

# Release of Ropinirole from Acrylate-Vinylacetate Transdermal Formulations: Modulation Based on Polymer-Drug Interactions <sup>†</sup>

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**Abstract:** Optimization of transdermal formulations requires solving simultaneous challenges as the selection of release polymers. The interactions between the formulation components must be taken as a way to modulate its performance. Selection of acrylic polymers with different functionalizations for the transdermal formulation of a tertiary amine drug (ropinirole HCl) have been investigated. Aim of this work is to characterize the influence over drug release of certain experimental interactions. Solubility-crystallization and pharmacopoeial release tests have been used to evaluate the influence of drug loading and the pH of the release media. Area under the curve of dissolved amounts and percentage of release have been used as discriminant variables in mutual influence with the physical state of the drug. Elucidation of release mechanisms has been performed with data fitting of relevant modelistic equations. Fickian release and erosion contribution have been related with drug loading and the risk of burst effects. In conclusion, a rationale to select the best suitable polymer for ropinirole HCl has been demonstrated in terms of efficiency and extent of release.

**Keywords:** ropinirole; transdermal; acrylate-vinylacetate copolymer

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## 1. Introduction

Formulation of transdermal patches is challenging. In addition to an acceptable tolerability and suitable skin adhesion, the selection of an adequate modified release polymer is a crucial parameter to achieve the expectable release profiles of drug and, if present, its associated enhancers [1]. Acrylic copolymers have suitable solubility characteristics for a wide range of drugs, and are common adhesives in many transdermal formulations. They are very well tolerated on the skin and can painlessly be removed with cohesion from hairy skin. Although its potential adhesivity is lower than that of rubbers, they have largely replaced polyisobutylenes because their properties remain stable over a wide range of temperatures achieving a very high storage stability [2]. In this sense, different preformulated grades of acrylates are commercially available having different functional to modulate the formulations, particularly the required balance between release and retention of the drug.

Drug solubility in the polymer is a limitant factor to maximize the transdermal concentration gradient. This measurement is not easy to standardize and this information is difficult to find in the literature and probably not comparable between different papers.

Sachdeva et al. (2013) [3] calculated this value as the highest concentration without crystallisation after a stability stress. Jenquin and McGinity (1994) [4] performed measurements by differential scanning calorimetry (DSC) and certain companies offer a user friendly database [5] for a rapid estimation of solubilities in their copolymers.

In addition to the solubility, it is also interesting to know the individual interactions between the drug and the coating radicals of the copolymer. In fact, the over-saturation degree induces unpredictable burst effects that difficult the achievement of a reproducible release and the mutual interactions in the formulation environment (e.g., ionic binding, Van der Waals) have to be investigated in a case-by-case basis.

In this study, chemical interactions between different acrylates and ropinirole, a drug used to treat parkinsonism have been investigated for a set of model-formulations using pharmacopoeial App. V release tests and solubility informations. Ropinirole ClH (CAS: 91374-20-8) is a zwitterionic molecule with acceptable biopharmaceutical properties for transdermal administration (log P = 3.16, molecular weight 260.37, bioavailability around 50%). It has also a remarkable water solubility and pKa values of 6.64 and 10.28 [6]. Nowadays it is used in therapeutics as a modified release oral product and is a reasonable candidate for transdermal administration.

In this work, release results have been parametrized under different approaches to allow a rational selection of the best type of acrylate for an efficient drug release and to provide information to apprehend the rationale of its drug formulation.

## 2. Material & Methods

### 2.1. Experimental

#### 2.1.1. Preparation of Formulations

A series of transdermal laminations were prepared with an own-laboratory developed cast-moulding device considering the following variables: type of polymer, drug proportion and pH of release media. Ropinirole HCl was a gift from Disproquima (Barcelona, Spain). Ethylacetate, absolute ethanol were purchased to Scharlab SL (Spain). Three pressure sensitive adhesives: carboxylic and hydroxylic acrylate-vinylacetates (DuroTak 87-2051 and 87-4287) and a carboxylic acrylate (DuroTak 87-2353) named (DT51, DT87, and DT53 onwards) currently available from Henkel Gmbh (Kirchhundem, Germany) were used. A 100 µm polyester foil was used as backing liner. A fluoropolymer protected polyester, Scotchpak 1022 from 3M (Saint Paul, MN, USA) was used as release liner.

