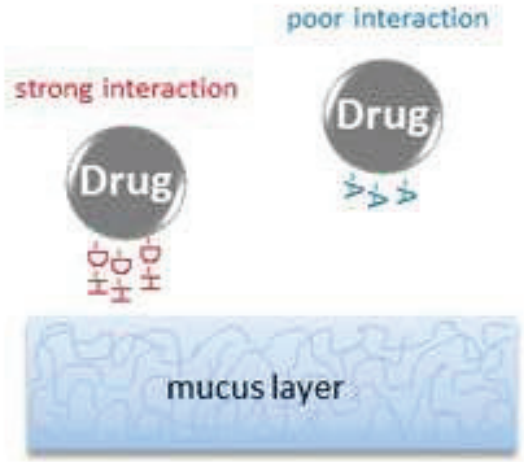
Profile of the intermolecular forces governing the interaction of drugs with mucin

Graphical Abstract (for review)



Profile of the intermolecular forces governing the interaction of drugs with mucin

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Abstract

The study highlights the balance of the intermolecular forces governing the interaction between drugs and mucin. The interaction strength is expressed as a retention factor *k* (data retrieved from the literature (Gargano et al., 2014)) obtained by a new bio-affinity chromatographic method in which the stationary phase is based on covalently immobilized mucin (porcine gastric mucin, PGM). A Quantitative Structure-Property Relationship (QSPR) between *log k* and 82 VolSurf+ descriptors was established and mechanistically interpreted. Results evidence how the hydrogen bonding donor (HBD) properties of solutes favor the interaction with mucin whereas the hydrogen bonding acceptor properties (HBA) are detrimental for binding.

Keywords

Absorption, mucin, QSPR, VolSurf+

Main text

Estimating the extent of oral drug absorption is a step of great value in drug candidates selection (Hughes et al., 2011). Among issues modulating drug absorption mucus penetration cannot be ignored. In fact mucus is the first barrier that drugs must overcome to be absorbed and gain access to the circulatory system (Sigurdsson et al., 2013). The major constituents of mucus are water (95-99.5%) and high molecular weight glycoproteins called mucins. (Sigurdsson et al., 2013). In the mucus these large oligomeric glycoproteins form networks which are a chemical and physical barrier that not only protect the epithelial but also limits the use of oral administered and inhalatory drugs.

Two main mechanisms limit diffusion through mucus gel: a) interaction with mucus components (i.e. electrostatic and hydrophobic interactions with mucins) and b) size filtering related to the size of the mesh spacing between the mucin fibers. Whereas the first mechanism concerns both drugs in solution and nanoparticles, the second is relevant only for nanoformulations. In 2013 the review by Sigurdsson and coworkers highlighted that no definitive picture of the nature of the molecular interactions between drug molecules and mucus components can be drawn (Sigurdsson et al., 2013). Chromatography using biomimetic stationary phases is of great relevance in early drug discovery since it is expected to provide insight for biological partition/distribution processes. (Valkó, 2004). Recently a paper reported on a bio-affinity chromatographic method which uses a novel stationary phase based on covalently immobilized mucin and explores its use as a tool to screen drugs for their affinity to mucin (Gargano et al., 2014).

Since we are interested in highlighting the nature of the interaction between drugs and mucin, we submitted the Gargano's data to a Quantitative Structure-Property Relationship (QSPR) study, which produced a statistical model. Then to extract information about the balance of intermolecular forces governing the system we used the Block Relevance (BR) analysis (Ermondi and Caron, 2012)(Caron et al., 2013).

