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Release of ropinirole from acrylate-vinylacetate transdermal formulations: modulation based on polymer-drug interactions

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INTRODUCTION

Optimization of transdermal formulations requires simultaneous challenges to be solved as the selection of release polymers. Ropinirole HCl(CAS: 91374-20-8) is a zwitterionic molecule with acceptable biopharmaceutical properties for transdermal administration. It has a remarkable water solubility and pKa values of 6.64 and 10.28, also a low molecular weight of 260.3746 g/mol [1]. In general terms, fitting of release-indicating equations to experimental results is a predictive description of expectable interactions between the physicochemical properties of ropinirole and acrylate polymers in transdermal dried laminations. Considering that it is known that PSAs with -COOH functional group are known to interact with amine containing compounds through hydrogen bonding between the -COOH and the amino group of APIs reducing their skin permeation [2].

PURPOSE

A series of transdermal formulations were prepared with different acrylates (DuroTak 87-2051, 87-4287 and 87-2353) to check the interactions with the different functional groups of the polymers, check the effect of drug saturation in the polymer, as well as the influence of the polarity of the formulation environment on the properties of drug retention applying the pharmacopoeia release test for transdermals.

METHODS

Preparation of transdermal formulation

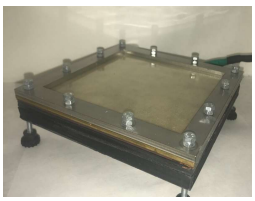


Figure 1. *Laboratory-developed cast-moulding device.*

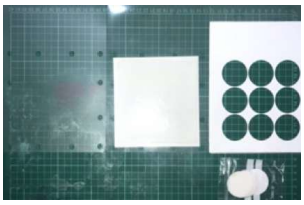


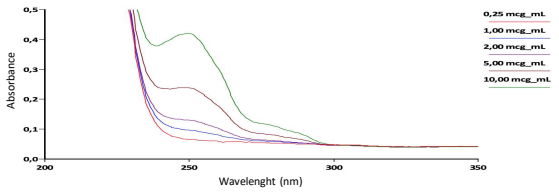
Figure 2. Manufacturing sequence. (Lamination, protection and cutting of the patches).

Figure 3. *Batch replicas mounted on the SSDA.*

Figure 4. Detail of the vessel on top of the SSDA.

Drug-Polymer suspensions were laminated and the solvent evaporated by bottom-heating at 50°C for 60 minutes. Once dried and cold, the adhesive surface was covered with a siliconized liner and die-cut to obtain the batch of patches.

Dissolution test (Apparatus V)



Graph 1. Graph where the absorbance peak is appreciated as well as the higher the absorbance concentration.

Using an Erweka DT-80 dissolution apparatus, the release test is performed by placing the patches in a modified stainless steel disk assembly (SSDA) to attach the patches to the disk without additional adhesive. The SSDA holds the patch flat, with the release surface uppermost and parallel to the bottom of the paddle blade. A distance of 25 ± 2 mm between the bottom of the paddle blade and the surface of the SSDA is maintained during the test. We use 500 mL of buffer solution, taking samples every 0.5h, 1h, 2h, 4h, 8h, 12h, 18h, 24h, 30h, 34h and 36h. Take 5mL of sample and replace with new buffer. The samples are analyzed in an Agilent model Cary 60 spectrophotometer. A standard line of the active principle is made and the absorbance is read at 250nm to calculate the concentration.

RESULTS

Solubility data

After curing, formulations were inspected under optical microscopy with polarized light. Crystalline points 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 5.

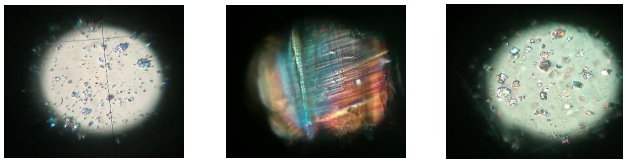


Figure 5. Optical microscopy with polarized light. 5% formulations with DT51, DT53 and DT87 (left, center and righty respectively)

Release results

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

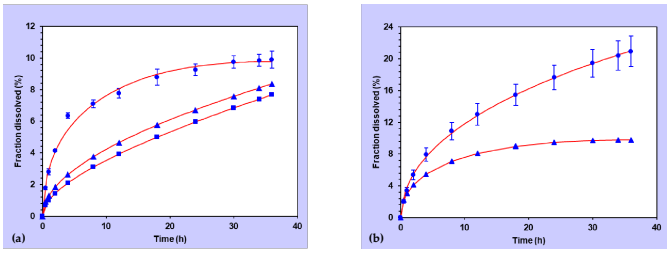


Figure 6. Figure 2. Observed and predicted release profiles (with Peppas-Sahlin equation) of Ropinirole with DT53. (a) Profiles at pH 6 from 10% (circle), 5% (triangle) and 1% (square) formulations; (b) Profiles of 10% formulation at pH 6 (triangle) and pH 10 (circle). Standard deviations are indicated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

