Vaping Liquids: A Formulator’s Dream?

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Summary

e-liquids used in e-cigarettes are treasure troves of excipients: propylene glycol, ethylene glycol, vegetable glycerine, flavourings of all sorts, nicotine, and even water! This is an e-armoury that scientists would love to access to develop more stable, more flexible inhalation formulations.

Propylene glycol and vegetable glycerine are the main constituents of e-liquids, with concentrations in excess of 90% w/w. This is magnitudes higher than the nearest inhalation products: Clenil Modulite, Qvar and Symbicort pMDI are formulated with ethanol (typically 5 to 10% w/w) or glycerol (< 2% w/w) or polyethylene glycol (< 0.3 % w/w).

The pharmaceutical industry has been very conservative about using new excipients in inhaled delivery. The high levels of excipients used in e-liquids are an opportunity for formulations scientists to explore new formulation spaces. Molecules that are insoluble in water of HFA propellants could be formulated as solutions.

The mass use of e-liquids is akin to a giant worldwide open source clinical and epidemiology trials of new excipients. The evidence of their side effects is currently ambiguous, often clouded by the presence of flavourings, but also because of the combustion in vaping hardware. So far, the dangers of the inhalation of high levels of propylene glycol of glycerol remain moot.

This is good news for formulators. What should the industry do? Test new excipients? Or sit on the fence and let new formulation opportunities go to the vaping industry? Inhaled drug delivery has missed the vaping wave, will it miss the new excipients wave?

Introduction

The rise of e-cigarettes has been meteoric, the global e-cigs market is expected to grow over USD 50 billion by 2025, with 2.2 million e-cigs users in Britain alone in 2015, and 2.75 millions e-cig smokers in the US out of a population of 45 million smokers [¹]. e-cigs are inhaled drug delivery systems for nicotine. Unlike inhaled drug delivery therapies, they are not much regulated and consequently do away with the barriers and common practices of the pharma industry and readily mix excipients to improve product performance.

The use of excipients at high concentrations to control product performance is a dream come true for formulation scientists: free from safety and regulatory constraints, new products can be created. The uptake of these adventurous formulations by smokers and vapers is both exciting and worrying. Exciting because it opens a new formulation universe and worrying because it pushes users in unknown toxicological territories. The mass use of e-liquids is akin to a giant worldwide open source clinical and epidemiology trial of new excipients, and vapers are paying for it. Following this informal trial and learning on how these excipients affect or not users is a must. There is much to gain from looking at an industry that has outpaced the inhalation industry with the use of excipients.

e-liquids composition

The composition of e-liquids relies on 5 basic ingredients: glycerol (vegetable glycerine, herein VG), propylene glycol (herein PG), flavourings (an endless list of possibilities), nicotine (the active ingredient) and water. These are mixed liberally from a number of sources. The main component of the e-liquids is PG. A typical composition would be 60 %w/w PG, 0-40 %w/w VG, 0-20 %w/w ethylene glycol (EG), 0-10% nicotine and 5 %w/w flavourings[²]. These concentrations of PG and VG and the presence of the flavourings is well above what would be considered acceptable in a pMDI, nebulé or nasal spray. The e-liquid industry justification for the use of these excipients is that they are GRAS (generally regarded as safe) according to the FDA concept of food approved substances. The premise is that if it can be eaten it might be OK to inhale.

In addition to the liquid themselves, one should mention a host of contaminants. The excipients are not always sourced from the most reliable of suppliers, and no extractables and leachables studies are mandatory: nitrosamines, aldehydes, heavy metals can be expected. Of these ingredients only one is truly toxic and lethal: nicotine, but curiously no one challenges its presence.
The use of PG and VG is to solubilise nicotine. Both are ordinary components of tobacco in cigarettes, where they are used as humectants to prevent the drying out of the tobacco. VG has been identified as a natural component of oriental tobacco and flue cured tobaccos, typically at low concentrations below 0.5 %w/w. PG has the disadvantage over VG that it oxidises at high temperatures into formaldehyde. E-cigs typically heat up the liquids at 400°C, high enough for oxidation and decomposition to occur.

