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SOLUTION PROPERTIES AND THE MASKING OF UNPLEASANT TASTES OF NICOTINE – SWEETENER - WATER MIXTURES

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ABSTRACT: Solutions properties of sapide molecules provide fundamental information on type (hydrophobic or hydrophilic) and degree of hydration. Physico-Chemical properties like intrinsic viscosity, Apparent Specific Volume (ASV) and related parameters for bitter molecule (nicotine) and bitterness inhibitors (carbohydrate sweeteners, artificial sweeteners) and their mixtures were determined to study the role of water structure in the mechanism of unpleasant taste inhibition. The hydrophobicity of bitter molecule (nicotine) is manifested by ASV value of 0.920 cm^3g^{-1} obtained in artificial buffered saliva (pH ≈8.2). Under these conditions nicotine (3-(1-methyl-2-pyrrolidinyl)pyridine is in neutral form, the most potentially hydrophobic. Experimental results indicate that viscometric constant (intrinsic viscosity [η], Huggins constant k', B coefficient) could discriminate between different sapid molecules tested at our laboratory. The ASV value of carbohydrate sweeteners falls within the sweet region. The bitterness of nicotine is manifested by ASV as high as 0.920 cm^3g^{-1}, which falls in the bitter region. Solution properties also determined for sweet-bitter mixtures validate an improvement in the fitting of solute molecules with solvent structure through the decrease of ASV which falls in the range of ASVs of sweet molecules. The results of viscometric constants and hydration number of sweet-bitter mixtures illustrate an obvious effect of sweet molecules on the hydration property of nicotine. The effect of sweetener on the solution property of bitter molecule (nicotine) is attributed to a modification of hydration. This experimental result validates the assumption in designating sweetener as bitterness inhibitor. The mechanism of inhibition of bitterness by sweet molecules may be credited to the arrangement of water molecules hydration which is more mobile.

INTRODUCTION: Taste is a chemical sense, caused by sapid molecules interacting with receptor cells of taste buds on surface of the tongue. The mechanism of taste chemoreception is very complex [1] and proceeds through multiple steps: First, accession of stimulus to the receptor site through saliva, followed by correct orientation of the molecule on receptor site, Second; the transmission of the taste through nerve impulses, a process known as transduction [2]; and finally, recognition of the taste perceived in terms of its quality and intensity [3]. The first two steps suggest that, for any molecule to have access and fit to receptor site, it must be of an optimum molecular volume and the right shape [4-6] to pack within the water structure. This has led to work on the molar volume of sapid substances [5, 7].

Molecules must have the respective sapophores in order to evoke a taste sensation e.g., AH, B, γ glucophore for sweetness [8], protons for sourness [9]. The stereochemistry of the molecule, particularly the hydroxyl groups at positions 2 and 4 of monosaccharide molecule determines their fit within the water structure [10]. The orientation of stimuli towards the receptor site and perception of sweet taste depends on molecule polarization and on the balance between hydrophilic and hydrophobic sites as well as the mobility of water around the stimulus accounts for understanding sweet taste chemoreception [11, 12].

Also, it is known that sour and salty tastants modulate taste receptor function by direct effect on specific ion channels in the membrane, sweet and bitter tasting compounds seem to bind to closely located receptors, which are coupled to G-proteins. On the other hand, similarities exist between sweet and bitter modalities. Glycosidic stimuli, which seem to possess both sweet glucophore and bitter picrophore bind to bitter and sweet receptors simultaneously [13]. It was found that standard taste substances are capable of eliciting the four primary tastes. In case of sucrose it elicits some bitterness and quinine sulphate was perceived as tasteless or sweet by some subjects [14]. Moreover, many artificial sweeteners like saccharin or aspartame show bitter after-taste. It is generally accepted, that hydrophilic, hydrophobic and steric factors are responsible for both sweet and bitter tastes [13, 15], and their balance may give rise to structure-activity relationship [16].

A holistic approach proposed by Shallenberger [8] indicated that sweetness and bitterness are respectively linked to symmetric and asymmetric character of the sapophore. Schifferstein and Frijters [17] have reported quinine hydrochloride (QHCl), when mixed with sodium chloride (NaCl), the taste character of NaCl was unaffected, while the bitterness of QHCl was suppressed by 50-70%. Kemp and Beauchamp [18] verified that the suppression of bitter taste was concentration dependent for QHCl. Thus, binary combinations of certain taste stimuli may result in asymmetrical changes.

