ABSTRACT SUMMARY

We analyzed the compatibility of drugs and drug vectors in view of their physico-chemical and pharmacokinetic properties. Successful nanotherapeutics in clinical trials and market, DrugBank drugs, their anatomical therapeutic chemical (ATC) classification, and logPs were examined and correlated. Our results show that logP of drugs may be used as a guide to design optimized drug delivery systems by tuning drug loading/release, site of therapeutic action and pharmacokinetic properties, which are tightly coupled in the final drug delivery platform.

INTRODUCTION

The technological advances in biomedical, bioengineering and material sciences gave birth to many novel drug delivery platforms [1, 2]. Liposomes were among the first drug delivery vectors that appeared decades ago, and have successfully entered clinical trials and market. They were succeeded by micelles, albumin, carbon nanotubes, polymeric particles, hydrogels and others. Drug delivery systems are frequently developed or researched around the available technologies and drugs, while the choice of a particular drug and vector may not be the most optimal in the view of drug loading, release or pharmacokinetic aspects.

The use of the nanoparticles opened ways to manipulate drug delivery through the use of blood flow characteristics and various biological mechanisms. Enhanced permeability and retention (EPR) of delivery vectors is widely accepted as the cause of augmented drug delivery. Biological systems like the mononuclear phagocyte system (MPS) further contribute to diverse accumulation of particles in organs. Consequently, in nanotherapeutics pharmacokinetics of drug and carrier are blended to improve therapeutic efficacy.

EXPERIMENTAL METHODS

DrugBank database of drugs was used as a representation of current drug market, with 6711 entries at the time of the study. The entire dataset was parsed and analyzed with Knime, extracting experimental partitioning coefficient (logP), half-life (t_{1/2}), ATC codes and bioavailability of drugs.

Data about anatomical, therapeutic and chemical classification (ATC) together with defined daily dose and admission route was gathered according to ATC codes of drugs. The first and second levels of ATC classification were used to categorize drugs by anatomical location and the therapeutic action, accordingly.

Statistical analysis was performed with StatSoft Statistica 10 software package. Normally distributed categorical datasets went through the parametric one-way ANOVA. Pairwise comparison of heterogenous and homoscedastic categories was performed with Turkey HSD (Honest Significant Difference) test for samples with unequal N (Spjotvoll/Stoline).

RESULTS AND DISCUSSION

29 nanotherapeutic formulations in clinical trials and market were examined, with the majority of them being used against cancer. The analysis revealed 4 majors groups of carriers with increasing average logP of loaded drugs: liposome (interior), liposome (membrane),
albumin, and micelles (Figure 1). The comparison with DrugBank data has shown that only 14% drugs may not be compatible with the existing delivery vectors based on logP. 

By following the classification of drug logP values according to the second ATC level, 58 out of 88 groups were found statistically different from at least one another group (Figure 2). Distributed within a range of 7 logP units, groups revealed a truly divergent physico-chemical space of compounds. Therefore, it may be predicted that loading/release of these drugs will exhibit significant differences.

The analysis of half-life showed that 50% of drugs in DrugBank have a half-life shorter than 6 h. Delivery vectors were able to increase half-life by up to two hundred times (Figure 3). The analyses of bioavailability and dosage revealed a large quantity of present drugs that may benefit from formulations in vectors.

CONCLUSION

The analysis has revealed correlation between logP of drugs and delivery vector media, also logP dependent patterns of drug distribution and formulation half-life, with more hydrophobic drugs facing greater challenges to increase their half-life with carrier. The overall results reveal huge potential of drug carriers within the pool of excising drugs, while outlined correlations between logP, loading/release, affinity to vector and therapeutic groups may help improving the design of delivery vectors and their formulations with drugs.

REFERENCES


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