To obtain a QSPR model we firstly transformed in the logarithmic scale the 25 experimental *k* values different from zero (Gargano et al., 2014). *log k* were then imported into VolSurf+ (VS+, version 1.0.7, *http://www.moldiscovery.com*) as response variables (Y). 82 VS+ molecular descriptors (X) were calculated for any compound using standard settings as described elsewhere (Caron et al., 2013). A relation between Y and Xs (all data are available in Table S1) was sought using the Partial Least Squares (PLS) algorithm implemented in the software. The PLS analysis results are reported in Table 1 and show that a statistically significant model was found ($R^2 = 0.91$). The validation of the model was performed by means of an internal validation procedure as discussed elsewhere (Ermondi et al., 2014). In particular, a Random Groups (RG) approach was used. A very good cross-validated correlation coefficient Q^2(RG) was found (0.58 in Table 1). The correlation between predicted *vs* experimental values is shown in the Supporting Information (R^2 about 0.70, Fig. S1). As desired, the slope is close to 1 and the intercept is close to 0.

Table 1. PLS analysis results (n = number of observations, R^2 = cumulative determination coefficient, Q^2 (RG) = cross-validated correlation coefficient, LV = number of latent variables, SDEP = standard error on the prediction).

System	N	R^2	Q^2(RG)	LV	SDEP
log k mucin	25	0.91	0.58	4	0.38

To provide a mechanistic interpretation of the QSPR model we applied the BR analysis (Ermondi and Caron, 2012)(Caron et al., 2013) which mandates the organization of the VS+ descriptors used for obtaining the PLS model into six blocks (namely, Size, Water, DRY, N1, O and Others, definitions and more details in Fig.1) of straightforward significance. In a very simplistic way, the BR analysis gives the relevance of the blocks to the model.

Fig. 1 outlines that the blocks have more or less the same relevance to the model ranging from 19% of the weight of all blocks played by the DRY (yellow in Fig. 1) to the 15% of the Others (in grey

in Fig. 1) block. Some blocks are positive (i.e Size, DRY, O and Others) and their height shows how much the property described by the block increases the interaction with mucin. Two blocks are prevalently negative (i.e. OH2 and N1) and indicate how much the property decreases the solutes skills in interacting with PGM.

Fig. 1. BR analysis output. The significance of any block is given in the corresponding colour code.

<insert Figure 1 here>

Fig. 1 supports that large dimensions (Size block in green) and solutes hydrogen bonding donor (HBD) properties (O block in red) promote the interaction of drugs with mucin. Conversely, hydrogen bonding acceptor (HBA) properties (blue block) are detrimental for the interaction. The contribution of solvation (described by the DRY and OH2 probes) to retention is in line with what found for few RP chromatographic systems (Ermondi and Caron, 2012) apart from a slightly higher relevance of the positive portion of the DRY block. This evidence and the mostly positive value of the Others block (Fig. 1) could be related to the highly hydrated and uniquely structured gel features of mucin.

The relevance of solutes HBD properties is in line with the experimental evidence that mucin molecules behave as anionic polyelectrolytes at neutral pHs (Sigurdsson et al., 2013). Moreover our model supports the crucial and detrimental role played by HBD properties in permeability studies (Potter et al., 2014).

Since lipophilicity is expected to be important in governing the interaction of drugs with mucin (Sigurdsson et al., 2013), we calculated log $D_{oct}^{7.4}$, the logarithm of the distribution coefficient at pH 7.4 in the octanol/water system (MoKa software v.2.5.4, *http://www.moldiscovery.com,* was used). Then we plotted *log k* values (describing the interaction between drugs and mucin) *vs* log $D_{oct}^{7.4}$. A poor relationship is found (data not shown).

Summing up, to limit mucus binding, drug candidates should have a limited number of HBD groups. However to avoid solubility issues the number of HBA groups can be increased. The design of new drugs for the treatment of a number of pathologies marked by mucus hyperproduction (e.g. cystic fibrosis) could be improved by the application of these simple rules to candidates selection.