Theoretical ropinirole solubilities in polymer were predicted from a commercial database [5]. The three different acrylate polymers were formulated with three concentration levels of ropinirole. Formulations were prepared by dispersing, in a closed vial under continuous stirring, the drug in ethylacetate and then adding the required amount of DuroTak dispersion until homogeneity (30 min). Laminar extensions were obtained by mould-casting and the volatile content was slowly evaporated with thermoelectric progressive heating until 50 °C during 60 min. [1,7,8]. Thermogravimetric analysis confirmed the absence of any residual content and, so, formulation curing. Afterwards, the adhesive side of the lamination was protected with a siliconized release liner and punched out in circles. Individual thickness and weight were reported to accurately estimate the individual drug dose and specimens were hermetically stored until investigation of drug release from each formulation.

#### 2.1.2. Optical Microscopy

A polarized light monocular microscope (Nikon, model S-P0, Barcelona, Spain) was used to inspect the formulations at 400×. A minimum of ten fields were observed and representative photographs were recorded.

### 2.1.3. Drug Release

Pharmacopoeial Apparatus V (Erweka DT 80, Gomensoro, Madrid, Spain) was used to investigate in quadruplicate ropinirole release for 36 h at pH 6 or pH 10 with 500 mL glycine buffer solution [9] satisfying sink conditions. Twelve 5 mL samples from each vessel were taken at times of 0 h, 0.5 h, 1 h, 2 h, 4 h, 8 h, 12 h, 18 h, 24 h, 30 h, 34 h and 36 h with immediate buffer replacing. Samples were placed in a stoppered test tube and drug concentrations were estimated by UV-spectrophotometry (Cary 60 UV-VIS, Agilent, Santa Clara, CA, USA), taking advantage of the maximum absorbance peak of Ropinirole at 250 nm.

### 2.2. Release Parameters

Release profiles were plotted previously to parameter calculation. All individual curves were described with amodelistic parameters to perform an homogeneous statistical comparison. Additionally, different release equations were fitted under the hypothesis that release results could be affected by polymer erosion and/or nonocclusion of drug (burst effect).

#### 2.2.1. Descriptive and Explicative Parameters.

Percentage of dissolved drug at 24 h (Q24) and area under the curve of released quantities (AUCq) were calculated for all replicates. Apart from the foregoing, release equations were fitted by non-linear regression. The following equations of time-dependent released drug fractions were fitted: Higuchi (Equation (1)), Higuchi F<sub>0</sub> (Equation (2)), Pepsas-Sahlin 0.5 (Equation (3)), First order-Fmax (Equation (4)) [10–13] using non-linear regression (DDsolver) [14].

$$F = kH * t^{0.5} \tag{1}$$

where kH is the Higuchi release constant.

$$F = F_0 + kH * t^{0.5} \tag{2}$$

where kH is the Higuchi constant and F<sub>0</sub> is the initial drug fraction in solution generated by a burst release.

$$F = k_1 * t^{0.5} + k_2 * t \tag{3}$$

where k<sub>1</sub> is the constant about the relative contribution of drug diffusion to drug release and k<sub>2</sub> is the descriptive constant of the time-dependent polymer relaxation. The exponents were the proper values for laminar formulations

$$F = F_{max} * [1 - \text{Exp}(-k_1 * t)] \tag{4}$$

where F is the released drug fraction, k<sub>1</sub> is the first-order constant and F<sub>max</sub> is the maximum released drug as time infinite.

#### 2.2.2. Model Selection

Selection of the best-model was based on the observation of graphical plots, the best adjusted determination coefficient (Rsqr max), Akaike information criterion (AICmin) and subrogated Model selection criterion (MSCmin) given by the program. The best-fit equation was reported for each set of replicates.

In cases where Equation (3) was the best descriptive function, Equation (5) was used to describe the exponential reduction of the fickian component [12]:

$$F = 1/(1 + ((k_2/k_1) * tm)) \tag{5}$$

Description of the erosive contribution was achieved by graphical comparison of the corresponding plots of the mean values of each set of four replicates.

### 2.2.3. Comparison of Release Parameters

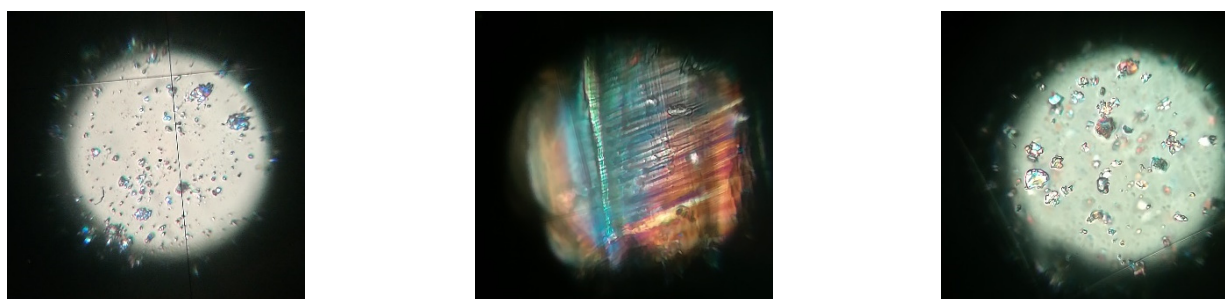
Comparison of the different sets of results was performed, at first, by grouped graphical plotting, an ANOVA of AUC<sub>q</sub> and Q24 series (SPSS v.26), and searching for the majoritary equation with the lowest AIC value in each group of replicates.

