Materials Today: Proceedings xxx (xxxx) xxx

Contents lists available at ScienceDirect

Materials Today: Proceedings

journal homepage: www.elsevier.com/locate/matpr

DFT-based theoretical model for predicting the loading and release of pH-responsive paracetamol drug

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
DFT
MSN
Paracetamol
pKa
pH-responsive drug

ABSTRACT

Here, we provide a theoretical framework that integrates quantum mechanical calculations with classical pKa theory to forecast the degree of interaction of drug molecules with carrier surfaces across the whole pH range. The drug loading and release of a pH-responsive drug delivery system is demonstrated using paracetamol drug carried using mesoporous silica surface with and without trimethylammonium (TA) functional group. The model is explained on the basis of possible combinations of surface (S) and drug (D) molecules as neutral (0) and deprotonated (1) pH-dependent states. The relative probabilities of these states depend on the pKa values of the drug as well as surface and the desired pH. Paracetamol, an analgesic and antipyretic drug, is required to be absorbed in small intestine and not in the stomach. It's seen that Paracetamol is caught in the MSN-TA nano-vehicle when it goes through the acidic environment of the stomach and then released in the slightly basic pH of the intestine. The reported model from the literature is used for forecasting the loading and release pH for the Paracetamol using mesoporous silica surface.

Selection and peer-review under responsibility of the scientific committee of the Indo-European Conference on Advanced Manufacturing and Materials Processing.

1. Introduction

The drug, the way it's delivered and the target location where it's delivered are of utmost importance factors in the treatment of various diseases. If the drug delivery mechanism is ineffective, even the therapeutic molecule itself may fail during the clinical trial in such circumstances. [1–2]. The process of discovering a new medicine and obtaining clinical approval is expensive and time-consuming. Numerous drug carrier molecules, including liposomes, micelles, dendrimers, polymers, microspheres and nanoparticles were reported, which were purposely developed utilising organic and inorganic compounds to avoid these issues. The intended effects of the medication molecules are obtained similarly to wearing new clothing or coating on an old medicine. Low toxicity, biodegradability, biocompatibility, good cellular absorption, sustained, and targeted distribution are requirements for an effective drug delivery system. Efficient use of drug delivery system, diseases can be prevented with little to no side effects, a low dose, and a low dosage frequency [1–2].

Nanoparticles (NPs) are one of the best candidates for the development of improved drug delivery systems because they have special qualities like being small enough to pass through cell membranes, being able to pass through tiny arterioles and endothelial without causing clotting, and stabilising the drugs [3–5]. The utilisation of liposomes, co-polymers, micelles, SiO_2, Carbon, and maghemite nanoparticles for the trapping of pharmaceutical drugs has already been extensively studied and reported for the enhancement of drug delivery [6]. Meso-porous SiO2 NPs (MSNs) (2–50 nm) have garnered a great deal of interest recently as potential drug delivery systems due to their numerous advantages, including good biocompatibility, low apparent cytotoxicity, biodegradability, good excretion, ordered and uniform size, high

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https://doi.org/10.1016/j.matpr.2023.04.364
2214-7853/
Selection and peer-review under responsibility of the scientific committee of the Indo-European Conference on Advanced Manufacturing and Materials Processing.

surface areas, excellent stability, and effective and modifiable surface properties [7–12].

The literature main investigation was reportedly conducted utilising the two types, MCM-41 and SBA-15, which offer silanol-containing surfaces and suitable routes for drug carriers. [13] Even though the silanol-group only offers weak H-bonding, functionalized mesoporous systems must still be designed in order to introduce stronger host–guest interactions. Mesoporous SiO_2 NPs that have been carefully functionalized (using $-NH_2$ & –COOH groups). Since these mesoporous SiO_2 NPs have a large surface area (often larger than 1000 m^2 g^{-1}) and a huge amount of pores, they have a better loading capacity than the majority of organic carriers, including liposomes, micelles, and dendrimers. When exposed to interior circumstances, such as pH and temperature, mesoporous SiO_2 NPs can release drugs [14–17].

