Design And Development Of Novel Techniques To Improve The Factors Affecting Medication Solubility And Dissolution Of Bio Availability Drugs

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ABSTRACT
A medicine or other chemical that may be taken orally is said to be orally bioavailable, which indicates that it can be absorbed and utilized by the body after being consumed. One of the key factors in achieving the needed medication concentration in the bloodstream for pharmacological effects is solubility. Poorly soluble medicines have insufficient bioavailability in gastrointestinal fluids due to their weak solubility and slow dissolving rate. To make medications more soluble and hence boost their bioavailability, several pharmaceutical procedures have been devised. Each strategy has its own benefits and drawbacks. Understanding the elements that affect a drug's solubility and dissolution aids in the creation of novel techniques that increase a drug's bioavailability.
Keywords: solubility, dissolution, bioavailability, factors, techniques.

INTRODUCTION

The quantity of a solute that dissolves in a solvent at a particular temperature is known as its solubility. One of the key factors in achieving the needed medication concentration in the bloodstream for pharmacological effects is solubility. [1] Drugs that are non-polar are not absorbed by tissues because they are not soluble in water. Medications with low solubility are utilized to produce medication caps. For instance, if you ingest a high number of specific vitamins, they are not very soluble. They may linger inside your body for a long period and have detrimental consequences because of their limited solubility. They are utilized to create medication caps that contain the medicine due to their limited solubility.

More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are not soluble in water. These poorly water soluble drugs having slow drug absorption leads to low bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important parameter to achieve their bioavailability and to get required pharmacological response.[2]

The poor solubility and low dissolution rate of poorly soluble drugs causes' insufficient bioavailability in gastrointestinal fluids. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be improved by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids.

For BCS class II drugs, the rate limiting step is not the absorption but the drug release from the dosage form and solubility in the gastric fluid. So by increasing the solubility we can increase the bioavailability for BCS class II drugs.[3]

Types of bioavailability are as follow:

Absolute Bioavailability: When the drug is administered through the intravenous route, the bioavailability ofthe drug achieved will be 100 percent. ...

Relative Bioavailability: It is the bioavailability of the drug when obtained and it is compared with a referencestandard.

Factors Influencing Solubility Of Drugs

The factors that influence the solubility of drugs are listed as internal and external factors.

A. Internal factors

Internal factors are governed by the molecular structure. If the drug molecule has more intermolecular interactions with the solvent, then it increases the solubility. For example, if an organic drug molecule has more hydrogen bond donating/ accepting groups like -OH, -NH2, -COO

and so on, then it can form more hydrogen bonds with solvent (water). Hence it is more soluble in water.

B. External Factors

External factors includes the following

Temperature – drugs are generally more soluble at higher temperatures.[4]

PH - Acidic and basic drugs have equal solubility in water medium. For acid drugs, the equilibrium is HA(s) ⇌H+(aq) + A-(aq); as pH decrease (more H+), the equilibrium shifts to left and drug is less soluble, and vice versa. For base drugs, the equilibrium is BH+(aq)⇌B(s) +

H+(aq) ; as pH decrease (more H+), the equilibrium shifts to left and drug is more soluble, and vice versa.[5] **3.**

Contact area with solvent - Drug particles having greater contact surface area withsolvent have higher solubility rate. For example, powdered drug is more soluble than the coarse drug because powdered drug particles have greater contact surface area with solvent molecules.

Dosage form - Gaseous drug is more soluble than liquid drug, whereas liquid drug is more soluble than solid one. Gas molecules can more readily disperse in solvent medium than liquid molecules, and liquid molecules disperse more readily than solid molecules.

Polarity- Polarity of the solvent, polarity of the solute also affects the solubility of the drug molecules.[6]

Salvation- salvation /hydration, hydrogen bond interactions between solvent and solute, bonding in the crystal and bonding to solvent molecules also affects the solubility. High melting point organic compounds are usually less soluble than low meltingpointcompounds. Liquid - liquid solubility can be affected strongly by the ratio of the ingredients that are used.