Breslin and Beauchamp [19] evaluated the role of sodium chloride in suppressing the bitter sensation elicited by several compounds (urea, quinine HCl, magnesium sulphate, KCl, amiloride HCl and caffeine) in mixed solutions. The bitterness suppression varied directly with the concentration of NaCl and inversely with concentration of bitter agent. The change in taste modalities (sweet, bitter and sweet-bitter mixtures) for chlorinated sucrose was explained by physiochemical properties of its aqueous solution [20].

Similarly, the bitter taste of certain pharmaceuticals can be masked by addition of chitosan (derived from polysaccharide of chitin). The bitterness and anti-sweet character of gymnemic acid has been successfully eliminated by treating a mixture of starch and gymnemic acid with cyclomaltodextrin glucosyltransferase. The bitterness disappeared, and anti-sweet activity was greatly reduced about 15-fold. The addition of γ–Cyclodextrin to gymnemic acid was effective in reducing the bitterness and anti-sweet character [21]. β–Cyclodextrin masks bitter taste of drugs like propantheline bromide in aqueous solutions [22]. Recently, Funasaki and co-workers [23] have successfully applied ultraviolet spectroscopic (UV) method in taste chemoreception to estimate the bitter taste of oxyphenonium bromide (OB) and the suppression of bitter taste (OB) by the addition of α-, β-, γ-cyclodextrin.

However, considering the overall taste sensation as a bioelectrical phenomenon initiated at the surface of receptor membrane, it is obvious that the polarity of the tastant as well as structure of water around the site can affect taste sensation. Therefore, determining the size of hydrated stimuli and the mobility of water around them is a fundamental discovery to the understanding of the mechanism of sweet, bitter and sweet-bitter tastes.

The main objective of our work was to determine the physicochemical properties of nicotine and bitterness inhibitors and its binary mixtures in aqueous medium. As nicotine is a dibasic compound with 2 dissociation constants (pK_a = 3.4 and 8.2), the hydration properties might influence the pH, in buffered medium. This was determined in artificial saliva at pH = 8.2. At this pH, the neutral form of nicotine was predominant.

Moreover, Nicotine (3-(1-methyl-2-pyrrolidinyl) pyridine) in the neutral form was mainly hydrophobic. This property was analogous to that of bitter molecule although nicotine is known to have an irritant effect. Our earlier studies indicate that sucrose interacts with the bitter compound caffeine [24] to mask bitterness and interactions can be interpreted by hydration properties of each of the sapid substances and of their mixtures.

In the present study, we have applied volumetric methods such as intrinsic viscosity and apparent specific volumes to explore the modification of water structure around the bitter and sweet stimuli and their mixtures are reported for the first time.

MATERIALS AND METHODS:

Chemicals Used: Nicotine, a Sigma product, was used without any prior treatment. The potential inhibitors of the unpleasant taste of nicotine such as sucrose, maltitol, aspartame, β-cyclodextrin, Na-gluconate and K-gluconate were purchased from Sigma Chemicals and acesulfame-K was a gift from Nutrinova, France. The inhibitors namely palatinit® and furaneol were also supplied by GSK. The other chemicals namely $NaHCO_3$, $K_2HPO_43H_2O$, NaCl, KCl, $CaCl_2.2H_2O$, NaN_3 used in preparation of artificial saliva were purchased from Sigma Chemicals and used without further purification.

Artificial Saliva: The artificial saliva is composed of $NaHCO_3$ (5.208g), K_2HPO_43H2O (1.369 g), NaCl (0.877g), KCl (0.477g) and $CaCl_2.2H_2O$ (0.441g) in 1 litre of HPLC grade doubly distilled water (adjusted to pH 8.0). NaN_3 was used at a concentration of 0.5 g/l to prevent microbial growth [25, 26].

Sample preparation: All the chemicals were reagent grade obtained from Sigma Chemicals, France. They were dried to constant weight at 40°C over phosphorus pentoxide prior to dissolving in water or buffer. Water used for the preparation of artificial saliva was HPLC grade. The concentrations used for the present study range from 0.3 to 3% (w/v) for sugars, polyols and 1% (w/v) nicotine. All the measurements were carried out at 25±0.02°C. Analysis was repeated (at least 3 times) until constant values were obtained.

