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Editorial

Exploiting databases and computer softwares in drug formulation: Mining the treasures

Editorial

In one of the conversations between me and one of my senior colleagues, she told me "What lucky researchers you are!", interested to know the reason behind this statement, I asked: "Why?!", and she replied: "because in our time we didn't have all these available search engines, scientific databases, open resources and data manipulation tools". Later, I had a discussion with one of my colleagues – now we are co-authors – who expressed his interest in examining new aspects of formulation: "we can use computer simulations to examine many aspects of different formulations, literally virtualizing our lab" he said.

We gave this conversation some thorough thinking (actually thinking outside the box!) which led us to the interesting conclusion; that though we truly have all these data resources, yet, we still perform our research studies in the most common traditional way. What have we done with all these treasures? Why can't we correlate the results obtained from different studies together? Why can't we start our studies in a different way other than the traditional try-and-error and the wet experimentation screening of the available drugs and/or carriers in different conditions and performing several modifications reaching our objectives whether; high loading or sustained release or targeting or whatsoever? We came up with the convincement that the advancement in technology and computer science programs should be reflected in the

drug delivery and formulation sciences in the most intelligent way. This should be attained to fulfil the ultimate goal for all scientists to leave their experimental results all over the years as footsteps for followers to walk on.

According to the questions that were aroused in our mind based on the above conversation, we started performing a new project aiming at exploiting previous results obtained from different research groups and correlating these results through computational pharmaceutics and predictive modelling aiming to reach different and novel conclusions. Indeed, the data available in literature are treasures, but they need mining and efficient utilization to extract the desired information.

The story went as follows with our first research project: we first concentrated on one common carrier *viz.* solid lipid nanoparticles (SLN) comprising one lipid: Tripalmitin®, in particular, and adopted "data mining" of already published results to answer the following question: Could we predict the encapsulation efficiency of a drug in SLN? Through searching the different scientific databases such as: Pubmed, ISI web of science and google scholar, we collected the published research results regarding the different drugs loadings. We then 'virtualized' our system by simulating the investigated carrier through molecular dynamics using the open-source software Gromacs. We prepared the chemical structures of the reported drugs and performed energy minimization to search for the lowest energy conformer. The interesting part came up when we docked the constructed drugs on the simulated carrier and we knew we are on the right track when we could find a strong relationship between the obtained Δ G (the free energy of docking the drugs on the simulated carrier) and the mass loaded per 100 mg of the carrier and also between the same parameter and the entrapment efficiencies percentages. Impressive; this means that instead of experimenting the loading of new drugs or derivatives of the investigated drugs in the laboratories, we can do this virtually!! And this can just be done using available PC's and laptops! These results encouraged us to go further, so we tried another popular carrier; the PLGA nanoparticles, and again the results of docking using the freely available Auto

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Dock Vina® software were amazing. To validate our hypothesis, we loaded a model drug, curcumin, on both carriers. The percentages bias were less than 10% confirming our hypothesis that the proper usage of molecular dynamics simulations and docking experiments can replace the tedious effort, time and money consuming wet-lab experiments. We introduced this new insight as what we called "Computer-assisted drug formulation design" in a manuscript that was published in 2015 in the prestigious journal "Molecular Pharmaceutics" [1]. We believe that this approach should be implemented in all forthcoming formulation studies. Imagining how this approach would save researchers and formulators huge time, effort and resources spent in wet lab experimentation and exhaustive trials, is really amazing. "Creative thinking inspires ideas. Ideas inspire change" Barbara Januszkiewic.

How did the aforementioned conversations lead us to all of these results?! Well, Einstein always used to say "Curisoity has its own reason for existence".

Building on our obtained results, a new idea came up in order to facilitate more the predictive modelling process of drug loading into a carrier. "Instead of thinking outside the box, get rid of the box!" Deepak Chopra. The literature reported drugs were translated into their main constitutional, electronic and topological chemoinformatic descriptors such as: the molecular weight, the atomic predicted log P (xlog P), total polar surface area (TPSA) and fragment complexity (calculation includes number of bonds, number of non-hydrogen bonds and heteroatoms in the drug chemical structure). A supervised-learning predicting tool was introduced in this part: the artificial neural networks. These networks are very efficient machine learning tools that can easily capture and model relationships in a very robust and accurate way. The calculated descriptors were introduced as inputs or x-factors in the artificial neural networks together with the corresponding obtained free energies of binding (docking) as outputs. In this way the drugs are translated to just numerical values from which the free energies of binding can be predicted for any new drug on these particular carriers without even performing simulations and docking experiments and consequently the drug loading can be calculated through the first obtained relationship correlating the drugs loadings with the free energies of binding [2].

In 2016, we repeated the same work on the solid lipid nanoparticles but utilizing autodock vina and adopting a new and a rarely used machine learning method in the pharmaceutical and chemistry field which is the Gaussian Processes. Interestingly, we obtained better preciting results with percentages bias of almost 7% [3].

We are sure that our approach to computer assisted formulation design will gain more and more ground as it matures due to the versatility of the computational tools used and the type of information obtained, being predictive or explanatory in nature. It is thus our vision that the 'ultimate formulation' can be achieved, and that using computer assisted formulation design will be one of the main tools – if not the main tool – to achieve that.

References

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