## 3. Results

### 3.1. Solubility Data

All predicted solubilities of ropinirole in polymer were below 1% (w/w) and in the following rank: DT51 ≥ DT53 > DT87. Both carboxylic acrylates achieved similar levels, being higher than for the hydroxilic one (DT87). Then, all formulations were prepared above their respective solubilities.

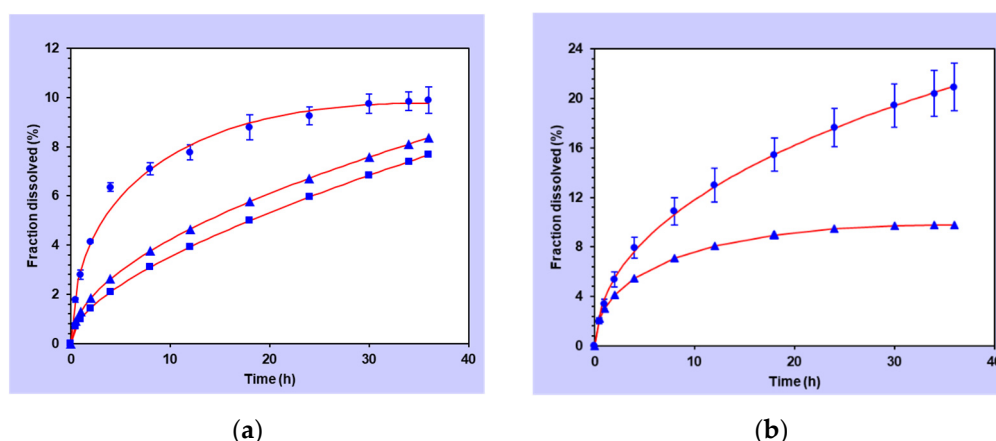
After curing, formulations were inspected under a microscopy with polarized light. Crystalline residues below 35 μm were observed. No differences seemed to be detected between DT51 and DT87 in the mean number of insoluble particles per field. In case of DT53, a conoscopic refringence was observed. Illustrative images are depicted in Figure 1.



**Figure 1.** Optical microscopy with polarized light. 5% formulations with DT51, DT53 and DT87 (left, center and right respectively).

### 3.2. Release Results

Results were plotted grouped by experimental sets. A representative plot of different results is reported in Figure 2.



**Figure 2.** Observed and predicted release profiles (with Peppas-Sahlin equation) of Ropinirole with DT53. (a) Profiles at pH 6 from 10% (circle), 5% (triangle) and 1% (square) formulations; (b) Profiles of 10% formulation at pH 6 (triangle) and pH 10 (circle). Standard deviations are indicated for the fastest profiles.

### Release Parameters

Mean and SD results of AUC<sub>q</sub> (until 36 h) and Q24 for each set of replicates are summarized in Table 1. The highest release values were achieved with DT53.

**Table 1.** Amodelistic release parameters in the different conditions.

Polymer	Drug Concentration	pH	AUCq(36 h)	SD <sub>AUC</sub>	Q24	SD <sub>Q24</sub>
DT51	1%	6	4010.31	461.97	7.25%	0.65
	5%	6	4257.70	2263.93	1.37%	0.70
	10%	6	6519.53	1202.29	0.92%	0.24
DT51	1%	10	4250.77	1334.82	5.66%	1.35
	5%	10	5096.31	998.21	1.88%	0.43
	10%	10	9797.59	1113,25	1.67%	0.28
DT53	1%	6	2465.69	240.98	6.08%	0.92
	5%	6	13,838.46	1100.00	6.11%	0.27
	10%	6	45,965.68	2346.86	9.26%	0.35
DT53	1%	10	6439.40	1672.07	14.45%	2.81
	5%	10	26,764.40	1395.65	12.79%	0.85
	10%	10	79,751.50	3268.24	17.66%	1.55
DT87	1%	6	4470.79	1718.34	9.27%	2.76
	5%	6	13,205.45	646.84	5.36%	0.64
	10%	6	15,313.37	4873.60	3.83%	1.65
DT87	1%	10	4151.08	835.52	8.63%	1.06
	5%	10	12,706.81	1134.98	5.64%	1.49
	10%	10	13,022.45	3014.94	2.75%	0.80

Concerning the Anova for parameter comparisons, results of the statistical significances of F are summarized in Tables 2 and 3.