Density and Intrinsic Viscosity [η] measurements: Intrinsic viscosity [η] results are derived from the time for a given volume to flow through a capillary at a constant temperature of 25 ± 0.02°C in a semi-automatic Schott AVS 400 viscometer. A triple extrapolation procedure was applied for the accurate determination of [η] (Mathlouthi and Seuvre [12]). Huggins constant k' was obtained from Huggins equation [27]. Apparent specific volumes were calculated using the density results obtained with a Paar densitometer (DMA 45). Hydration numbers were estimated according to Herkovitz and Kelly [28].

Measured solution properties and their significance:

Intrinsic Viscosity [η]: Intrinsic viscosity was obtained from the triple extrapolation of reduced specific viscosity $[\eta_{sp}/c = (\eta - \eta_o)/\eta_o c]$, inherent viscosity $[(\log\eta/\eta_o)/c]$ and the reduced differential viscosity $[(\eta - \eta_o)/\eta c]$ towards c = 0, where η and η_o are the viscosities of the solution and solvent, respectively, c the concentration in g/dl.

Intrinsic viscosity [η] is generally considered as a shape factor accounting for the hydrodynamic radius of the hydrated molecules. It is strongly dependent on the conformation, size and state of hydration of the molecule. Pauling [29] has stressed on the fact that the sizes and shapes of molecules are of great significance in determining their physiological behaviour.

Huggins Constant (k'): The Huggins constant k' was derived from Huggins relation [30] (Huggins, 1942):

$$\eta_{sp}/C = [\eta] + k' [\eta]^2 c + \ldots\ldots..$$

The Huggins constant k' describes the ease exchange of water molecules between the hydration shell and the bulk water. K' accounts for the effect of the following hydrated solute molecule on the bulk water at a certain distance beyond the primary hydration shell given by h, the hydration number.

B-Viscosity Coefficient: The B- viscosity coefficient is attributed to an overall hydrodynamic volume of the solute. The B-coefficient, which is generally comparable to intrinsic viscosity [η] is the sum of B_{size} and $B_{structure}$.

B_{size} is the part of overall volume originating from the size and shape of the hydrated solute; $B_{structure}$ is the part of volume originating from the effect of solute on solvent structure. It is expressed in litre mol^{-1}. As a general rule, the larger the hydration shell of solute, the higher the value of B_{size}. Likewise, the more the solute affects the 3D structure of liquid water in solution, either by hydrophilic or hydrophobic effect, the higher the value of $B_{structure}$.

Apparent Specific Volume (ASV): Apparent specific volume reflects a static packing of solute molecules within the structure of water and is indicative of the degree of compatibility between the solute and the water structure. ASV is perhaps the most valuable parameter and was found to discriminate the four basic tastes [7]. The pleasant region of taste is that corresponding to the sweet range (0.52-0.72 cm^3/g). The more an inhibitor in a mixture with nicotine approaches this range, the more efficient in masking the bitterness might it be considered.

Hydration Number (h): Hydration number (h) is derived from the B-viscosity coefficient and apparent specific volume [28].

The values of hydration number give the number of water molecules in the hydration sphere of solute with solute-water lifetime longer than water-water lifetime in bulk water. Diffusion and kinetics proceeses involve hydration water as the solute which diffuses is transferred surrounded with its primary hydration shell.

RESULTS AND DISCUSSION: The change of water structure in the solvent medium affects the intrinsic (extrapolated to zero concentration) solution properties.

Addition of 1% (w/v) in aqueous solutions of sweeteners allowed determination of the change in solution properties of these inhibitors of unpleasant taste of nicotine. We have also investigated the modification of intrinsic properties of nicotine in the presence of 1%(w/v) of inhibitors. High concentrations of inhibitor are required to obtain linearity of the extrapolated functions of reduced specific viscosity (η_{sp}), inherent viscosity (η_{inh}) and differential reduced viscosity (η_{diff}) and the correlation coefficient ($r^2 > 0.98$).

Intrinsic properties of Selected Inhibitors: Results of Intrinsic viscosity [η], Huggins constant (k'), the values of B, B_{size}, $B_{structure}$, apparent specific volume and hydration number are given in **Table 1** for selected carbohydrates (Sucrose, Na-Gluconate, K-Gluconate, Palatinit®), flavour enhancer (Furaneol), artificial sweeteners (Aspartame, Acesulfame-K) as well as other potential inhibitors like AMP, β-Cyclodextrin and bitter molecule nicotine in artificial saliva.