Nutrient bioavailability

The FDA has defined bioavailability as the rate and extent to which the active substances or therapeutic moieties contained in a drug are absorbed and become available at the site of action (Shi and Le Maguer 2000). This definition also applies to active substances (nutrients) present in foods. However, even today nutrient bioavailability is an important but often nebulous concept associated with the efficiency of absorption and metabolic utilization of an ingested nutrient (Gregoryand others 2005). Another term that is commonly used is bioaccessibility, which is defined as the amount of an ingested nutrient that is available for absorption in the gut after digestion (Hedren and others 2002). Thus, it is not equivalent to speak of bioavailability or bioaccessibility. If the amount of recovered nutrient after digestion is of relevance then the term to use is bioaccessibility. On the other hand, bioavailability of nutrients is usually measured in the blood plasma of humans (in vivoassay) so factors such as the individual variability, physiological state, dose, and presence of other meal components come into play (Faulks and Southon 2005). These authors established that although all of a nutrient is potentially bioaccessible, in reality almost no nutrient is totally converted during digestion into a potentially absorbable form. In almost every case, bioaccessibility and bioavailability of a nutrient aregoverned by the physical properties of the food matrix, which affect the efficiency of the physical, enzymatic, and chemical digestion processes (Boyer and Liu 2004). Table 1 summarizes commonly used definitions pertaining to the utilization of an ingested nutrient.

Methods To Increase Solubility Of Drugs The techniques that are used to improve the solubility can be categorizedas follows: physical modification, chemical modifications of the drug substance, and other techniques.

A. Physical Modifications

These methods include Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and crystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.

B. Chemical Modifications

These methods include Change of pH, use of buffer, complexation, and salt formation.

C. Miscellaneous Methods

Miscellaneous Methods include Supercritical fluid process; use of surfactants, solubilizers, cosolvency, hydrotrophy, and by using novels excipients.[7]

Let's see all these methods in detail.

Machine learning/model development

FE classifications were predicted using two ML algorithms, ANN and SVM. To facilitate direct comparison of the predictive power of both algorithms the same training:test split was used. Principal Component Analysis (PCA) using the Unscrambler XI (Camo Analytics, US) was applied for a randomised assignment of training:test data. Training set criteria was that it covered the chemical space of the test set and ensured an almost equal representation of positive, negative and no FE drugs in the training set to avoid any potential for classification bias. Such imbalance in datasets has proved to be a widely reported obstacle to classification problems in ML in the past (Cervantes et al., 2020). In accordance with previous reports of classification prediction using ML algorithms (Alhalaweh et al., 2014, Alhalaweh et al., 2015), initial variable reduction was conducted. Either a one-way ANOVA analysis with Tukey Multiple comparisons test (parametric) or Kruskal-Wallis analysis with Dunn's multiple comparison test (non-parametric) were applied to the training data. Variables with a p-value less than 0.05 for at least one class pair in the respective post tests

were highlighted for further investigation. A correlation analysis of these identified variables was carried out with highly correlated variables clustered into the same group and the most significant variable of the group chosen for inclusion in the model development. Final models as well as BCS predictions were compared in terms of various accuracy statistics including, overall accuracy of prediction, as well as sensitivity, precision, specificity and matthews correlation coefficient (MCC) for each FE class, as previously defined (Bisgin et al., 2018), where TP, FP, TN and FN refer to true positive, false positive, true negative and false negative results respectively. MCC was previously suggested as a reliable statistical metric for ML performance quality evaluation (Chicco and Jurman, 2020). A high MCC score (close to 1) is only achieved if the model obtained good results in all four confusion matrix metrics (TP, FP, TN, FN).
Overall Accuracy:∑i=1MTPi∑i=1MTPi+FNix100% Sensitivity:TPTP+FNx100%

recision:TPTP+FPx100% Specificity:TNTN+FPx100%

MCC:(TPxTN)−(FPxFN)(TP+FN)x(TP+FP)x(TN+FN)x(TN+FP)