**Table 2.** Effects of pH on release profiles considering amodelistic parameters. Stastitcal probabilities (significances in bold).

Polymer	AUCq			Q24		
	1%	5%	10%	1%	5%	10%
DT51	$7.45 \times 10^1$	$5.23 \times 10^1$	<b><math>7.11 \times 10^3</math></b>	$1.04 \times 10^1$	$2.63 \times 10^1$	<b><math>6.79 \times 10^3</math></b>
DT53	<b><math>3.31 \times 10^3</math></b>	<b><math>6.62 \times 10^6</math></b>	<b><math>2.85 \times 10^6</math></b>	<b><math>1.31 \times 10^3</math></b>	<b><math>5.51 \times 10^6</math></b>	<b><math>4.26 \times 10^5</math></b>
DT87	$7.49 \times 10^1$	$4.74 \times 10^1$	$4.54 \times 10^1$	$6.80 \times 10^1$	$7.39 \times 10^1$	$2.84 \times 10^1$

**Table 3.** Effects of drug loading on release profiles considering amodelistic parameters. Stastitcal probabilities (significances in bold).

Polymer	AUCq		Q24	
	pH6	pH10	pH6	pH10
DT51	$8.03 \times 10^2$	<b><math>1.65 \times 10^4</math></b>	<b><math>1.10 \times 10^4</math></b>	<b><math>1.27 \times 10^4</math></b>
DT53	<b><math>4.29 \times 10^{11}</math></b>	<b><math>1.66 \times 10^{11}</math></b>	<b><math>5.78 \times 10^5</math></b>	<b><math>1.67 \times 10^2</math></b>
DT87	<b><math>1.49 \times 10^3</math></b>	<b><math>1.48 \times 10^4</math></b>	<b><math>7.63 \times 10^3</math></b>	<b><math>1.83 \times 10^4</math></b>

Results in Table 1 point to the effects of pH on both carboxylic acrylates (DT51 and DT53) accounting for higher values of AUCq and Q24 at pH10 than in pH6. This effect was more pronounced in absence of vinylacetate. Statistical significance (Table 2) is achieved in all cases concerning DT53 and only in DT51 high load.

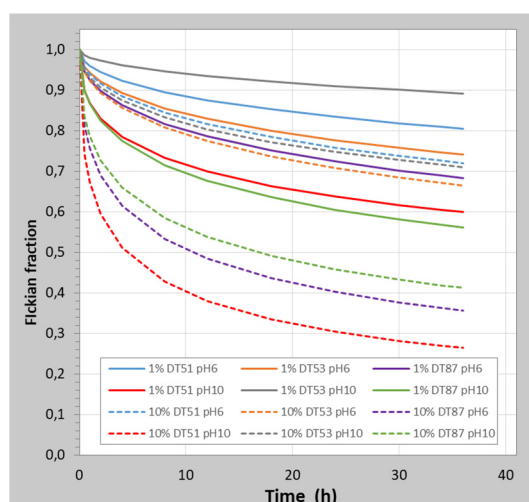
Concerning model fitting, MSC results were concordant with AIC comparison without any additional descriptive information so, being parsimonious, all the model selections were primarily based on AIC as summarized in Table 4.

**Table 4.** Best descriptive equations for each set of replicates based on AIC values. (H: Higuchi, HF<sub>0</sub>: Higuchi with F<sub>0</sub>, PS: Peppas Sahlin 0.5).

Polymer	pH6			pH10		
	1%	5%	10%	1%	5%	10%
DT51	HF <sub>0</sub>	PS	HF <sub>0</sub>	HF <sub>0</sub>	PS	PS
DT53	HF <sub>0</sub>	PS	PS	PS	PS	PS
DT87	PS	H	PS	PS	H	PS

This discrimination pointed to Peppas & Sahlin (1989) equation (Equation (3)) as the best descriptive equation for the acrylate DT53 profiles except for the lowest concentration at pH 6.0. The acrylate-vinylacetates exhibited a lower release, and Higuchi-F<sub>0</sub> was more descriptive than PeppasSahlin if remarkable burst effects were present. Therefore, Higuchi-F<sub>0</sub> tended to be best descriptive for the highest drug concentrations in the more retentive copolymers, probably with lower solubilities than DT53. In fact, burst release was higher with DT51, the most retentive acrylate, than for the others.