The entire acidic and basic pH range is represented by several organs in the pH responsive drug delivery system, including the stomach (pH 1.0–3.0), duodenum (pH 4.8–8.2), small intestine (pH 6.0–7.5), colon (pH 7.0–7.5), and ileum/jejunum (pH 7.4 – 8.0). These pH changes were thoroughly investigated for the creation of drug / medicine delivery devices that respond to pH [18–24]. The unique intermolecular interactions caused by pH differences determine the physicochemical equilibrium between the drug transfer system and the drug and its target organ. Experiments have been used largely to study a variety of pH-dependent interactions in order to find the best or most effective drug delivery options. Utilizing computational modelling, it is reported that optimum medication delivery candidates can be found through cost-effective and practical screening. [10,25–29]. To understand the fundamental workings of the drug delivery system, new materials for drug delivery can be logically created by computations and then tested in experiments. In our earlier studies, we have demonstrated the loading and release mechanism of sulfasalazine and alendronate drugs using DFT calculations. [30–31] Paracetamol is one of the most common analgesic and antipyretic drug. Overdoses of paracetamol can cause potentially fatal liver damage, therefore, the actual way out is focused and regulated drug delivery. [32] In this work we present the CASTEP based computational studies of the pH-responsive loading and release of Paracetamol drug using functionalized and bare silica surface. The drug molecule needs to be transported to the small intestine without absorbing in stomach. [33] Paracetamol drug molecules are caught in the MSN / MSN-TA nano-vehicle when it goes through the acidic environment of the stomach and is then released in the somewhat basic pH environment of the intestine. The loading of the paracetamol drug molecules on the MSNs surface with / without functionalised were studied using DFT calculations. Inamdar et. al. studied the bottom-up nature of the interaction of drugs (sulfasalazine and alendronate) and silica surface at various pH [30–31]. The authors were the first to describe the computational approach that is frequently applied in this field. The presented model from these references was expanded in order to forecast the loading and release of paracetamol, the optimum choice for the pH responsive drug delivery system, at varied pH levels.

2. Materials and methods

All the computations have been done using CASTEP [34] module of MATERIALS STUDIO 2016. Density functional theory (DFT) within the generalized gradient approximation (GGA) using the functional of Perdew, Burke and Ernzerhof (PBE) [35] was applied to the exchange–correlation function [36]. The calculations used medium plane wave cut-off energy of 489.8 eV and ultrasoft pseudo-potentials in the Vanderbilt's formulation [37]. SCF cycles were set at 500 cycles during the CASTEP computations for the geometry optimizations. In the trimethylammonium (TA) functionalized silica surface (F-silica), the middle Si atom in the second row's –OH group is replaced with the TA group, whereas the middle Si atom in the last row's –OH group was stripped away to deprotonate the silica surface. We used the silica (1 0 1) surface as a model for periodic silica surface in the MSM mimic calculations. The CASTEP computation framework made use of the interactions between silica and the F-silica surface and the paracetamol drug molecule.

The structure of the paracetamol drug molecule is as shown in the Fig. 1 and it has reported to possesses pK_a value of 9.5. [38–39] The acid – base reaction of the paracetamol drug at its pKa value is as depicted in the Fig. 2.

3. Result and discussion

Lee et al reported the synthesis of mesoporous SiO_2 NPs (MSN) with positively charged TA functional groups and demonstrated the sulfasalazine drug getting loaded in acidic pH (2–5) while the drug was released in the basic (pH 7.4) buffer solution. [40] Theoretical model based on pKa/DFT for forecasting sulfasalazine drug loading and release in pH-responsive drug delivery system was presented in our prior study. [31] Here we have extended the approach to the more common analgesic and antipyretic drug, Paracetamol.

The pKa of paracetamol molecule is reported to be 9.5. [38–39] Based on the pK_a values, drug molecules (D) exist mainly in two forms, neutral (0) and in deprotonated (-1) at various pH, i.e.the pKa of the drug leads to the formation the two species of the drug as neutral and deprotonated (Fig. 2). We have used the Silanol groups (SiOH) in the silica surface, the reported pK_a value as 4.5 in the literature [41–43], we used this pK_a value to study the pH responsive drug loading and releasing mechanism using DFT. The silica surface (S) also exist in two states i.e. neutral (0) and in deprotonated (-1). At any given pH, the fraction (F) can be calculated using Henderson-Hasselbalch equation [44] as shown **equation (1.1)** results in Fig. 3.

$$\begin{aligned} &\textit{For deprotonated molecule}: F_{-1} = \frac{1}{1+10^{pK_a-pH}}, \\ &\textit{For neutral molecule}: F_0 = 1 - \frac{1}{1+10^{pK_a-pH}} \end{aligned} \tag{1.1}$$

Thus two states of drug [D^0, D^{-1}] and surface [S^0, S^{-1}] provides four possible combinations viz. S^0 D^0, S^0 D^{-1}, S^{-1} D^0 and S^{-1} D^{-1}.