Particle size reduction

Solubility of the drug depends mainly upon the particle size of the drug, as the particle size decreases the surface area of the powder particles increases thereby it increases the solubility of the drug and in turn it increases the absorption of the drug particles.[8] The size reduction methods help in increase of surface area of particles by decreasing the particle size, resulting in the increase in drug solubility. Size reduction involves well established milling procedures, which are typical part in formulation of drug and its preparation. It can be accomplished by micronization and nanosuspension methods.[9]

Micronisation

Micronization is the process of reducing the size of solid particles. Traditional techniques for micronization include mechanical methods such as milling and grinding. Modern techniques make use of the properties of supercritical fluids and manipulate the principles of solubility. Micronisation increases the solubility by decreasing the particle size of the drug. Decrease in the particle size of the drug increases the surface area and it will increase the dissolution rateof the drug. Micronization of drugs is done by milling techniques by using jet mill, rotor stator colloid mills and so on. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. This process is employed to the drugs like griseofulvin, progesterone, spironolactone diosmin, and fenofibrate. For each drug, micronization improves their digestive absorption, and consequently their bioavailability and clinical efficacy.

Example: Micronized fenofibrate exhibited more than 10-fold (1.3% to 20%) increase in dissolution in at 30 minutes.[10] Progesterone can be micronized by making very tiny crystals[11] micronized progesterone canbe supplied assublingual tablets, oil caps, or transdermal creams.[12] Creatine is the other drug that is micronized and used.[13]

Nano suspension

Nano suspensions are colloidal dispersed particles. These are solid-liquid systems having particle size less than one micrometer. Nano suspensions decrease the particle size thereby increasing solubility of the particles.

Nano suspensions are of great importance in case of substances that are sparingly soluble in water .Biopharmaceutical properties of drugs like absorption and bioavailability areenhanced by formulating them as nanosuspensions.Some marketed nanosuspensions are Rapamune (sirolimus) and Prograf (tacrolimus).[14] Nanosuspension can be achieved by precipitation. It is simple and economical method inwhich the drug substance is dissolved in a solvent and the resulting solution is then added to non-solvent for precipitating the crystals.[15] Ball milling or bead milling process can also be employed for producing nano particles. Use of piston gap homogenizer is an improved technique in the production of nanoparticles. In this technique, the microfine suspension is forced through a gap (5-50 μm) under high pressure (1500-4000 bar) that results in the formation of desired size product.[16]

Micellar solubilisation

Micellar solubilization is very useful in improving the solubility of hrdrophobic drugsinaqueous environment. Micellar solubilization is defined as ―the process of incorporating the solubilizate (the component that undergoes solublization) into or onto the micelles‖. For Solublization to take place system should contain a solvent, an association colloid and at least one other solubilizate.[17]

The surfactants are used to improve the dissolution of poorly soluble drug products. Surfactants reduce surface tension and improve the dissolution of lipophilic drugs in aqueous medium. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles and increases their solubility. This is known as micellization and

generally improves the solubility of poorly soluble drugs.

Commonly used nonionic surfactants are polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauroylmacroglycerides, and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions to dissolve the poorly soluble drugs.[18,19]

The poorly soluble compounds that use Micellar solubilization process are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone.[20]

Hot-melt method [Fusion method]

In this method the physical mixture of a drug and a water-soluble vehicle are heated directly until they melt. The melted mixture is then cooled and solidified rapidly in an ice bath with vigorous continuous stirring. The final solid mass is then crushed, pulverized, and sieved, and finally compressed into tablets with the help of tableting agent.

The melting point of a binary system is dependent upon its composition, that is, the selection of the carrier and the weight fraction of the drug in the system.[21]

An important necessity for the formation of solid dispersion by using hot-melt method is the miscibility of the drug and the carrier in the molten form. Another important requirement is the thermostability of both the drug and the carrier. The main advantages of this direct melting method is its simplicity and economy.

Solvent evaporation method

In the solvent evaporation method, the drug is dissolved, dispersed or emulsified into an organic polymer solution, which is then emulsified into an external aqueous or oil phase. The microspheres are formed after solvent diffusion/evaporation and polymer precipitation.