Based on the parameters of Peppas-Sahlin, the main effect on the Fickian and non-Fickian release was observed between different drug load levels (see Figure 3). No differences were observed between pH values for the same formulation.



**Figure 3.** Loss of fickian diffusion along the experimental time for all the formulations at the minimum and the maximum drug load. Continuous lines: 1% load, Discontinuous lines: 10% load.

#### 4. Discussion

##### 4.1. Drug Solubilisation

Inspection with optical microscopy confirmed the presence of crystals in the dispersions based on acrylate-vinylacetate copolymer. Crystals sizes fall in the same range of the chemical specifications of the raw material without growing habit, suggesting that no intermediate solubilization in ethylacetate had been achieved during the formulation process. In case of the acrylic polymer (DT53) a pseudo-dissolution of the drug in the polymeric matrix suggests a significantly higher solubilisation than with copolymer DT51 although numerical predictions of solubility are similar. Actually, the database prediction is poorly discriminant because it is only made according to the logP and water solubility of the drug.

##### 4.2. Effect of Formulation Variables on Ropinirole Release

Concerning the effect of pH, the interaction of ropinirole (a 3<sup>ary</sup> amine), with the carboxylic polymers (DT51 and DT53) has been clearly assessed. Among both polymers the effect was more remarkable with DT53, free of vinylacetate, given the insolubility of this

monomer that increases the retention of the drug in absolute terms. No significant differences were found with DT87, which is an only-hydroxylic copolymer and, thus, non pH-sensitive although the drug is ionized and non-ionized, at each respective pH. As a whole, the relevance of the interaction between the drug and the carboxylic radicals of the polymer is shown to be higher than the mere effect of changing the ionization state of the drug and, thus, its own solubility. In this sense, the addition of minor components in the formulation to modify the environmental pH can be used to future optimization of the release profile of the drug.

With regard to drug loading, no formulation is a solid solution [4]. Statistical differences are found in practically all cases (see Table 3). In this sense, there are two main aspects to discuss. Differences in AUC<sub>q</sub> express the extent of release, that is higher as higher is the drug loading, although not linearly proportional in case of the more retentive formulations. Additionally, the percentages Q<sub>24</sub> are indicative of the efficiency of the formulation and the value at 24 h is more discriminant of the shape of the curve than the value at last time (36 h). As an example, Q<sub>24</sub> values of the 1% replicates are higher than the respective values at 10% and the absolute released amounts (although statistically different) tend to be closer to each other than it might seem at first. Therefore, exploitation of drug is better at low drug loading levels if using retentive polymers (DT87 and DT 51) and practically similar with the three formulations with DT53. This polymer achieves the highest extent and efficiency of drug release (14.97% if considered as a whole), releasing the drug proportionally to its drug loading.

#### 4.3. Descriptive Equations of Ropinirole Release from the Formulations

Considering, at first, the formerly discussed microscope observations, release kinetics with crystal-containing formulations (DT51 and DT87) cannot follow a first order release but with a pseudo square root component. Release equations 1 to 4 were selected to hypothesize the mechanism of release and to scrutinize the influence of polymer erosion and/or the relevance of non-occluded drug (burst effect) in the drug release profiles.

DT53, the less-retentive copolymer is a carboxylic acrylate without vinylacetate. At pH10, the tertiary amine of RP is not ionized and, conversely, it is fully ionized at pH6. In addition to the solubilisation properties of the polymer, and based on the interaction of -COOH functional groups with amine-containing compounds through hydrogen bonding [15], the influence of pH becomes useful to modulate the rate and extent of its in vitro release.

In general terms, fitting of release-indicating equations to experimental results has confirmed previous hypothesis about expectable interactions between this basic drug and the acrylate polymers when formulated in transdermal dried laminations. The physico-chemical properties of ropinirole and the experimental study conditions can play a useful role to modulate its release profile.

## 5. Conclusions

During the development of a transdermal formulation of Ropinirole, the presence of an interaction between the drug and the acrylic polymers is found. Carboxylic polymers provide pH-dependant release properties while hydroxyl polymers not. The comonomer vinylacetate reduces the release rate of the drug. Resulting drug release with “retentive” polymers is similar regardless drug loading and the highest efficiency with these formulations is achieved at a low drug loading. Acrylic polymers without vinylacetate achieved the highest drug solubilisation and, thus, release extent providing the release of ca. 15% of drug loading.

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