REVIEW ARTICLE

Biopharmaceutical classification system: A strategic tool for oral drug delivery technology

Nikhil K Sachan, A Bhattacharya[1], Seema Pushkar, A Mishra[2]

University Institute of Pharmacy, C.S.J.M. University, Kanpur - 208 024, [1]Department of Pharma. Sciences, Dibrugarh University, Dibrugarh - 786 004, Assam, [2]A.N.D College of Pharmacy, Babhnan, Gonda - 271 313, U.P, India

The biopharmaceutical classification system (BCS) is a new concept in the field of pharmaceutical science and technology. This is a valuable tool for the formulation scientists, for the selection and design of the formulation of any drug substance. The recent developments have also enabled us to predict the solubility and permeability characteristics of the drug molecule in the early development stages so that the necessary structural changes can be made to the molecule in order to optimize the pharmacokinetic parameters. The BCS has also got a place in various guidance documents of regulatory importance. This article reviews the criteria for classifying drugs according to the BCS and discusses further potential applications of the BCS, including the developments of new drugs and controlled release products.

Key words: *Biopharmaceutical classification system, biopharmaceutical, drug delivery, preformulation*

INTRODUCTION

The oral route of drug administration is the most important method for administering drugs for systemic effects. When a new drug is discovered, one of the first questions, a pharmaceutical company asks is whether or not the drug can be effectively administered by the oral route, for its intended effect. The development of dosage forms especially for the prolonged release purpose has been a challenge to formulation scientists, because of many independent factors governing the absorption of the drug from the gastrointestinal tract[1] and competitive objectives, that is, any action taken to improve one objective or set of objectives may cause another objective or set of objectives to degrade.[2] For example, modifying the solubility of the drug substance to prolong its release in the gastrointestinal tract may cause a reduction in the overall payload of formulation. A trial and error method of formulation does not allow the formulator to know how close a particular formulation is to the optimum solution, and finding the correct compromise is not straightforward and simple. Hence a fast screen is needed, to enable them to formulate intelligently. For this purpose the drug substances are categorized into four classes based on their solubility parameter and permeability to bio-membranes, and such a classification system is called as a Biopharmaceutical Classification System (BCS).[3] The BCS was first devised in 1995, by Amidon *et al.* and since then it has become a benchmark in the regulation of bioequivalence of oral drug products. The BCS serves as a guiding tool for formulation scientists, for recommending a strategy to improve the efficiency of drug development by proper selection of dosage form and bioequivalence tests, to recommend a class of immediate release (IR) solid dosage forms, for which bioequivalence may be assessed based on *in-vitro* dissolution tests, and to lay the effect of excipients(s) on drug permeability.[4] The BCS guidance takes into account three major factors, dissolution, solubility, and intestinal permeability, which govern the rate and extent of drug absorption from immediate release solid dosage forms. The concept of BCS provides a better understanding of the relationship between drug release from the product and the absorption process. In this respect, the rate-limiting step is of primary relevance. The bioavailability will be affected only by the *in vivo* performance of the dosage form, if dissolution/drug release is rate limiting for the dosage form. In contrast, as long as the permeation through bio-membranes is a rate-limiting process, bioavailability and bioequivalence are not so dependent upon the drug release behavior of the dosage form.[5] Each class of the BCS is having its designated rate-limiting step and the possible tactics for its modification that enable the formulator to select and optimize a dosage form for the drug substance belonging to a particular class of BCS. The BCS has also been included in various guidance documents of regulatory importance.[5,6]

Address for correspondence:
Mr. N. K. Sachan, University Institute of Pharmacy, C.S.J.M. University, Kanpur - 208 024, Uttar Pradesh, India.
E-mail: nikhilsachan@gmail.com