Solvent evaporation involves emulsification of polymer in aqueous phase and then dispersion in a volatile solvent like dichloromethane, chloroform, and ethyl acetate. Then the solvent is evaporated by using high temperature, vacuum, or by continuous stirring. Size of the particles can be controlled by adjusting parameters like evaporation, temperature, controlling the rate of
evaporation, and by manipulating stirring rate.

This method is being practiced for the development of nanoparticles which uses respective polymers such as PLA, PLGA, PCL, polyhydroxybutyrate, etc. loaded with various drugs like tetanus toxoid, testosterone, loperamide, cyclosporin A, and indomethacin . This method can also be used this to prepare PLGA nanoparticles for various drug loading. .This method is used to develop PEG-coated, PEG-PLA copolymer nanospheres to load modelprotein, HAS.[22]

Precipitation technique

This is a process in which the condensation of a solid occurs from a solution during achemical reaction. In this technique the drug is dissolved in a solvent, which is then added to anti solvent to precipitate the crystals.

The main advantage of this technique is simple and economical. The drawback of this technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with antisolvent.

Precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media.[23] Nanosuspension of Danazol and Naproxen has been prepared by precipitation technique to improve their dissolution rate and oral bioavailability.

The size reduction of naproxen was also associated with an apparent increase in the rate of absorption by approximately 4-fold.[24]

Solid dispersion

This method is very effective for increasing the dissolution rate of poorly soluble drugs, hence it improves their bioavailability. When solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting product with improved surface area produces higher dissolution rate and bioavailability in case of poor water soluble drugs. In addition, the solid dispersion of drug dissolves immediately to saturate the gastrointestinal fluids, and excess drug precipitates as fine colloidal particles or oily globules of submicron size.[25] The use of solid dispersions has been studied extensively. The commercial use of solid dispersions has been very limited, primarily due to the manufacturing difficulties and stability problems. A significant problem with the systems is the difficulties in the formulation development and subsequent scaling-up. Thermosensitive drugs and carriers may be destabilized during the melting or solvent-facilitated melting process since high melting temperatures are usually applied. The soft and tacky properties of solid dispersion powders result in poor flow ability, mixing property and compressibility, which may complicate the operations and render poor reproducibility of physicochemical properties of final products. However, problems associated with the miscibility and thermostability of molten drugs and carriers limit the application of this technique. Moisture & Temperature increases deteriorating effect on solid Dispersion than physical mixtures.[26]

Media milling

Milling involves the application of mechanical energy, the physical break down of coarse particles to finer ones. Fine drug particulates are especially desired in formulations that are designed for parenteral, respiratory and transdermal use. The mechanisms by which milling enhances drug dissolution and solubility include alterations in the size, specific surface area and shape of the drug particles as well as milling-induced amorphization and/or structural disordering of the drug crystal. Technology advancements in milling are the production of drug micro- and nano-particles on a commercial scale.[27]

The nanosuspensions are prepared by using high shear media mills. The milling chambercharged with milling media, water, drug, and the stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2 to 7 days). The milling medium is composed of glass, Zirconium oxide, or highly cross linked polystyrene resin. High energyshear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particle.[28]

Super critical fluid [SCF] process

A supercritical fluid (SCF) is a material that can be either liquid or gas, used in a state above the critical temperature and critical pressure where gases and liquids can co-exist. Itcan effuse through solids like a gas, and dissolve materials like a liquid.

The formation of small particles of a substance with a narrow size distribution is an important process in the pharmaceutical and other industries. Supercritical fluids can achieve this by rapidly exceeding the saturation point of a solute by dilution, depressurization or by both.