From **Table 1**, the intrinsic viscosity was found to be higher for nicotine (3.561 cm^3g^{-1}) as compared to sugars, polyols and organic acids. The higher [η] is a result of increased resistance to flow due to the bigger drag force experienced by the molecule in aqueous solution. Likewise the value of ASV for nicotine (0.920 cm^3g^{-1}) has the highest value at the upper limit of hydrophobic substances. The ASV values for nicotine are rather characteristic of hydrophobic a volatile molecule which is the case for nicotine. The overall effect of nicotine on water structure is such that at least 4.54 H_2O/nicotine are immobilized around it.

The hydrophobicity is high enough to extend the immobilization of water molecules beyond the hydration shell. This effect makes the flow of hydrated nicotine hindered by densely structured water in clathrate like cages (higher intrinsic viscosity). As there is only a weak exchange of water (k'_h = 0.579) between hydration shell and the bulk water, nothing prevents nicotine from escaping to a more hydrophobic phase, i.e air, which explains its volatility. The next most volatile among the studied molecules is maltol (no effect on water structure B_{size} = 0.036 and no exchange of water k'_h =-4.13) are observed from **Table 1**. The value of intrinsic viscosity of pure sucrose solution is found to be 2.332 cm^3g^{-1} and 2.487 cm^3g^{-1} for maltitol.

The intrinsic viscosity [η] of maltitol is found to be higher than sucrose. This may be due to the presence of linear chain of the glucitol moiety, which modifies the molecular conformation in solution, contributes to an increase in the size of the hydrated molecule. The intrinsic viscosity [η] of Na-gluconate is found to be higher (η= 2.532 cm^3g^{-1}) as compared to sucrose solution, which may be due to the presence of Na^+ ions.

It is well known that Na^+ ions have a structure maker effect on water, which means that water becomes less mobile. Moreover, the [η] value obtained for Palatinit® is comparable to that of maltitol. It might be recalled that palatinit is a mixture of 50% GPS (Glucopyranosyl-D-sorbitol) and 50% GPM (Glucopyranosyl-D-mannitol). The slight differences like an increase in intrinsic viscosity ($[\eta] = 2.63$ cm^3g^{-1}) instead of ($[\eta] = 2.49$ cm^3g^{-1}) for maltitol (Glucopyranosyl-D-sorbitol) is due to an increase in hydrophobicity due to the mannitol moiety of GPM. Hydration shell of Palatinit® contains 8 water molecules whereas maltitol has a hydration number of approximately 7. Both carbohydrates have a good fitting with water structure manifested by a value of ASV ≈ 6.30 cm^3g^{-1} in the middle of sweetness region.

The value of intrinsic viscosity [η] for acesulfame-K is found to be the lowest (η=0.925cm^3g^{-1} of all studied molecules. It is due to the presence of K^+ ions. It is known that K^+ ions have a structure breaker effect on water, which means that water becomes more mobile. No permanent hydration shell is observed around acesulfame-K, which considerably reduces the hydrodynamic volume estimated from intrinsic viscosity.

The fact that acesulfame- K is dissociated in water to give K^+ + acesulfame anion makes it a mixture of 2 species. K^+ ion has a negative hydration (Samilov [29]) and acesulfame- K^+ is at origin of hydration number h= -2.02, and the negative value of $B_{structure} = -0.091$. The overall picture of acesulfame-K manifested by its hydration characteristics (k'_h and h) is such that this small molecule does not attract water molecules to its vicinity. This behaviour is opposed to that of nicotine and one can expect that mixtures of nicotine and acesulfame-K balance their opposite effects and yield a structure compatible with water with pleasant taste.

The intrinsic viscosity of aspartame is found to be 2.152 cm^3/g^{-1}. It was comparable to that of sucrose (2.332 cm^3/g^{-1}). However, the high value of k'_h shows that it is not the same type of hydration. Aspartame (Aspartyl-phenylalaine methyl ester) is rather a hydrophobic molecule, including a polar region (CO-NH peptide bond). This opposition in polarity between hydrophobic (phenyl group) and hydrophilic sides of aspartame are at the origin of an increased mobility of water molecules manifested by a high value of $k'_h = 5.93$. Aspartame, although an enhancer of water mobility should not be considered as the best candidate to mask nicotine bitterness. It is only partially polar and predominantly apolar, which is manifested by a large ASV situated in the region of hydrophobic bitter molecules (ASV = 0.746 cm^3/g^{-1}).

