E-liquids from Evolution to Salt Revolution

By Robin Ward

AlchemEurope™ NicSelect™ Premium Vaping Nicotine

Since vaping first entered the mainstream as a healthier or a significantly less harmful way for smokers to get their daily nicotine hit, there have been steady and continuous improvements in vape hardware.

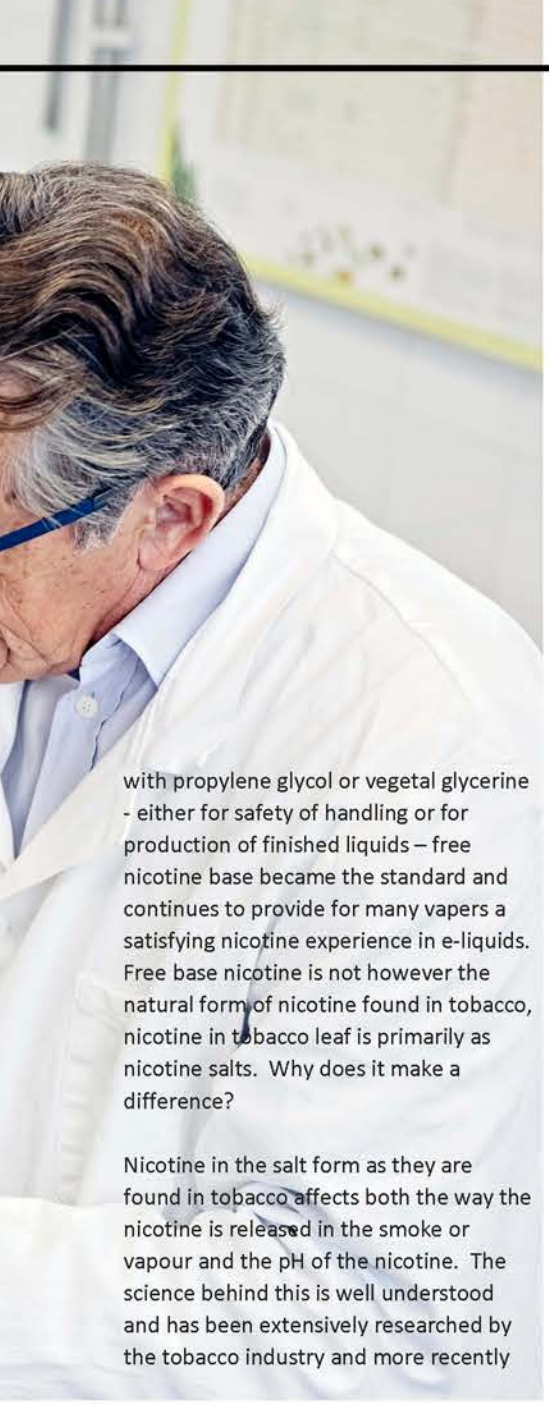
Early generations of cig-a-likes and mods were notoriously inefficient, and it was not uncommon for vapers to load their tanks with e-liquids containing 36 mg/ml or 48 mg/ml or even higher. When the European law makers announced with the advent of TPD that e-liquids would be limited to a maximum of 20 mg/ml there was outrage among vapers, but the reality was that this limit – as apparently Draconian as it seemed initially – was largely offset by improvements in equipment with better coils, batteries and sophisticated digital interfaces allowing users to vary voltages and other parameters to tailor their own vaping experience.

Whilst vaping equipment took leaps forward in the last years, the science of e-liquids has remained relatively static.

True, controls on emission, improved analytics and a negative list on certain ingredients were introduced as part of the implementation of TPD to address safety concerns and there was some innovation and general improvements in flavours but these improvements, whilst important, were not "game changers" and did not address a key e-cigarette weakness, the fact that some smokers transitioning from tobacco do not always find the nicotine experience or hit the same or as satisfying as cigarettes, leaving the door back to tobacco ajar.

Nicotine salts it appears are a "game changer" and the reason behind this may lie in the differences between the natural salt form of nicotine as found in tobacco leaf and the nicotine in e-liquids known a free nicotine base.

Free base nicotine versus nicotine salts. Free base nicotine was the "go to" ingredient for e-liquids during the developmental years of vaping and e-liquids, and for good reason. Free base nicotine (Nicotine EP or USP) was in production, available and understood as a well-defined pure and known source of nicotine already in regular use for nicotine patches, gums and lozenges. So as an easy to source ingredient to mix

