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Computationally Designed Prodrugs for Masking the Bitter Taste of Drugs

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The palatability of the active ingredient of a drug is a significant obstacle in developing a patient friendly dosage form. Organoleptic properties, such as taste, are an important factor when selecting a certain drug from the generic products available in the market that have the same active ingredient. It is a key issue for doctors and pharmacists administering the drugs and particularly for the pediatric and geriatric populations. Nowadays, pharmaceutical companies are recognizing the importance of taste masking and a significant number of techniques have been developed for concealing the objectionable taste [1].

Molecules dissolve in saliva and bind to taste receptors on the tongue giving a bitter, sweet, salty, sour, or umami sensation. Sweet and sour taste receptors are concentrated on the tip and lateral borders of the tongue respectively. Bitter taste is sensed by the receptors on the posterior part of the tongue and umami taste receptors are located all over the tongue. The sensation is the result of signal transduction from taste receptors located in areas known as taste buds. The taste buds contain very sensitive nerve endings, which are responsible for the production and transmission of electrical impulses via cranial nerves VII, IX, and X to certain areas in the brain that are devoted to the perception of taste [2]. Bitter taste receptors are believed to have evolved for organism protection against the ingestion of poisonous food products. Bitter tastants [3-7] are very diverse in their chemical structure and physicochemical properties [8,9]. In humans, bitter taste perception is mediated by 25 G-protein coupled receptors of the hTAS2R gene family [10]. The structural basis for hTAS2R's unique ability to recognize a large number of chemically diverse and low-affinity agonists is not fully understood. Assignment of some bitter tasting compounds to individual receptors has been accomplished [11-16] but remains unknown for many others.

Drugs such as macrolide antibiotics, non-steroidal anti-inflammatories, and penicillin have a pronounced bitter taste [17]. Masking the taste of water soluble bitter drugs, especially those given in high doses, is difficult to achieve by using sweeteners alone. As a consequence, several approaches have been investigated and have resulted in the development of more efficient techniques for masking a compound's bitter taste. All of the developed techniques are based on the physical modification of the formulation containing the bitter tastant. Some of these techniques include: (1) taste masking with flavors, sweeteners, and amino acids [18]. An example of this approach is the use of monosodium glycyrrhizinate with flavors to mask the bitter taste of guaifenesin (an expectorant); (2) taste masking with lipophilic vehicles such as lipids, lecithin, and lecithin- like substances [19]. An example of a drug formulation containing lecithin-like substance is the one composed of magnesium aluminum silicate with soybean lecithin and talampicillin HCl (antibiotic drug); (3) coating is one of the most efficient and commonly used taste masking techniques. It is classified based on the type of coating material, coating solvent system, and the number of coating layers. Taste is masked in famotidine (a drug for ulcer treatment) by using a combination of water soluble polymers such as polyvinylpyrrolidone, and insoluble polymers, such as cellulose acetate [20]; (4) microencapsulation processes used are commonly based on the principle of solvent extraction or evaporation [21]; (5) sweeteners are generally used in combination with other taste masking technologies. Taste masked lamivudine (antiretroviral drug) is prepared by using lemon, orange, and coffee flavors [22]; (6) taste suppressants and potentiators, such as Linguagen's bitter blockers (e.g. adenosine monophosphate), are used for masking the bitter taste of various compounds by competing with binding to the G-Protein Coupled Receptor sites (GPCR) [23]; (7) resins are used to mask bitter tastants by forming insoluble resinates through weak ionic bonding with oppositely charged drugs and maintaining a low concentration of the free drug in a suspension thus decreasing its bitter taste [24]. The ion exchange resin Amberlite is used to formulate taste masked, fast dissolving, and orally consumable films of dextromethorphan (a cough suppressant) [25]; (8) in inclusion complexes, the drug molecule fits into the cavity of a complexing agent and forms a stable complex that masks the bitter taste of a drug by decreasing its oral solubility [26]; (9) pH modifiers are capable of generating a specific pH microenvironment in aqueous media that has the ability to facilitate *in situ* precipitation of the bitter drug compound in saliva thus reducing the overall taste sensation for liquid dosage forms [27]; (10) in adsorbates, the compound may be adsorbed or entrapped in the matrix of the adsorbate pore, which may result in a delayed release of the bitter tastant during passage through the oral cavity and mask the taste [28].