Results of determination of ASV reveal that sucrose, maltitol, palatinit, β-cyclodextrin and AMP exhibit ASVs in the sweet range of taste quality (0.52-0.71 cm^3g^{-1}). The ASV of Na-gluconate (0.498 cm^3g^{-1}) is lying the borderline of sweet-sour range (0.33-0.55 cm^3g^{-1} for sour substances). The ASV value for maltol is found to be 0.766 cm^3g^{-1}, which is in agreement with its bitter-sweet flavour. The ASV value of furaneol (0.895 cm^3g^{-1}) was in the upper border of bitter region and is volatile, but can be characterized by its smell. The ASV values of intense sweeteners namely acesulfame-K and aspartame is found to be 0.55 cm^3g^{-1} and 0.746 cm^3g^{-1}. The value of acesulfame-K falls on sweet-sour range and aspartame lies just within the bitter region of the ASV range, it also has a sweet taste and only becomes slightly bitter at increased concentrations.

A comparison of ASVs of acesulfame-K (0.55 cm^3g^{-1}) and aspartame (0.746 cm^3g^{-1}) shows that acesulfame-K has a much lower ASV. This shows that acesulfame-K seems to be more compatible with water structure than aspartame. Moreover, the chemical structure of acesulfame-K is smaller than aspartame, so that the stereochemical disposition of its atoms in space would be expected to disturb water structure much less than that of aspartame. In addition, aspartame, being non-ionic, seems to exhibit very different solution properties than acesulfame-K. The molecule is thought to participate in hydrophobic hydration. The water molecules form stronger hydrogen bonds between themselves. The effect of hydrophobic hydration on the structure of water reduces the water mobility in the vicinity of the solute.

The value of hydration number (h) is found to be higher for β-cyclodextrin (h=11.2) as compared to other sugars and polyols studied. The hydration number (h) gives an estimate of the number of water molecules strongly bound to the solute. It is interesting to mention that acesulfame-K has a negative hydration number.

TABLE 1: SOLUTION PROPERTIES OF PURE SUCROSE, NA – GLUCONATE, MALTOL, PALATINIT®, MALTITOL, AMP, ASPARTAME, FURANEOL, ACESULFAME-K, CYCLODEXTRIN AND NICOTINE IN ARTIFICIAL SALIVA

Properties	Sucrose	Na-Gluconate	Maltol	Palatinit®	Maltitol	AMP	Aspartame	Furaneol	Acesulfame-K	β-CD	Nicotine
η (cm^{3}g^{-1})	2.332	2.532	2.195	2.631	2.487	2.221	2.152	2.789	0.925	2.136	3.561
k'_h	1.27	0.926	-4.13	1.396	0.985	0.919	5.93	1.811	1.484	2.964	0.579
B (dm^{3}mol^{-1})	0.796	0.552	0.277	0.905	0.855	0.771	0.633	0.353	0.186	2.422	0.578
B_{size} (dm^{3}mol-^{1})	0.522	0.271	0.242	0.541	0.543	0.57	0.549	0.286	0.277	1.917	0.373
$B_{structure}$ (dm^{3}mol^{-1})	0.274	0.281	0.036	0.364	0.312	0.201	0.084	0.067	-0.091	0.505	0.204
$V°_2$ (cm^{3}g^{-1})	0.61	0.498	0.766	0.628	0.631	0.657	0.746	0.895	0.55	0.675	0.92
h	6.08	6.24	0.79	8.087	6.92	4.459	1.877	1.479	-2.02	11.22	4.54

Water-water linkage has a longer lifetime than that of water-solute. The relatively smaller hydration number for aspartame (h=1.9) may be due to the opposition between hydrophobic and hydrophilic sides of the molecule which induces a high mobility of water molecules which do not remain bound to solute molecules (H-bond lifetime for water-solute shorter than in bulk water). Viscosity B coefficients give an information about the solute contribution to solute/solvent interactions (Jones and Dole [31]). B is the sum of two parameters namely B_{size} and $B_{structure}$. The contribution of $B_{structure}$ to B coefficient for Palatinit® and β-Cyclodextrin is found to be highest as compared to other molecules studied. This is due to its structure maker effect. The negative values of $B_{structure}$ observed for acesulfame-K, underline their negative hydration and the greater mobility of water around these solutes.

