

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	
László Ritter et al.	)	Group Art Unit: 1618
	)	
	)	Examiner: Westerberg, Nissa M.
Application No.: 16/425,028	)	
	)	
Filed: 05/29/2019	)	

Title: TOPICAL AMLODIPINE SALTS FOR THE TREATMENT OF ANORECTAL DISEASES

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION OF GENOVÉVA FILIPCSEI, Ph.D. UNDER 37 C.F.R. § 1.132

I, Dr. Genovéva Filipcsei, declare that:

1. A copy of my curriculum vitae is attached as Exhibit A.
2. Some of my formal education includes a MSc in chemistry specialized in colloid chemistry and a PhD in chemistry specialized in polymer sciences and physical chemistry.
3. As indicated in the attached *curriculum vitae* (Exhibit A), I have worked in the field of polymer chemistry and drug development for over 15 years and in the development of smart drug delivery systems and modification of the pharmacokinetic properties of poorly soluble drugs using nanotechnology at Budapest University of Technology and Economics for 10 years and a pharmaceutical company for 8 years.
 - a. I worked at Budapest University of Technology and Economics where I directed research between 1998-2008. I was an associate professor between 2007-2008. I gave lectures and led laboratory courses for the graduate students at the

university. I have been a member of more than 10 Ph.D. theses defense committees.

- b. I am the Chief intellectual property officer at NanGenex, Inc. that was formed to develop and commercialize novel formulations for poorly soluble drugs. Accordingly, I have a financial interest in the outcome in this matter.
4. As further indicated in the attached *curriculum vitae*, I have published multiple peer reviewed articles on drug delivery, and recently on continuous flow formulations that are the subject matter of the claimed invention.
5. Given my experience and education, I am qualified to testify as to at least the level of ordinary skill in the art of formulating poorly soluble drugs leading to improvements in pharmacokinetic properties.
6. Based on my education, background and experience as a chemist and inventor, I am aware of the literature in this area. In addition, I have read Twidwell et al. (US 2016/0129091), cited as art herein. I have reviewed the Office Action dated February 19, 2020.
7. I have overseen the preparation of formulations as taught in Twidwell containing emu oil for comparison to formulations of the pending claims. More specifically, the stability and in vitro permeability of Example 7 of the instant application (which uses propylene glycol as the penetration enhancer) was compared to a similar formulation using emu oil as the penetration enhancer, as described by Twidwell. The composition prepared based on Twidwell contained:

	Sample No.	
	#89	#90
pH	7	7
Component	Quantity (% w/w)	
Amlodipine besylate	0.14	0.14
Hydroxyethyl cellulose	2	2
Ethanol	9.6	9.6
Methyl parahydroxybenzoate	0.1	0.1
Glycerin	40	40
Propylene glycol	25	-
Emu-oil	-	25
Water	23.16	23.16

8. Topical pharmaceutical gel compositions were stored at different conditions in order to investigate their stability. After 3-day storage at 4°C, room temperature, and 40°C, phase separation was observed for the topical pharmaceutical compositions containing emu oil (Figure 1.). Similar phase separation was not observed for the topical pharmaceutical gel compositions containing propylene glycol.

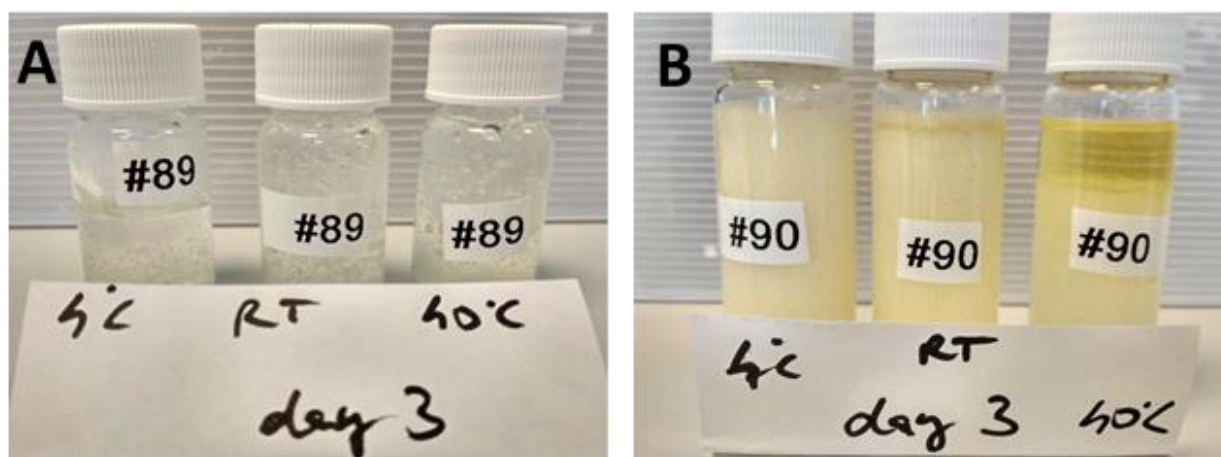


Figure 1. Visual stability observation of the topical pharmaceutical gels prepared using propylene glycol (A) or emu oil (B) as penetration enhancers.