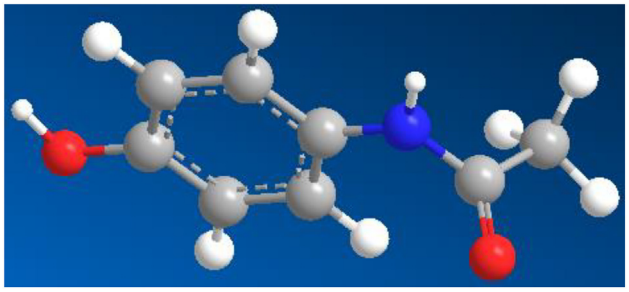

Fig. 1. Molecular structure of Paracetamol drug.

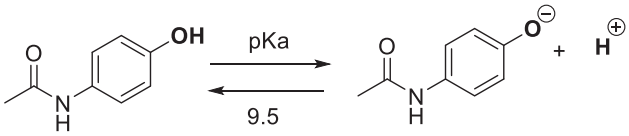

Fig. 2. Acid – base reactions of the paracetamol drug at its pKa.

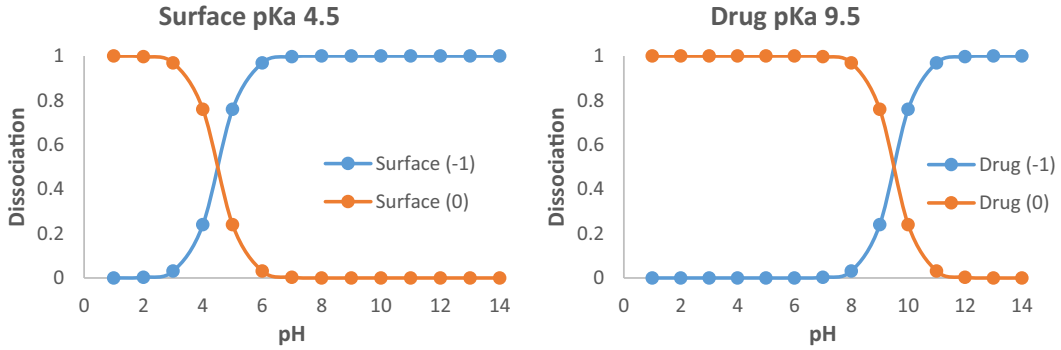

Fig. 3. Illustration of dissociation of silica surface and paracetamol drug with pH based on their pK_a values.

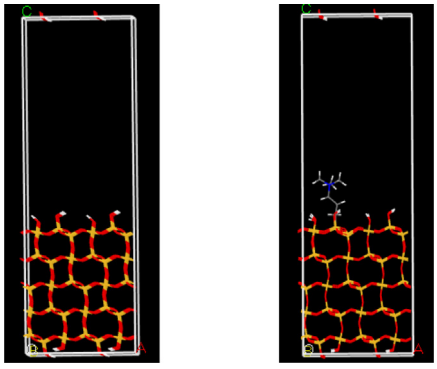

Fig. 4. The bare silica surface (A) and F-silica surface (B).

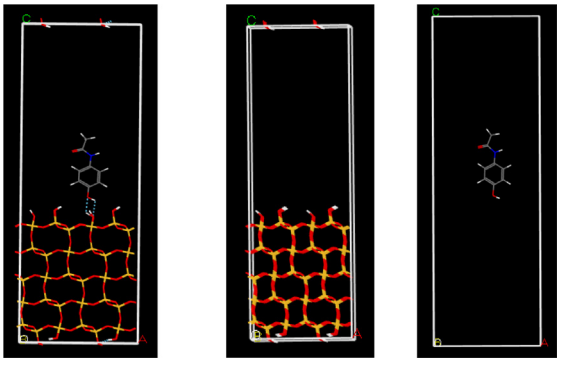

Fig. 5. The interaction energy (Eint.) calculated using the optimized CASTEP energy for each term in the equation (1.2) for the drug and bare silica surface.