This process occur faster in supercritical fluids than in liquids, promoting nucleation or spinodal decomposition over crystal growth and yielding very small and regularly sized particles. Recent supercritical fluids have shown the capability to reduce particles up to a range of 5-2000 nm.[29]

Pharmaceutical co crystals are the novel crystalline forms of Active Pharmaceutical Ingredients which are formed by using Supercritical fluids. Supercritical fluid technology offers a new platform that allows a single step generation of particles that are difficult or even impossible to obtain by traditional techniques. The generation of pure and dried new co crystals (crystalline molecular complexes comprising the API and one or more conformers in the crystal lattice) can be achieved due to unique properties of SCFs by using different super critical fluid properties.[30]

CONCLUSION

For poor water soluble drugs, dissolution is the rate determining step for oral absorption.

Absorption of drugs is mainly dependent on solubility of drugs which is further influenced by drug dissolution. The methods described can be used alone or in combination to improve the solubility of drugs. A good formulation with good oral bioavailability can be achieved by proper selection of solubility enhancing method. The selected method should also be cost effective.

REFERENCES

1. Vemula VR, Lagishetty V, Lingala S. Solubility enhancementtechniques. International Journal of Pharmaceutical Sciences Review and Research, 2010; 5(1): 41–51.
2. Sharma D, Soni M, Kumar S, Gupta GD. Solubility enhancement—eminent role in poorly soluble drugs. Research Journal of Pharmacy andTechnology, 2009; 2(2): 220–224.
3. Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancementtechniques for hydrophobic drugs. Pharmacie Globale, 2011; 3(3): 001–007.
4. Improving solubility & permeability in drug candidates. Conference, 23rd &24th.
5. June 2005,Pre-conference workshop: 22nd June, Thistle Marble Arch, London, UK, 2005.
6. James K. Solubility and related properties, Marcel Dekker Inc., Newyork, 1986; 127–146: 355–395.
7. Lu JX,FosterK,MurrayJ.Biochemistry Dissolution and Solubility[Updated 2020 Apr23].In:StatPearls [Internet].Treasure Island(FL): StatPearls Publishing,2020Jan.
8. Ketan T. Savjani, Anuradha K. Gajjar, * and Jignasa K. Savjani Drugsolubility; Importance and Enhancementtechniques. ISRN Pharm, 2012; 2012: 195727.
9. Swarbrick J. Ed, Encyclopedia of Pharmaceutical Technology, 3rd edn, Informa Healthcare, New York 2006.
10. Garala Kevin Shinde, AnilJadhav Namdeo R. Solubilization of poorly soluble drugs Journal Pharmainfo.net,2007; 5(6): 36-44.
8. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improvesolubility and dissolution rates. Advanced Drug Delivery Reviews, 2007; 59(7): 617–630.
9. Chaumeil JC, Micronization:a method of improving the bioavailability of poorly soluble drugs, 01 Apr 1998;20(3): 211-215.
10. Frank Z Stanczyk, Richard J Paulson SubirRoy: Menopause, 2005; 12(2): 232-237.
11. Hezave, Ali Zeinolabedini; Aftab, Sarah; Esmaeilzadeh, Feridun (11-01). "Micronization of creatine monohydrate via Rapid Expansion ofSupercritical Solution (RESS)". The Journal of Supercritical Fluids, 2010; 55(1): 316–324
12. Barrett E Rabinow, Nanosuspensions in drug delivery, Nature reviews Drug discovery, 2004; 3(9): 785-796.
13. Ghulam Murtaza: Solubility enhancement of simvastatin. Acta pol pham, Jul-Aug 2012; 69(4): 581-590.