Although the mentioned approaches have helped to improve the taste of some drugs formulations, the problem of the bitter taste of drugs in pediatric and geriatric formulations still creates a serious challenge to pharmacists. Thus, different strategies should be developed in order to overcome this serious problem. The novel chemical approach to be discussed in this editorial involves the design of prodrugs for masking bitter taste of pharmaceuticals based on intramolecular processes using Density Functional Theory (DFT) methods [29] and correlations of experimental and calculated reactions rates. No enzyme is needed to catalyze the interconversion of a prodrug to its corresponding drug. The rate of drug release is controlled by the nature of the linker bound to the drug. Bitter tastant molecules interact with taste receptors on the tongue to give bitter sensation. Altering the ability of the drug to interact with bitter taste receptors could reduce or eliminate its bitterness. This could be achieved by an appropriate modification of the structure and the size of a bitter compound. Bitter molecules bind to the G-protein coupled receptor-type T2R on the apical membrane of the taste receptor cells located in the taste buds. In humans, about 25 different T2R's are described. Additionally, several alleles are known and about 1000 different bitter phenotypes exist in human beings [30,31].

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Due to the large variation of structural features of bitter tasting molecules, it is difficult to generalize the molecular requirements for bitterness. Nevertheless, it was reported that a bitter tastant molecule requires a polar group and a hydrophobic moiety. A Quantitative Structure Activity Relationship (QSAR) model was developed and has been established for the prediction of bitterness of several tastant analogues. For example, it was reported that the addition of a pyridinium moiety to an amino acid chain of a variety of bitter amino acid compounds decreases bitterness, such as in the case of glycine. Other structural modifications, such as an increase in the number of amino groups/residues to more than 3 and a reduction in the poly-hydroxyl group/ COOH, have been proven to decrease bitterness significantly. Moreover, changing the configuration of a bitter tastant molecule by making isomer analogues was found to be important for binding affinity to enhance bitterness agonist activity (e.g. L-tryptophan is bitter while D-tryptophan is sweet) [32].

Recently, the DFT method was used to determine the factors that play a role in the rate-determining step and thus affect the reaction rate in a large number of intramolecular processes. Among these processes are: cyclization reactions of di-carboxylic semi-esters as studied by Bruice [33] and proton transfer between two oxygens in N-alkylmaleamic acids as studied by Kirby [34]. From these studies it was concluded that the reaction mechanism must be unraveled in order to enable assigning the factors that play the dominant role in the reaction rate. The information obtained was then used to design an efficient chemical device to be used as a prodrug linker that blocks the polar function responsible for the bitter taste of the drug. The designed linker has the potential to liberate the bitter tasting drug in a controlled manner (slow or fast release depending on the use of the parental drug). For example, exploring the mechanisms for proton transfer in Kirby's acetals [35] and Bruice's [33] S_N2-based-cyclization reactions of di-carboxylic semi-esters has led to the design of prodrugs of paracetamol and guiafenesen that are capable of masking the bitter taste of the parental drugs [36-43].

The bitter-tasting drug paracetamol is widely used as pain killer and fever-reducer. It was found in the urine of patients who had taken phenacetin and later on it was demonstrated that paracetamol was a urinary metabolite of acetanilide [44]. Phenacetin, on the other hand, lacks or has a very slight bitter taste [45]. Examination of the structures of paracetamol and phenacetin reveals that the only difference in the structural features is the nature of the group in the *para* position on the benzene ring. While in the case of paracetamol the group is hydroxy, in phenacetin it is ethoxy. Acetanilide has a chemical structure similar to that of paracetamol and phenacetin but lacks the group in the *para* position of the benzene ring, making it lack the bitter taste characteristic of paracetamol [45]. These combined facts suggest that the presence of the hydroxy group on the *para* position is the major contributor for the bitter taste of paracetamol. Therefore, it is expected that blocking the hydroxy group in paracetamol with a suitable linker could inhibit the interaction of paracetamol with its bitter taste receptors and mask its bitter taste.

In addition, unraveling the mechanism of proton transfer between two oxygens in Menger's rigid carboxylic amides [46] has led to the design of prodrugs that mask the bitter taste of atenolol, dopamine, pseudoephedrine, amoxicillin, cephalexin, and cefaclor. The role of the linker in these prodrugs is to block the free amine group in the corresponding parental drug and to enable the release of a drug in a programmable manner as well [36-43]. For example, the DFT calculations demonstrated that the efficiency in proton transfer between two oxygens in Kirby's N-alkylmaleamic acids and in a proton transfer between two oxygens in Menger's rigid carboxylic amides is largely sensitive to the strain energy difference between the intermediate and the reactant, the distance between the nucleophile and electrophile, and the attack angle by which the approach step commences. Using the correlation equations from the plots of the calculated and experimental EM values for the above mentioned processes, the $t_{1/2}$ for several prodrugs that mask bitter tastants can be calculated.

In the past, the prodrug approach for masking bitter tasting drugs was used for a very small number of drugs. The palmitate esters of chloramphenicol and clindamycin were made to mask the bitter taste of the corresponding drugs, and the diacetate ester of triamcelonone was synthesized to mask the bitter taste of triamcelonone [47]. Nowadays, the modern computational approach considers using a design of linkers with bitter tasting drugs to release the parental drugs in a programmable manner. With the possibility of designing prodrugs that have different linkers, the rate of release of the parental bitter tasting drugs will be controlled.

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