DOI: 10.4103/0973-8398.55042

CONCEPT BEHIND BCS

The *in-vivo* performance of orally administered drugs depends upon their solubility and tissue permeability characteristics. The release rate or solubility of the drug substance will not be a governing parameter if the absorption of the drug is permeation rate limited and in such cases the *in-vitro* dissolution study can be used to demonstrate the bioavailability (BA) or bioequivalence (BE) of the drug product through *in vitro - in vivo* correlation (IVIVC). On the other hand if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed *in-vivo* study will be required in such a case, to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately. Such a drug substance is a good candidate for controlled delivery provided they qualify in terms of their pharmacokinetics and pharmacodynamics for controlled release development. Also if a drug itself is having low solubility and a slow dissolution rate, the release will automatically get slower and the dosage form need not have an inbuilt release retardation mechanism, rather the absorption will now be governed by the gastric emptying rate. Therefore, the dosage form must be able to restrain within the absorption window for a sufficient time so that absorption can take place. In such case, a hydrodynamically balanced (floating) system or a mucoadhesive dosage form will serve the purpose. Hence the BCS can work as a guiding tool for the development of various oral drug delivery technologies.[7]

CHARACTERIZATION OF DRUG MOIETY

For a drug substance to be positioned in the BCS, its solubility and tissue permeability characteristics must be known:

SOLUBILITY AND DISSOLUTION

Dissolution is a process by which a solid substance (drug) goes into the solution, that is, mass transfer of molecules from the solid surface to the liquid phase.[8] The solubility is a property of substance by virtue of which it forms mixtures with other substances, which are chemically and physically homogeneous throughout. The degree of solubility (will be referred to as "solubility" hereafter) is the concentration of the solute in a saturated solution (in equilibrium with solid/drug) at any given temperature. The rate of dissolution and solubility are not the same. In contrast to solubility, the dissolution rate (i.e., the amount of solid substance that goes into the solution per unit time under standard conditions of temperature, pH, solvent composition, and constant solid surface area) is a dynamic process and better related to drug absorption and bioavailability. However, the rate of dissolution for a drug substance is proportionally related to its solubility in the dissolution medium. It has been investigated that unless a compound has aqueous solubility in excess of 1% (10 mg/ml) over the pH range 1-7 at 37°C potential bioabsorption problems may occur, and if the intrinsic dissolution rate is greater than 1 mg/cm^2/min then the absorption remains unimpeded.[9,10]

DETERMINATION OF SOLUBILITY

The solubilities are determined by exposing an excess of solid (drug) to the liquid in question (water/buffer) and assaying after equilibrium has been established. It usually takes 60 to 72 hours to establish equilibrium; sampling at earlier points is necessary. Solubilities cannot be determined by the precipitation method because of the so-called metastable (solubility) zone. The pH solubility profile of the drug is determined at 37 ± 10°C in the aqueous medium, with pH in the range of 1-7.5. A sufficient number of samples should be evaluated, to accurately define the pH solubility profile. A minimum of three replicate determinations of solubility in each pH condition should be carried out.[11] Standard buffer solutions described in pharmacopoeia (B.P. 2003)[12] are considered appropriate for use in solubility studies. The concentration of the drug substance in the selected buffer or pH condition should be determined using a validated solubility-indicating assay that can distinguish the drug substances from their degradation products.

DETERMINATION OF PERMEABILITY

Permeability along with solubility forms the backbone of BCS that helps in accessing oral absorption of drug molecules.[13] The various methods used for permeability screening are as mentioned below:

1. Determination of o/w pH partition profile of the drug
2. Studies of the extent of absorption inhumans - Pharmacokinetic mass balance and absolute bioavailability studies
3. Intestinal permeability studies - The following tissues can be used:
   i) *In-vivo* intestinal perfusion studies in human
   ii) *In-vivo* or *in-situ* perfusion studies in animals
4. *In vitro* permeation studies using excised human or animal intestinal tissue
5. *In-vitro* permeation experiments across a monolayer of cultured human intestinal cells
6. *$Caco_2$ cell lines* are derived from human colon carcinoma and used widely for permeability determination. The technique is expensive and requires specialized skills. $Caco_2$ cell lines are about 60% accurate in predicting human permeability/absorption
7. Initial screening can also be carried out using parallel artificial membrane permeability analysis (PAMPA), which is carried out on microplates. It measures the permeation of compounds through a phospholipid-coated filter medium that mimics intestinal cell structures.