9. The in vitro permeability of the topical gel compositions was tested as described in Example 6 of the instant application with one modification, the receiver compartment was pH=7.4 phosphate buffer saline. The formulation of Twidwell was compared to formulations of the pending claims (Figure 2.).

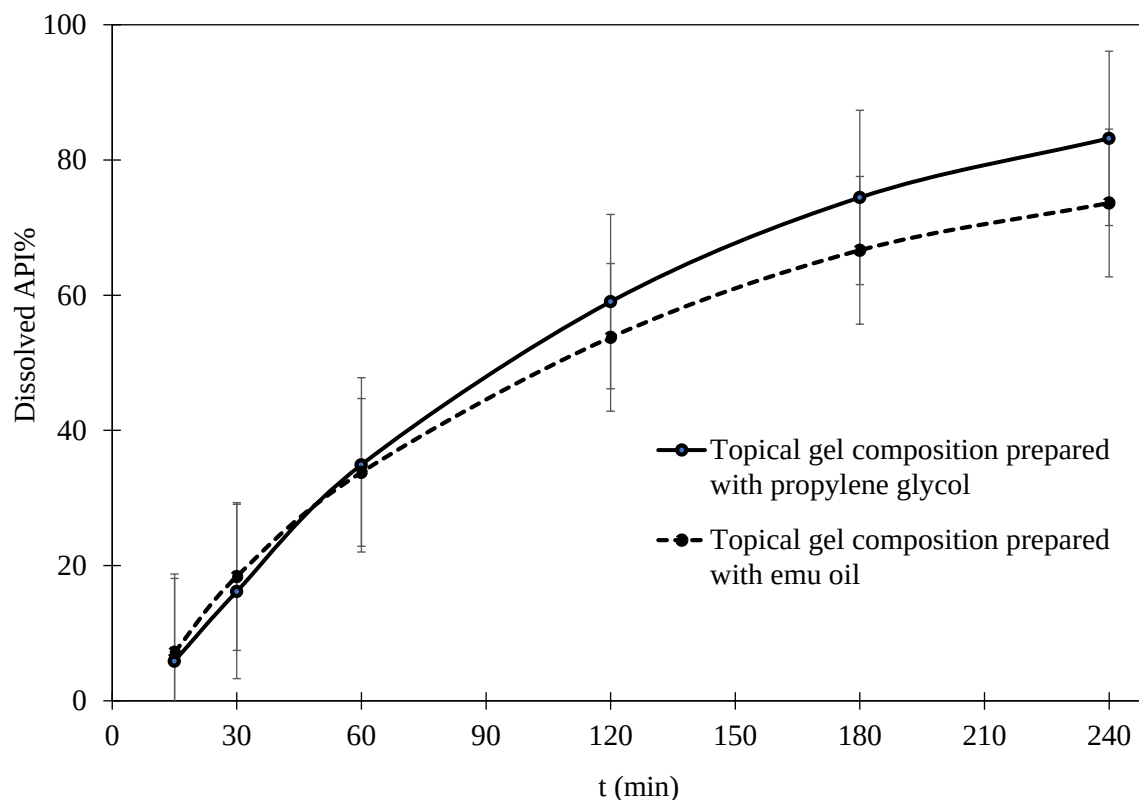


Figure 2. In vitro permeability of the topical pharmaceutical gels prepared using propylene glycol or emu oil as penetration enhancers.

10. It should be noted that the formulations claimed herein performed better than the formulations described in Twidwell. It was surprisingly found that the topical composition containing propylene glycol showed better in vitro permeability compared to the gel composition containing emu oil. A determination of the permeability over time was attempted. However, it was not possible to determine the permeability of the Twidwell formulations after 3 days, due to the phase separation described in paragraph 8.

11. The results show that the use of propylene glycol in place of emu oil has a significant impact on the properties of the formulation having similar composition.
12. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Genovéva Filipcsei, Ph.D.