**Zoom on PG & VG**

Although PG & VG are present in tobacco cigarettes, no adverse effects have been attributed directly to their presence. To review the effects of PG and VG one can look for evidence from other applications: theatre smoke, use as bactericide in hospital, aircraft de-icing and indeed pMDI and nasal products such as Clenil Modulate, Rhinaris and Flunisolide nasal sprays.

Theatre smoke can be generated by the heating of neat PG or VG. These are used in plays, concerts regularly. PG/VG/Ethylene Glycol mixtures are used to de-ice planes. Users, active and passive are regularly exposed to their aerosols. For a while in the 1950’s and 1960’s PG vapour were used to clean paediatric hospital wards [6] and was deemed to be safe.

What is interesting is the use of PG and VG in inhalation products. Clenil modulate relies on small amounts of VG (<2 %w/w) and polyethylene glycol (PEG) (<6 %w/w) [7]. Symbicort pMDI contains small amounts of PEG (<1 %w/w). Flunisolide nasal spray contains PG (<10 %w/w) and PEG (<15 %w/w) PG and VG are therefore no strangers to inhalation dosage forms. They are also good solubilisers for corticosteroids.

**Risks associated with PG & VG**

The risks associated with the regular use of aerosolised PG and VG have been reviewed in small a number of studies of varying quality. The best reviews are published by Konstantinos [8]. The evidence of their effect is mixed. 2 types of risks should be considered: short term risks associated with pathophysiological effects and long-term effects or epidemiology.

A couple of studies have looked at the effects of aerosolised PG in theatres on crew and actors [7,8]. The results point at potential chronic work-related wheezing and chest tightness associated with increased cumulative exposure to fogs over two years. “Acute cough and dry throat were associated with acute exposure to glycol-based fogs; increased acute upper airway symptoms were associated with increased fog aerosol overall. Lung function was significantly lower among those working closest to the fog source”. However, the larger study showed “no significant changes in lung function or the vocal cords for those exposed to glycols. Also, exposure to glycols wasn’t associated with increased rates of asthma”. An other study[9] looked at the acute exposure of PG mist in aviation: “short exposure to PG mist from artificial smoke generators may cause acute ocular and upper airway irritation in non-asthmatic subjects. A few may also react with cough and slight airway obstruction”. These are all short-term effects.

A more recent study looked at 1,018 vapers and their perception of PG effects [10]. 21.7 % vapors reported a cough due to PG. 27.8 % reported a sore or dry throat, was it PG or its decomposition products or even nicotine? The vast majority of these people didn’t have symptoms for long (39.6 % only had symptoms for less than a week, and 75 % had symptoms for less than a month). 3.8 % reported experiencing severe sore throat.

The only reliable clinical data on the tolerability of PG comes two clinical studies on flunisolide nasal spray [11,12]. In them, the tolerability of two PG concentrations were compared. In both studies, a statistically significant reduction of self-reported nasal burning, stinging and throat irritation in terms of severity, duration and tolerability was reported with lower PG levels. However, these studies might have been biased since the sponsor was also the manufacturer of the reduced PG formulation.

These studies do point that they are people who are sensitive to PG vapours although no study is systematic enough nor representative of chronic exposure to be meaningful.

**What should the industry do?**

E-cigs and inhalation therapies are very different. E-cigs rely on heating PG to create an aerosol. This leads to potentially harmful compounds. The quality of excipients is also a source of concern in e-cigs, as well as the use of flavourings. These may bring about most of the side effects associated with e-cigs excipients. The data on the toxicology of aerosolised PG and VG is at best ambiguous. The mass use of e-cigs does not seem to indicate unexpected dangers. However, the long-term effects of the chronic inhalation of PG and VG are only starting to unfold.

e-cigarettes developers are ahead of pharmaceutical scientists in formulating with new excipients. The large scale use of PG and VG opens new formulation horizons. Their use should be monitored: this is a worldwide real scale in vivo clinical/epidemiology study. Let’s test the effective toxic profile of PG and VG in the lungs and bring back PG and VG in inhaled formulations to formulate hydrophobic APIs.
References


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