Optimised structures of the silica surface without Functional group and with TA functional group using the help of CASTEP calculations are depicted in the Fig. 4. Drug binding affinity for the system for bare silica surface and F-silica surface is termed as interaction energy (Eint.) and is calculated using **eq. (1.2)** [45] and the corresponding optimized structures are as shown in the Fig. 5 and Fig. 6 respectively.

$$\boldsymbol{E_{int.}} = E_{(silica\ with\ FG+Drug)} - E_{(silica\ with\ FG)} - E_{(Drug)} \quad (1.2)$$

The corresponding CASTEP energy and the interaction energies obtained for the bare silica surface and F-silica surface as given in Table 1 and Table 2 respectively.

For the four combinations $S^0\ D^0$, $S^0\ D^{-1}$, $S^{-1}\ D^0$ and $S^{-1}\ D^{-1}$, the interaction energy was calculated and were added up after multiplying the fraction of combination gave rise to final binding energy at the given pH. The B.E. at the given pH was calculated by the sum of product of $E_{int.}$ and fraction present of the individual combination at that pH using **Equation (1.3)**.

$$E_{B.E.} = E_{S^0D^0}xF_{S^0D^0} + E_{S^0D^{-1}}xF_{S^0D^{-1}} + E_{S^{-1}D^0}xF_{S^{-1}D^0} + E_{S^{-1}D^{-1}}xF_{S^{-1}D^{-1}} \quad (1.3)$$

Started with the paracetamol drug, its interaction energy was calculated by placing it over the surface of silica with FG, graph obtained (depends on the drug's and the surface's pKa values) for the drug loading and release onto bare silica and F-silica surfaces is demonstrated in the Fig. 7.

The calculation yielded more negative numbers for $E_{B.E}$, which points to very strong binding. (Reflecting drug molecule loading on the surface), while the higher positive $E_{B.E}$values are suggestive of least or no interaction (Indicating the surface release of a drug molecule). Strong electrostatic repulsion between the silica surface and the negative drug molecules, which can be observed as very big positive B.E signifying no interaction, is what caused the release.

The drug loading and release mechanism observed based on the drug and surface pKa are as follows. It can be clearly observed that the paracetamol drug is getting loaded on the silica surface at acidic pH of 1 to 4, it is in loaded condition even upto pH 8. The drug molecule is seen getting released after pH increases to 8 and higher to basic medium (Figs. 7 and 8).

Here we observed that among the four combinations, the combination $S^0\ D^0$ is predominantly decides the drug loading in acidic stomach, while the combination $S^0\ D^{-1}$ is responsible for the release of the drug in the basic intestine pH.

Table 1
CASTEP output energy for the system without FG after geometry optimization for the four combinations and the calculation of Eint in kcal/mol.

System without FG	EQ + M	EQ	EM	Eint, eV	Eint kcal/mol
D (0) + S (0)	−103046.8325	−100486.3772	−2560.8312	0.3759	8.6457
D (0) + S (-1)	−103029.1689	−100468.3174	−2560.8312	−0.0203	−0.4669
D (-1) + S (-1)	−103029.9634	−100486.3772	−2546.2232	2.6370	60.6510
D (-1) + S (0)	−103011.7092	−100468.3174	−2546.2232	2.8314	65.1222

Table 2
CASTEP output energy for the system with FG after geometry optimization for the four combinations and the calculation of Eint in kcal/mol.

System with FG	EQ + M	EQ	EM	Eint, eV	Eint kcal/mol
D (0) + S (0)	−104052.3095	−101491.8629	−2560.8312	0.3846	8.8458
D (0) + S (-1)	−104036.8616	−101474.5793	−2560.8312	−1.4511	−33.3753
D (-1) + S (-1)	−104037.6736	−101474.5793	−2546.2232	−16.8711	−388.035
D (-1) + S (0)	−104018.2432	−101491.8629	−2546.2232	19.8429	456.3867