14. Barrett E Rabinow, Nanosuspensions in drug delivery, Nature reviews Drug discovery, 2004; 3(9): 785-796.
15. A.D.Mc Naught and A.Wilkinson. Blackwell Scientific Publications. Micellarsolubilization. Oxford, 2nded. Thegoldbook.M03887.ISBN 0-9678550-9-8, 1997.
16. Martin A. Physical Pharmacy. 4th edition. Baltimore, Md, USA: Willaimsand Wilkins, 1993. 20. Varun Raj Vemula, Venkateshwarlu Lagishetty, Srikanth Lingala. International journal of pharmaceutical sciences review andresearch, 2010; 5(1): 41-51.
17. Hsu CH, Cui Z, Mumper RJ, Jay M. Micellar solubilization of some poorly soluble antidiabetic drugs. AAPSPharmSciTech, 2008; 9(2): 939–943. [GoogleScholar]
18. Chiou WL, Riegelman S J ,Pharmaceutical applications of solid dispersionsystems,Pharm Sci., 1971 Sep; 60(9):1281-302
19. Rathna VN Gundloori, Naresh Killi, in Applications of Targeted Nano Drugs andDelivery Systems, 2019;93-131.
20. Muller RH, Bohm BHL, Grau J. Nanosuspensions: a formulation approach for poorly soluble and poorly bioavailable drugs. In: Wise D, editor. Handbook of Pharmaceutical Controlled Release Technology, 2000; 345–357. [Google Scholar]
21. Merisko-Liversidge E, Liversidge GG, Nanosizing: a formulation approach for poorly-water-soluble Compounds.Cooper ER Eur J Pharm Sci., 2003 Feb; 18(2): 113-20.[PubMed]
22. Chaudhari P, Current trends in solid dispersions techniques, Pharminfo.net, 2006; 4(3).
23. Singh MC, Sayyad AB and Sawant SD: Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion. Journal of Pharmaceutical Research, 2010; 3(2): 494-501.
24. Zhi Hui Loh,AsimkumarSamanta,Paul Wan SiaHeng:Overview of milling techniques for improving the solubilityof poorly water-soluble drugs.Asian journal of pharmaceutical sciences, 2015; 10(4): 255-274.
25. Kulkarni RM, PatravaleVB,Nanosuspensions: a promising drugdeliverystrategy.Date AA, J Pharm Pharmacol, 2004 Jul; 56(7): 827-40. [PubMed] [Ref list]
26. Sang-DoYeo, ErdoganKiran, Formation of polymer particles with supercritical fluids: A reviewThe Journal ofSupercritical Fluids, 34(3): 287–308.
27. L. Padrela, M.A. Rodrigues, S.P. Velaga, H.A. Matos and E.G. Azevedo Screening for pharmaceutical cocrystals using the supercritical fluid enhanced atomization process. Journal of SupercriticalFluids, 2009; 53(1–3): 156-164.
28. Corma A, Chane-Ching JY, Airiau M, Martinez C. 2004. Synthesis and catalytic properties of thermally and hydrothermally stable, high surface area SiO2-CeO2 mesostructured composite materials and their application for the removal of sulphur compounds from gasoline.J Catalysis 224:441–448.
29. Lin W, Huang Y, Zhou X, Ma Y. 2006. Toxicity of cerium oxide nanoparticles in human lung cancer cells.Int J Toxicol 25:451–457.
30. Dabbousi BO, RodriguezViejo J, Mikulec FV, Heine JR, Mattoussi H, Ober R, Jensen KF, Bawendi MG. 1997. (CdSe)ZnScore-shell quantum dots: Synthesis and characterization of a size series of highly luminescent nanocrystallites. J Phys Chem B 101:9463–9475.
31. Murray CB, Sun S, Gaschler W, Doyle H, Betley TA, Kagan CR. 2001. Colloidal synthesis of nanocrystals and nanocrystal superlattices. IBM Journal of Research and Development 45:47–56.
32. Alivisatos AP, Gu WW, Larabell C. 2005. Quantum dots as cellular probes.Annu Rev Biomed Eng 7:55–76. 36.Li X-Q, Elliott DW, Zhang W-X. 2006. Zero-valent iron nano-particles for abatement of environmental pollutants:Materials and engineering aspects.Crit Rev Solid State Mater Sci 31:111–122.
33. Zhang W. 2003. Nanoscale iron particles for environmental remediation: An overview.Journal of NanoparticleResearch 5:323–332.