CLASS BOUNDARIES USED IN BCS

1. A drug substance is considered highly soluble when the highest dose strength is soluble in £ 250 ml water over a pH range 1 to 7.5.
2. A drug is considered highly permeable when the extent of absorption in humans is determined to be 90% of an administered dose, based on the mass balance or in comparison to an intravenous dose.
3. A drug product is considered to dissolve rapidly when 85% of the labeled amount of drug substance dissolves within 30 minutes, using USP apparatus I or II in a volume of £ 900 ml buffer solution.

SELECTION OF DISSOLUTION MEDIA

The dissolution medium selected must be able to reflect the *in-vivo* conditions, to give a better *in vitro - in vivo* correlation (IVIVC). However the bile salts are present in the small intestine even in a fasted condition (average concentration @ 5 mM), standard buffer solutions have been used widely in the solubility analysis for BCS. In an attempt to duplicate the intestinal conditions *in-vitro,* two kinds of media have been designed,[14] one to simulate the fasted state small intestine and the other to simulate fed state conditions in the small intestine. These two dissolution media can be used in drug discovery and development and are acceptable in regulatory aspects too.

Hence for the drugs belonging to Class I and Class III (i.e., having high solubility), simple aqueous dissolution media such as simulated gastric fluid (SGF, without enzymes) or simulated intestinal fluid (SIF, without enzymes) are suggested. In contrast, for Class II and IV (i.e., drugs with low solubility), use of biorelevant media is recommended for dissolution testing. For example:

- To simulate fasting stomach condition - SGF plus surfactants
- To simulate fed state condition - Milk with 3.5% fat
- For fasted intestine - Low volume SIF. (For poorly soluble drugs)
- For fed intestine - High volume SIF. (For poorly soluble weak acid drugs).

The intrinsic dissolution rate can also be used as an alternative in BCS, especially in a case when the solubility of a drug cannot be accurately determined. Addition of a surfactant like *sodium lauryl sulfate (SLS)* or other surfactants may be required to mimic the solubilization *in-vitro*. For example, the recommended USP dissolution media for medroxy progesterone acetate tablet, danazol capsule, carbamazepine tablet, and flutamide tablet contain 0.5%, 0.75%, 1.0% and 2.0% SLS (USP26-NF21S1). Further research is required to explore the proper selection of dissolution of media and to develop a uniform media reflecting the *in-vivo* dissolution condition.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

The BCS is defined by four major classes and the drugs are classified based on three major factors governing bioavailability, namely, dissolution, solubility, and permeability. According to BCS the drug substances are classified as shown in Table 1. Each class of BCS has its own designated characteristics and thereby reflects suitability for a certain class of dosage forms and its relevance, or otherwise not, for controlled release.

CHARACTERISTICS OF THE DRUGS UNDER BCS[1,15]

Class I: *In-vivo* these drugs behave like an oral solution having fast dissolution and rapid bioavailability. Since the dissolution and absorption of class I drugs is very fast, bioavailability and bioequivalence are unnecessary for the products of such drugs. These drugs are good candidates for controlled drug delivery if they qualify pharmacokinetically and pharmacodynamically for the purpose. Gastric emptying is often the rate governing parameter in this case.

Class II: Drugs belonging to this class have low solubility and high permeability, hence, the dissolution rate becomes the governing parameter for bioavailability. These drugs exhibit variable bioavailability and need enhancement in the dissolution rate by different methods [Table 2] for improvement in bioavailability. These are also suitable for controlled release development.

Class III: Permeation through the intestinal membrane forms the rate-determining step for these drugs. Since absorption is permeation rate limited, bioavailability is independent of drug release from the dosage form. For example, the various ranitidine products having different dissolution profiles produce superimposable plasma concentration versus time profile *in-vivo*. These drugs generally exhibit low bioavailability and permeability enhancement

Table 1: Biopharmaceutical classification system

Solubility	Permeability	
	High	**Low**
High	Class I Propanolol, Metoprolol, Diltiazem, Verapamil, etc.	Class III Acyclovir, Neomycin B, Peptides, Captopril, Enalaprilate, Alendronate. Ranitidine, etc.
Low	Class II Ketoconazole, Mefanimic acid, Nisoldipine, Nifedipine, Nicardapine	Class IV Clorthiazide, Furosemide, Tobramycin, Cefuroxime

is generally required [Table 3]. These drugs are problematic for controlled release development.