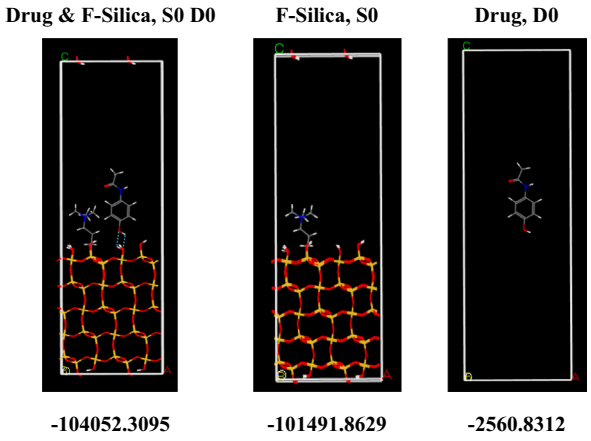

Fig. 6. The interaction energy (Eint.) calculated using the optimized CASTEP energy for each term in the equation 2 for the drug and TA functionalized silica surface.

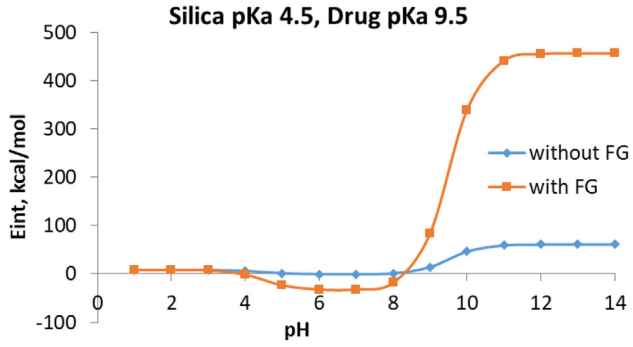

Fig. 7. Ph-dependent binding energies (eint) calculated for the paracetamol drug (pka value 9.5) with silica and f-silica surface (pka value 4.5).

4. Conclusion

The mechanism of the pH-dependent binding and transport of paracetamol drug molecules to the small intestine was successfully understood using DFT-based CASTEP calculations. To forecast the pH of loading and release of the paracetamol drug, the B.E. of the drug and surface in the potential combinations S^0 D^0, S^0 D^{-1}, S^{-1} D^0 and S^{-1} D^{-1} were employed. The negative values for $E_{B.E}$produced from the computation are suggestive of very strong binding of paracetamol drug on the silica surface, while positive $E_{B.E}$values are suggests least or no interaction. The paracetamol drug transport to the small intestine is seen facilitated with TA functionalization of the silica surface. Thus, utilising bare and functionalized silica surfaces, the previously described model is successfully used to guess the pH where the drug will bind and release.

CRediT authorship contribution statement

Rameshwar K. Dongare: Investigation, Writing – original draft. **Radhakrishnan M. Tigote:** Formal analysis. **Mahadev P. Shinde:** Formal analysis. **Adam A. Skelton:** Conceptualization. **Shashikant P. Patole:** Writing – review & editing. **Shaukatali N. Inamdar:** Supervision, Writing – review & editing.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

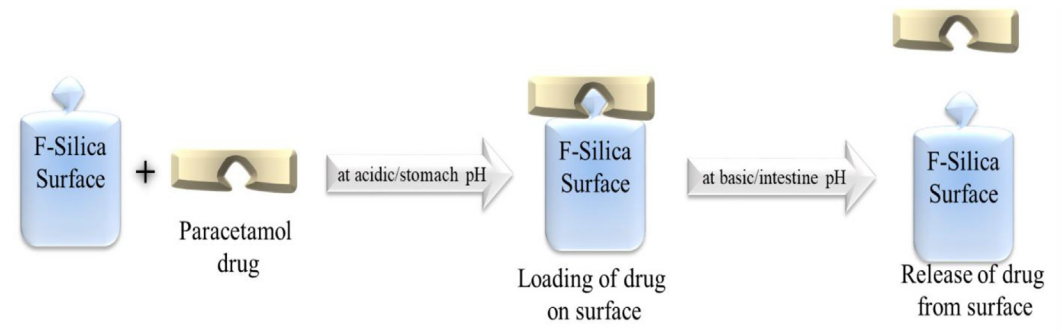

Fig. 8. Process of pH-responsive loading and release of Paracetamol drug using functionalized silica surface.

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