34. Royal Society/Royal Academy of Engineering. 2004. Nano-science and nanotechnologies: Opportunities and uncertainties.Two year review of progress on government actions: Joint Academies' Response to the Council for Science and Technology's Call for Evidence. RS Policy Document 35/06. The Royal Society, London, UK.
35. Klopffer W, Curran MA, Frankl P, Heijungs R, Kohler A, Olsen SI. 2007. Nanotechnology and life cycle assessment. Woodrow Wilson International Centre for Scholars Project on Emerging Nanotechnologies, Washington DC.
36. Kramer JR, Benoit G, Bowles KC, Di Toro DM, Herrin RT, Luther GW, Manalopoulis H, Robilliard KA, Shafer MM, Shaw JR. 2002. Environmental chemistry of silver. In Andren AW, Bober TW eds, Silver in the Environment: Transport, Fate, and Effects. SETAC, Pensacola, FL, USA, pp 1–25.
37. Doty RC, Tshikhudo TR, Brust M. 2005. Extremely stable water-soluble Ag nanoparticles. Chemistry of Materials 17:4630–4635.
38. Zhang W-X, Elliott DW. 2006. Applications of iron nanoparticles for groundwater remediation. Remediation 16:7–21.
39. Biswas P, Wu P. 2005. Nanoparticles and the environment. JAir Waste Manag Assoc 55:708–746.
40. Boxall ABA, Chaudhry Q, Sinclair C, Jones A, Aitken R, Jefferson B, Watts C. 2007. Current and future predicted environmental exposure to engineered nanoparticles. Central Science Laboratory, Department of the Environment and Rural Affairs,London, UK.
41. Hoet PH, Nemmar A, Nemery B. 2004. Health impact of nano-materials? Nat Biotechnol 22:19.
42. Klaine SJ, Cobb GP, Dickerson RL, Dixon KR, Kendall RJ, Smith EE, Solomon KE. 1996. An ecological risk assessment for the use of the biocide dibromonitrilopropionamide (DBNPA), in industrial cooling systems. Environ Toxicol Chem 15:21–31.
43. Di Toro DM, Zarba CS, Hansen DJ, Berry WJ, Swartz RC. 1991.Technical basis for establishing sediment qualitycriteria for non-ionic organic chemicals using equilibrium partitioning.Environ Toxicol Chem 10:1541–1583. 47.Wilkinson KJ, Lead JR, eds. 2006. Environmental Colloids: Behaviour, Structure and Characterization. John Wiley, Chi-chester, UK.
44. Madden AS, Hochella MF, Luxton TP. 2006. Insights for size-dependent reactivity of hematite nanomineral surfaces through Cu2 sorption.Geochim Cosmochim Acta 70:4095–4104.
45. Gustafsson O, Gschwemd G. 1997. Aquatic colloids: Concepts,definitions and current challenges.Limnol Oceanogr 42:517–528.
46. Buffle J, Leppard GG. 1995. Characterisation of aquatic colloids and macromolecules. 1. Structure and behavior of colloidal material. Environ Sci Technol 29:2169–2175.
47. Honeyman BD, Santschi PH. 1992. The role of particles and colloids in the transport of radionuclides and tracemetals in the ocean. In Buffle J, van Leeuwen HP, eds, Environmental Particles, Vol 1. Lewis, Boca Raton, FL, USA, pp 379–423.
48. Sigg L. 1994. The regulation of trace elements in lakes: The role of sedimentation. In Buffle J, de Vitre RR, eds, The Chemical and Biological Regulation of Aquatic Systems. Lewis, Boca Raton, FL, USA, pp 175–195.
49. Harrison RM, Harrad SJ, Lead JR. 2003. The global disposition of contaminants. In Hoffman DA, Rattner BA, Burton GA, Cairns J, eds, Handbook of Ecotoxicology, 2nd ed. Lewis, Boca Raton, FL, USA, pp 633–651.
50. Neihof RA, Loeb GI. 1972. The surface charge of particulates in seawater. Limnol Oceanogr 17:7–16.
51. Hunter KA, Liss PS. 1979. The surface charge of suspended particles in estuarine and coastal waters. Nature 282:823–825.
52. Gibson CT, Turner I, Roberts C, Lead JR. 2007. Quantifying the dimensions of nanoscale organic surfacelayers in natural waters. Environ Sci Technol 41:1339–1444.