Acknowledgements

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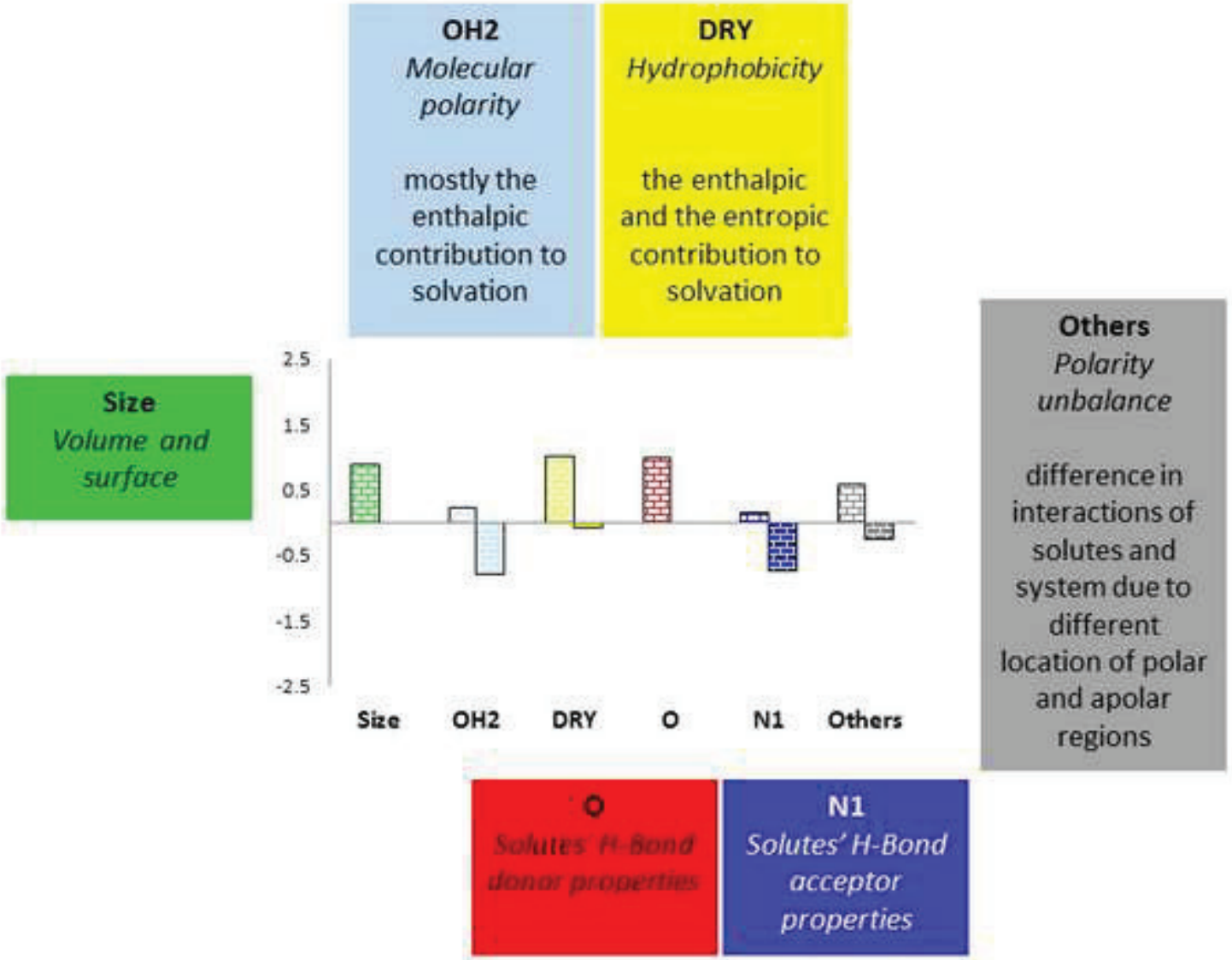
Figure(s)


OH2
Molecular polarity
mostly the enthalpic contribution to solvation
DRY
Hydrophobicity
the enthalpic and the entropic contribution to solvation
Size
Volume and surface
Others
Polarity unbalance
difference in interactions of solutes and system due to different location of polar and apolar regions
2.5
1.5
0.5
-0.5
-1.5
-2.5
Size
OH2
DRY
O
N1
Others
O
Solutes' H-Bond donor properties
N1
Solutes' H-Bond acceptor properties

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