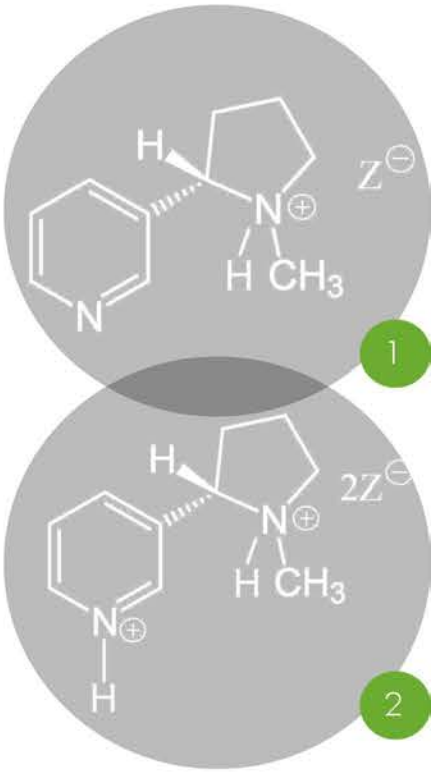


with propylene glycol or vegetal glycerine - either for safety of handling or for production of finished liquids – free nicotine base became the standard and continues to provide for many vapers a satisfying nicotine experience in e-liquids. Free base nicotine is not however the natural form of nicotine found in tobacco, nicotine in tobacco leaf is primarily as nicotine salts. Why does it make a difference?

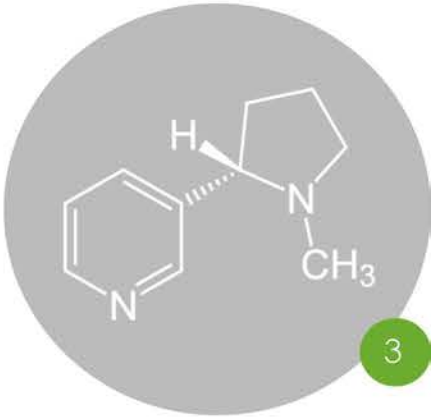
Nicotine in the salt form as they are found in tobacco affects both the way the nicotine is released in the smoke or vapour and the pH of the nicotine. The science behind this is well understood and has been extensively researched by the tobacco industry and more recently the vape industry with much of the work on nicotine salts originally made by the likes of Philips Morris and RJ Reynolds. The objective of this research was to understand what parameters affected the perception and experience of the smoker to give the smoothest "draw and inhale" and the best nicotine hit.The motives for the research are not for debate here but the same area of knowhow is now being applied to the next generation of e-liquids with a range of nicotine salts bases. Adopting the technology into vaping may be considered slightly controversial but if viewed in context of recreating the real cigarette nicotine experience and helping to add to the millions of people now benefiting from 95% harm reduction by no longer smoking then it is less so.

The Chemistry, sorted (or salted).
How do nicotine salts differ from nicotine freebase when vaped? As discussed above, nicotine in tobacco leaves exist in the salts form (i.e. as ions, refer to structures below) and such salts – in theory - are not the most effective way of delivering nicotine as they cannot cross biological membranes easily and are not easily vaporized.

> "The enhanced vaping experience that can be provided by nicotine salts appears to be important to unsatisfied first-time vapers helping them to make a more successful transition to vaping".



Philips Morris found a solution to this puzzle in tobacco products, discovering that natural tobacco salts can be converted into the free base in situ by impregnating the tobacco used in cigarettes with a salt e.g. diammonium phosphate, which releases ammonium ion when the cigarette is combusted. The ammonium ion then reacts with nicotine salts to release nicotine free base. This innovation was probably as important to the success of Marlboro brand as the Marlboro man himself. The free nicotine base thus obtained in situ can travel across biological membranes in our body (i.e. it is more bio available to lungs and brain which makes it more potent).



Thus, it appears that free nicotine base should the natural substance of choice for vaping but compared to salts, nicotine

free base is less stable, more susceptible to oxidation and formation of impurities. In addition, nicotine free base has pH 8.0, which makes the e-liquid harsher to vape as nicotine dose is increased which is particular important for transitioning heavy smokers.

The challenge was to find nicotine salts forms that are more vaporizable, releasing nicotine free base at lower temperatures. The answer was again found in the literature of tobacco research, specific nicotine salts particularly some organic acid salts such benzoate, levulinate and pyruvate offer all these qualities providing nicotine salts that are stable, easy to store, less susceptible to oxidation and suitable for vaping releasing nicotine at lower temperatures unlike natural nicotine salts.

The key functions of the organic salt acids in nicotine salts:

1. Help the nicotine salt vaporize at lower temperatures.
2. Lower the pH levels in the nicotine salt which results in a "smoother throat hit".
3. Improve nicotine absorption.

Are all nicotine salts created equal?
The differing benefits of the main salt combinations are not as yet fully defined, and perceptions vary in consumer testing and more research is in progress and more required. Based on the available data and feedback the 3 main salts indicates similar but also subtle differences in the vaping experience.

Nicotine benzoate. Benzoic acid reduces the pH of the nicotine free base give a soft and smoother nicotine hit especially at higher nicotine contents. Studies suggest that benzoic acid notably improves the stability of the nicotine molecule and may therefore preserve better the taste and flavour of an e-liquid. (see image 1 on page 41).

Nicotine levulinate. Levulinic acid may desensitizes the upper respiratory tract potentially allowing for the vaped nicotine to be inhaled deeper into the lungs. Some literature suggests that levulinic acid also may enhance the binding of nicotine to neurons that ordinarily would be unresponsive to nicotine. (see image 1 on page 41)..