Release parameters

Polymer	Drug concentration	pH	AUCq(36h)	Q24	SD_{Q24}
DT51	1 %	6	4010,31	7,25%	0,65
	5 %	6	4257,70	1,37%	0,70
	10 %	6	6519,53	0,92%	0,24
	1 %	10	4250,77	5,66%	1,35
	5 %	10	5096,31	1,88%	0,43
	10 %	10	9797,59	1,67%	0,28
DT53	1 %	6	2465,69	6,08%	0,92
	5 %	6	13838,46	6,11%	0,27
	10 %	6	45965,68	9,26%	0,35
	1 %	10	6439,40	14,45%	2,81
	5 %	10	26764,40	12,79%	0,85
	10 %	10	79751,50	17,66%	1,55
DT87	1 %	6	4470,79	9,27%	2,76
	5 %	6	13205,45	5,36%	0,64
	10 %	6	15313,37	3,83%	1,65
	1 %	10	4151,08	8,63%	1,06
	5 %	10	12706,81	5,64%	1,49
	10 %	10	13022,45	2,75%	0,80

Table 1. Amodelistic release parameters at the different conditions

Graphical comparison of the sets of results was performed previous to the ANOVA (SPSS v.26). Results of the statistical significance of F are summarized in Tables 2 and 3.

Polymer	AUCq			Q24		
	1%	5%	10%	1%	5%	10%
DT51	7,45E-01	5,23E-01	**7,11E-03**	1,04E-01	2,63E-01	**6,79E-03**
DT53	**3,31E-03**	**6,62E-06**	**2,85E-06**	**1,31E-03**	**5,51E-06**	**4,26E-05**
DT87	7,49E-01	4,74E-01	4,54E-01	6,80E-01	7,39E-01	2,84E-01

Polymer	AUCq		Q24	
	pH6	pH10	pH6	pH10
DT51	8,03E-02	**1,65E-04**	**1,10E-04**	**1,27E-04**
DT53	**4,29E-11**	**1,66E-11**	**5,78E-05**	**1,67E-02**
DT87	**1,49E-03**	**1,48E-04**	**7,63E-03**	**1,83E-04**

Tables 2-3. Comparison of the effect of pH (left side) and drug loading (right) for each polymer. Stastitical probabilities (significances in bold)

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. Statistical significance (Table 2) is achieved in all cases concerning DT53 and only in DT51 high load. This effect between pH6 and pH10 buffers was more pronounced in absence of vinylacetate.

Concerning model fitting, all the model selections were primarily based on AIC. This discrimination pointed to equation ($F = k_1 * t^{0.5} + k_2 * t$) as the best descriptive equation for the acrylate DT53 profiles except for the lowest concentration at pH6.0 The acrylate-vinylacetate exhibited a lower release, and Higuchi-F0 was more descriptive than PeppasSahlin if remarkable burst effects were present. Therefore, Higuchi-F0 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.

Polymer	pH6			pH10		
	1%	5%	10%	1%	5%	10%
DT51	HF0	PS	HF0	HF0	PS	PS
DT53	HF0	PS	PS	PS	PS	PS
DT87	PS	H	PS	PS	H	PS

Table 4. Best descriptive modelistic equation in all sets of experiments (H: Higuchi, HF0: Higuchi with F0, PS: Peppas-Sahlin 0.5)

CONCLUSIONS

During the development of a transdermal formulation of Ropinirole, the presence of an interaction between the drug and the acrylic polymers is found. Fitting of release-indicating equations to experimental results confirm its usefulness to describe the expectable interactions between the physicochemical properties of ropinirole and each acrylate polymer.

Carboxylic polymers provide pH-dependant release properties while hydroxyl polymers not. The comonomer vinylacetate reduces the release rate of the drug. Resulting drug releases is similar regardless drug loading and the highest efficiency with these formulations is achieved at a low drug loading. On the other side, acrylic polymers without vinylacetate achieved the highest drug solubilisation and, thus, release exent providing the release of *ca.* 15% of drug loading.

ACKNOWLEDGMENT:

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II. Ameen, D., & Michniak-Kohn, B. (2019). Development and in vitro evaluation of pressure sensitive adhesive patch for the transdermal delivery of galantamine: Effect of penetration enhancers and crystallization inhibition. European Journal of Pharmaceutics and Biopharmaceutics. https://doi.org/10.1016/j.ejpb.2019.04.008