307.3.3	116.2	15.3	12
Iv	Male	1	Solution	8.2	—	828.5	533.6	558.7	21.1	1.8	—

[a]C_o for intravenous; [b]V_d/F for oral; [c]CUF for oral; [d]Absolute bioavailability estimated from AUC_{0-t}.
AUC, area under the plasma concentration-time curve; HME, hot-melt extrusion; NC:Not calculated.

and short residence time. A comparison of the release profiles at supersaturated conditions between initial and after 15 days stored at open dish are shown on Figure 8. In view of the results obtained after accelerated stability at opened dish 15 days at 40°C/75%HR. Formulations composed by Eudragit E and PEG 8000 showed a significant ($P < 0.05$) slower release profile at every time single time point, In the formulation containing Kollidon VA 64, there was no significant ($P > 0.05$) changes observed since amounts dissolved of drug vs time (min) were maintained. The statistical results for each HME formulation are shown on Figures 9, 10, and 11.

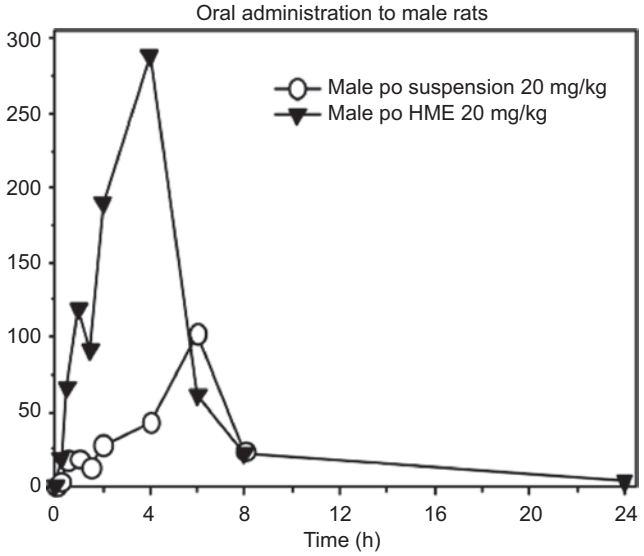

Figure 5. Comparative plasma concentration levels (ng/mL) achieved in male Wistar–Hannover rats of hot-melt extrusion formulation selected and drug.

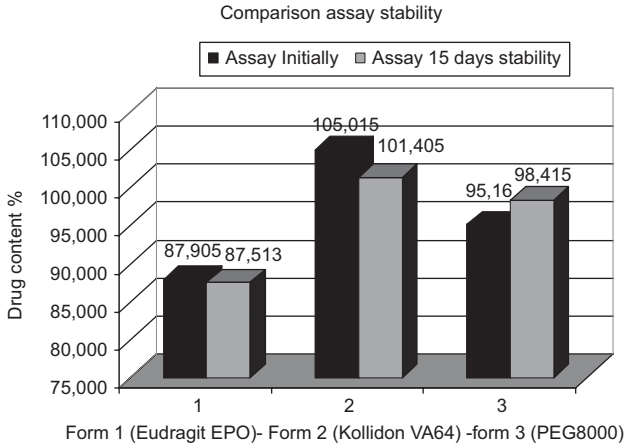

Figure 6. Results media of assay drug content (%) initially and after 15 days stability at 45°C/75%HR. ($n = 2$.)

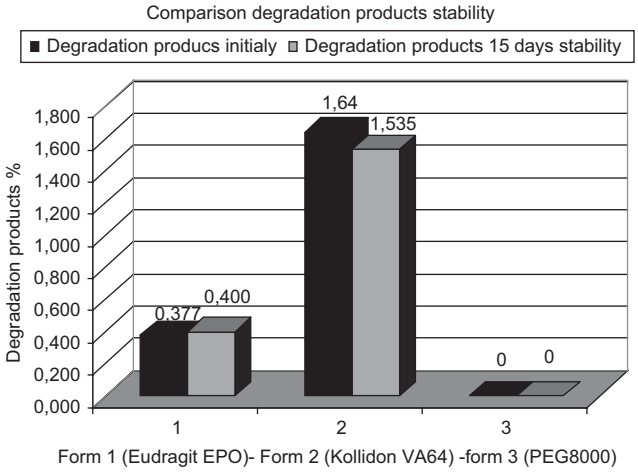

Figure 7. Results media of degradation products (%) initially and after 15 days stability at 45°C/75%HR. ($n = 2$.)

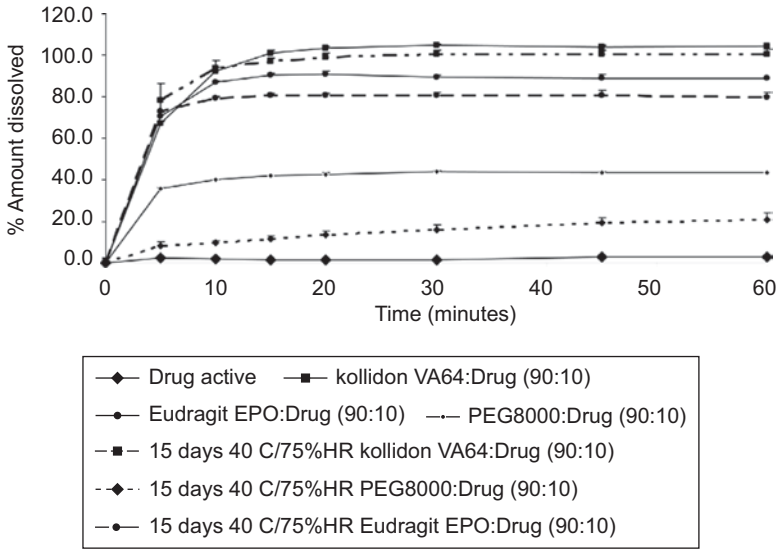

Figure 8. Comparison of the dissolution profiles at supersaturated conditions between the drug and the hot-melt extrusion formulations in HCl 0.1N. 1000 mL volume, 50 rpm speed. (Media of $n = 4$) after 15 days at opened dish conditions at 40°C/75% HR.