Alchem International production sites are all pharmaceutical GMP (ICH) rated

Nicotine pyruvate. Research suggest that pyruvic acid aids nicotine uptake, particularly at lower nicotine doses. In a study on nicotine inhalers, Nicotine pyruvate inhalations produce rapid increases in plasma nicotine concentrations, provide satisfaction and were well tolerated. ((see image 1 on page 41).

Market trends, opportunity knocks.
When used in higher wattage devices standard freebase nicotine is more than acceptable to most vapers but it is clear not all tobacco smokers find the experience of vaping free base nicotine e-liquids a satisfactory or satisfying experience and many still return to tobacco rather than transition fully to vaping leading to the desired reduced consumption of cigarettes (dual use) or complete cessation of tobacco use.

The enhanced vaping experience that can be provided by nicotine salts appears to be important to unsatisfied first-time vapers helping them to make a more successful transition to vaping. This is especially true as the average first-time user is more likely to go with lower-end devices like pens and cig-a-likes rather than the complex computer-like box mods. Any professional marketer, including vape shop owners, understands the value of appealing to a broad consumer base, satisfying virgin vapers (many heavy smokers) starting off with the cheap pens or mods then graduating these users to more complex and expensive devices later.

Another trend seen among vapers is the use of situation specific equipment, meaning that whilst at home or in specific situations the large battery power mods

are the favoured device the lack of portability leads to the use of the simple lower wattage pen like devices and cig-a-likes to give that "on the go" convenience of a box or cigarettes. This is where nicotine salts, with better nicotine delivery performance at low wattage, clearly come into their own offering a viable and satisfactory alternative to dual use with cigarettes when travelling or out and about socialising, meaning even conventional vapers are inclined to invest in these products for the sake of portability.

The future is bright, the future is well and truly salted.

With nicotine salts growing in popularity vape houses have new possibilities to extend or launch new product lines both as e-liquids and devices putting the innovation that was partially stalled by TPD back into the industry. As such, nicotine salts are a huge opportunity for the vape industry, and the more stores that carry them, the faster these products will spread, attracting more consumers with a better vapes experience and convenience.

NicSelect HQ Nicotine salts.
Breaking bad, how to cook (otherwise known as nicotine salt production).

The manufacturing of nicotine salts whilst not complex does requires an understanding of chemistry and reactions to ensure the salt is correctly formed – poorly produced salts have significant amounts of free nicotine and the acid salt unbound making them a a simple mix of the base ingredients rather than a true nicotine salt. When vaped these liquids will not provide the enhanced vaping experience and nicotine delivery.

Processing should also ensure the nicotine free base does not oxidize in process. Whilst some colouration is normal as the process involves heat, if a nicotine salts goes a dark yellow or orange colour it could indicate strong oxidation, potentially the formation of unwanted impurities as well as affect the organoleptic properties of the nicotine (taste, colour, smell) and other quality aspects.

NicSelect™ HQ Nicotine salts are employ special processes to ensure the correct formation of the salts. Once correctly formed nicotine salts are a more stable form of nicotine than free base with less potential for oxidation and therefore potentially providing a longer shelf life for e-liquids (in particular benzoic acid).

Do your maths!

Companies that are manufacturing and marketing e-liquids need to pay close attention to the specifications and mixing of nicotine salts products. Originally, we started selling nicotine salts as a % in the same way they had been marketed in the USA where no nicotine limits are yet established but for the European market our B2B customers found that confusing. The addition of the acid salts throws the normal definitions and equations and is also influenced by the PG:VG ratio. We are now expressing all our nicotine salts as % and as a simple expression of mg/ml as nicotine free base for easy of interpretation and onward processing.

This is important as the TPD expresses the maximum limits of nicotine in e-liquids as nicotine free base = 20 mg/ml.

As an example, NicSelect™ HQ Nicotine benzoate salt @ 13%on 30PG:70VG would contain.

Certificate of Analysis

Alchem International

Alchem International is a pioneer in the field of manufacturing high quality active ingredients (APIs) for the world's leading pharmaceutical, cosmetic and nutraceutical brands. The company's production sites are pharmaceutical GMP (ICH) rated. The company is the world's leading supplier of nicotine to the vaping industry offering a range of primary materials to manufacturers of e-liquids, including pure nicotine EP, tobacco absolute, diluted nicotine bases and nicotine salts; and diluted nicotine salt bases.

NicSelect™ HQ nicotine salts.

NicSelect™ HQ nicotine salts are manufactured at our European pharmaceutical rated GMP production site near Milan, Italy. We use strictly pharmaceutical grade ingredients, including our best in class NicSelect™ premium grade vaping nicotine to produce a range of nicotine bases on propylene glycol or vegetal glycerine and nicotine salts including nicotine benzoate, nicotine levulinate and nicotine pyruvate.

About the Author.

Robin Ward is Head of European Operations at NicSelect™, a division of the pharmaceutical manufacturer Alchem International, specializing in the production and supply of primary raw materials to the vaping industry. Contact details. rward@alchemeurope.com