Effect of (1%w/v) nicotine on the intrinsic properties of Inhibitors: The results of intrinsic viscosity [η], Huggins constant (k') and other calculated parameters of the aqueous solutions of inhibitors (sucrose, Na-gluconate, maltitol, Palatinit® acesulfame-K, aspartame, maltol, AMP, β-cyclodextrin) in the presence of 1% nicotine are given in **Table 2**. These results show that intrinsic properties of nicotine are not affected by inhibitors. For example, the values of intrinsic viscosity [η] of Na-gluconate-nicotine mixtures (1% w/v nicotine) are found to be lower (2.604 cm^{3}g^{-1}) as compared to pure nicotine in artificial saliva (3.604 cm^{3}g^{-1}). This leads to the conclusion that addition of organic acids probably modifies the hydration properties of nicotine in aqueous solutions. Such an effect explains the inhibition of bitter taste due to Na-gluconate.

The behaviour of carbohydrates maltitol and Palatinit® is comparable. They maintain their hydrophilic hydration in presence of nicotine. This is seen from the increase in the hydrodynamic volume [η] and B-coefficient. The hydration number is increased but the mobility of water described by k'_h is decreased. This means that nicotine reduces the mobility of the bulk solvent but has only negligible effect on the specific hydration of carbohydrates. On the other hand, acesulfame-K solution is more affected by the presence of 1% nicotine.

The hydrodynamic volume is reduced ([η] = 0.776 cm^3/g^{-1}) as well as B-coefficient. Negative hydration due to K^+ is maintained (h=-2.42, B_{st} =-0.11). However, the bulk solvent being structured by nicotine, this yields an increased value of k'_h. The antagonism of nicotine (hydrophobic structure maker) and acesulfame-K (structure breaker) makes that this couple of molecules (which might undertake ionic interactions) works like aspartame alone in the aqueous medium (k'_h = 5.9, see **Table 1** for aspartame and **Table 2** for nicotine-acesulfame-K mixture). Our expectations from the interpretations of intrinsic properties of acesulfame-K are confirmed. This artificial sweetener, because of its ionic character and its structure breaker effect on water seems a good candidate as bitterness inhibitor for nicotine.

Moreover, Aspartame hydration is lowered in presence of 1% nicotine. It seems that this molecule which owes its quality of sweetness to retaining water molecules around its opposed polar and apolar sides has a lesser effect on water mobility due to the hydrophobic effect of nicotine.

TABLE 2: VISCOMETRIC CONSTANTS AND APPARENT SPECIFIC VOLUMES OF PURE INHIBITORS IN SALIVA AND IN (1%) NICOTINE SOLUTION

Properties	Sucrose	Na-Gluconate	Maltol	Palatinit®	Maltitol	AMP	Aspartame	Furaneol	Acesulfame-K	β-CD
η (cm^3g^{-1})	2.309	2.604	2.262	2.738	2.498	2.227	1.943	2.964	0.776	1.964
k'_h	1.654	0.605	-1.414	0.834	1.032	7.554	2.109	-0.04	5.884	2.044
B (dm^3mol^{-1})	0.787	0.568	0.285	0.942	0.859	0.773	0.572	0.379	0.155	2.228
B_{size} (dm^3mol^{-1})	0.533	0.274	0.203	0.547	0.529	0.483	0.546	0.282	0.264	1.863
$B_{structure}$ (dm^3mol^{-1})	0.254	0.294	0.082	0.395	0.33	0.289	0.026	0.098	-0.109	0.366
$V°_2$ (cm^3g^{-1})	0.623	0.502	0.645	0.636	0.614	0.557	0.742	0.881	0.526	0.656
h	5.647	6.54	1.826	8.78	7.335	6.426	0.57	2.168	-2.42	8.129

The ASV value of aspartame remains in the bitterness region and this is not favourable to its use as inhibitor. Beta- cyclodextrin is only slightly affected by the presence of nicotine. Its hydration is lowered but the overall trend remains the same. Maltol and furaneol also have some changes in their intrinsic properties. Their overall hydration is reduced.

As we mentioned earlier, the value of Apparent Specific Volume (ASV) is a good discriminator of taste (As a general rule, a decrease in ASV means a better inhibition of nicotine taste). The results of determination of ASV calculated from density data for nicotine-inhibitor mixtures are reported in **Table 2**.