Results for statistical analysis ANOVA. Formulation kollidon VA64:Drug (90:10)

					95% interval confidence	
Formulation	Time (min)	Number	Mean(FD%)	Std.Error	Lower limit	Upper limit
initial	10	4	87.00	1.6	86.42	94.28
15 days	10	4	90.35	1.6	83.06	90.93
initial	15	4	95.20	0.85	93.11	91.28
15 days	15	4	93.67	0.85	91.59	95.76
initial	20	4	97.57	0.99	95.14	101.01
15 days	20	4	95.52	0.99	93.09	97.96
initial	30	4	96.60	0.98	96.20	101.00
15 days	30	4	96.90	0.98	94.50	99.30
initial	45	4	97.80	0.96	95.43	100.17
15 days	45	4	96.67	0.96	94.43	99.04
initial	60	4	98.50	1.12	95.75	101.24
15 days	60	4	96.95	1.12	94.20	99.69

Figure 9. Results of the analysis of variance obtained at *in vitro* supersaturated conditions after 15 days at opened dish conditions 40°C/75%HR ($n = 4$). Formulation Kollidon VA64:drug.

Results for statistical analysis ANOVA. Formulation kollidon VA64:Drug (90:10)

					95% interval confidence	
Formulation	Time (min)	Number	Mean(FD%)	Std.Error	Lower limit	Upper limit
initial	10	4	97.97	0.84	95.93	100.02
15 days	10	4	90.72	0.84	88.68	92.77
initial	15	4	101.55	0.81	99.58	103.52
15 days	15	4	92.28	0.81	90.34	94.52
initial	20	4	102.15	0.84	100.10	104.2
15 days	20	4	90.20	0.81	90.15	94.25
initial	30	4	100.87	0.97	98.02	103.25
15 days	30	4	92.40	0.97	90.02	94.25
initial	45	4	100.25	1.26	97.15	103.34
15 days	45	4	92.30	1.26	89.21	95.39
initial	60	4	99.97	1.34	96.68	105.36
15 days	60	4	91.35	1.34	88.06	94.64

Figure 10. Results of the analysis of variance obtained at *in vitro* supersaturated conditions after 15 days at opened dish conditions 40°C/75%HR ($n = 4$). Formulation Eudragit E:drug.

Results for statistical analysis ANOVA. Formulation PEG8000:Drug (90:10)

					95% interval confidence	
Formulation	Time (min)	Number	Mean(FD%)	Std.Error	Lower limit	Upper limit
initial	10	4	41.95	0.46	40.81	43.09
15 days	10	4	9.95	0.46	8.81	11.09
initial	15	4	44.20	0.61	42.69	45.70
15 days	15	4	11.93	0.61	10.42	13.43
initial	20	4	44.95	0.66	12.29	15.56
15 days	20	4	13.93	0.66	43.31	46.58
initial	30	4	46.30	0.87	44.14	48.45
15 days	30	4	16.37	0.87	14.22	18.50
initial	45	4	45.85	1.12	43.36	48.34
15 days	45	4	19.75	1.12	16.98	21.97
initial	60	4	45.65	1.32	42.43	48.87
15 days	60	4	21.17	1.32	17.95	24.39

Figure 11. Results of analysis of variance obtained at *in vitro* supersaturated conditions after 15 days at opened dish conditions 40°C/75%HR ($n = 4$). Formulation PEG 8000:drug.

Conclusions

According to the results obtained solids solutions of CB-1 antagonist and the polymers, Eudragit E, PEG 8000 and Kollidon VA can be prepared successfully at 10% of drug loading by HME process.

The polymers Eudragit E, Kollidon VA 64, and PEG 8000 showed miscibility with the drug substance as predicted by Hansen solubility parameter values and as is indicated in the Initial DSC studies and after forced stability at conditions 40°C/75%HR.

An increase in aqueous solubility was observed for the CB-1 antagonist solid solutions prepared by hot-melt. Dissolution performance at sink conditions and non-sink conditions revealed from HME formulations much improved drug dissolution comparing with raw drug.

A faster rate and a higher extent of CB-1 antagonist exposure in rats was found when orally administering the HME formulation selected respect to the drug substance, reinforcing results obtained from *in vitro* test.

Results from the stability study at 40°C/75%HR during 15 days proved partial conversion to crystalline state of PEG 8000 resulting in a decrease of amount dissolved vs time. The HME formulation composed by Eudragit E showed after stability a slight decrease of the release profile the reason of this effect may be due to that not all the hydrogen bondings are formed directly after extrusion leading to a stronger bonding between drug and polymer chains.

It was observed that Kollidon VA64 keeps the drug dissolved within the polymer and maintains the release profile at non-sink conditions.

The results of these studies suggest that it is possible to develop a HME formulation which increases the drug solubility of an antagonist CB-1, which may be a potential solid dosage form for the treatment of weight management, overweight and obesity.

Acknowledgments

The authors would like to thank all the people who have collaborated in the performance of this article either all people involved directly or indirectly in the project and especially the people part of preformulation area for their ability, effort and dedication. Andreas and Catherine from Evonick Gmbh for their collaboration.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. All the experimental has been done in ESTEVE lab.

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