The results indicate that the addition of sucrose, Na-gluconate, maltol, palatinit, AMP, acesulfame-K and β-cyclodextrin tend to shift the ASV value of Nicotine (0.92 cm^3g^{-1}) from bitter region to sweet region (0.52-0.71 cm^3g^{-1}). The ASV values for Nicotine-Aspartame is found to be 0.742 cm^3g^{-1}, which is an appreciable lowering from the upper limit of bitter region to nearly upper limit of sweet region.

Effect of (1%w/v) inhibitor on the intrinsic properties of Nicotine: Nicotine is well known as a highly lipophobic molecule although ionisable in buffered with pH<8.2. The use of a buffered saliva at a pH =8.2 limits the study to the hydration properties of nicotine to the non-charged form. The presence of inhibitors in the range of concentrations (0.2 - 1% w/v) does not affect the pH of solution. The solution properties reported in **Table 3** describe the change in Nicotine intrinsic properties in presence of 1% inhibitor.

From the values of hydrodynamic hydration given by intrinsic viscosity this is slightly increased in presence of carbohydrate inhibitors except for β-cyclodextrin (BCD). This additive interacts with both the aqueous solvent and nicotine. It entraps nicotine inside its crown like structure and the hydrodynamic volume given by intrinsic viscosity might be that of the nicotine-BCD complex. The volatile additives Maltol and Furaneol only slightly affect [η]. Acesulfame-K does not change hydration shell of nicotine but modifies water mobility. Aspartame although at a concentration of 0.2% because of its low solubility, contributes to decrease the hydration shell of nicotine (decrease in [η]) probably owing to specific hydration properties described earlier.

The mobility of water given by k'_h is more perturbed than the hydration shell. This is the case for hydrophilic inhibitors like sucrose, maltitol and Palatinit®. Their effect on the structure of the solvent is opposed to that of nicotine.

The hydrophobic molecules (furaneol, maltol and aspartame) contribute to increase k'_h of nicotine. Again acesulfame-K gives a moderate contribution to change the dynamic hydration properties of nicotine (k'_h =0.707, $B_{structure}$= 0.218) instead of 0.578 and 0.204 respectively.

The static hydration is derived from ASV and h values. The more the ASV is decreased, the more the inhibitor effect is high. If we base our classification on this parameter, we have: Acesulfame-K > Sucrose > Gluconate-Na > Aspartame > Furaneol > Palatinit ≈ Maltol > BCD. The hydration number is slightly increased except for BCD which probably forms a hydrated complex with nicotine.

TABLE 3: SOLUTION PROPERTIES OF NICOTINE IN PRESENCE OF (1% W/V) SUCROSE, NA-GLUCONATE, PALATINIT®, MALTITOL, FURANEOL, ACESULFAME-K, ASPARTAME (0.2%), MALTOL (0.2%) IN ARTIFICIAL SALIVA

Properties	Sucrose (1%)	Na-Gluconate (1%)	Maltol (0.2%)	Palatinit® (1%)	Maltitol (1%)	Aspartame (0.2%)	Furaneol (1%)	Acesulfame-K (1%)	β-CD (1%)
η (cm^3g^{-1})	3.687	3.72	3.67	3.73	3.67	3.145	3.445	3.536	3.025
k'_h	0.399	0.012	0.296	-0.128	0.142	3.12	1.009	0.707	3.914
B (dm^3mol^{-1})	0.598	0.604	0.596	0.605	0.596	0.51	0.559	0.573	0.489
B_{size} (dm^3mol-1)	0.349	0.352	0.372	0.374	0.367	0.36	0.366	0.355	0.381
$B_{structure}$ (dm^3mol-1)	0.249	0.251	0.224	0.234	0.229	0.15	0.193	0.218	0.108
$V°_2$ (cm^3g^{-1})	0.863	0.869	0.918	0.921	0.906	0.888	0.902	0.816	0.94
h	5.535	5.583	4.969	5.152	5.083	3.343	4.283	4.852	2.392

CONCLUSIONS: In order to overcome the problems associated with the bitter unpleasant taste of nicotine used in pharmaceutical formulations (e.g. nicotine patches and chewing gums), the solution properties of some artificial sweeteners were studied. Interpretation of results gives an overall picture of the hydrophilicity, hydrophobicity and water mobility of these molecules in solution.

The results of the present work, which should be completed by sensory evaluations studies, allow us to conclude that Acesulfame-K appears as one of the most efficient molecule in reducing the hydrophobicity of nicotine as compared to other bitterness inhibitors.

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