Class IV: Drugs of this class exhibit poor and variable bioavailability. The overall bioavailability is governed by several factors such as rate of dissolution, intestinal permeability, gastric emptying, and so on. These drugs are generally not suitable for oral drug delivery or else some special drug delivery technologies such as nanosuspensions will be needed.

QUANTITATIVE BCS (QBCS)[16]

The experience gained with intensive experiments has shown that the process of dissolution can be dependent on the amount of drug present at the site of absorption (dose), in addition to the solubility of drug in the dissolution fluid. It was argued and demonstrated (Rinaki *et al.* 2003)[16] that solubility is a static equilibrium parameter and cannot adequately describe the dynamic character of the dissolution process for the entire dose administered. Hence, a single solubility value is inadequate or the purpose of biopharmaceutical classification, because the drugs are administered in various doses; therefore, the dose consideration should be taken into account. This is also emphasized in the FDA guidance for the industry, "Waiver of *in vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutic Classification System," which states that the highest dose strength of an immediate release product should be considered for study. Rinaki *et al.* dealt the biopharmaceutical system in a quantitative manner, relying on the central role of dose/solubility ratio for the absorption phenomenon in conjunction with the mean time concept for dissolution, transit, and uptake of the drug in the intestine. These considerations led to the development of the quantitative version of BCS, termed quantitative BCS (QBCS). The QBCS relies on a (permeability, dose/solubility ratio) plane with cutoff points 2×10^{-6} cm/s to 2×10^{-5}cm/s for permeability and 0.5 to 1.0 for the dose solubility ratio. Permeability estimates, (P_{app} that is the apparent permeability) were derived from Caco-2 cell studies and a constant intestinal volume content of 250 ml was used to express the dose solubility ratio as a dimensionless quantity (q). Drugs are classified into four quadrants of a plane, around the cutoff points, according to their P_{app}, and q values, establishing four categories, that is, I ($P_{app} > 10^{-5}$ cm/s, $q \leq 0.5$), II ($P_{app} > 10^{-5}$ cm/s, $q > 1$), III ($P_{app} < 2 \times 10^{-6}$ cm/s, $q \leq 0.5$), and IV ($P_{app} < 2 \times 10^{-6}$ cm/s, $q > 1$). A region of borderline drugs ($2 \times 10^{-6} < P_{app} < 10^{-5}$ cm/s, $0.5 < q < 1.0$) has also been defined. For category I, complete absorption is anticipated, whereas, categories II and III exhibit dose/solubility ratio - limited and permeability -and limited absorption, respectively. For category IV both permeability and dose/solubility ratio control drug absorption.

Table 2: Methods for enhancing the dissolution and absorption of class II drugs

Methods for enhancing solubility of drugs
Buffering the pH of microenvironment
Use of salts of weak acids and weak bases
Use of solvates and hydrates
Use of selected polymorphic forms
Complexation
Prodrug approach
Use of surfactants
Methods enhancing the surface area of the drug
Micronization
Use of surfactants
(Enhancing effective surface area by facilitating proper wetting)
Solvent deposition
(Depositing poorly soluble drugs on inert materials)
Solid dispersions
(Dispersion of drugs in the solid matrix of water-soluble carriers)

EXTENSION TO BCS: (BCS CONTAINING SIX CLASSES)

Bergstrom *et al*. devised a modified Biopharmaceutical Classification System, in which they categorized the drugs into six classes based on the solubility and permeability.[17] The solubility was classified as "high" or "low" and the permeability was allotted as "low", "intermediate," or "high". This new classification was developed based on the calculated surface area descriptors on the one hand and solubility and permeability on the other. Surface areas related to the nonpolar part of the molecule resulted in good predictions

Table 3: Most commonly used and researched mucosal permeation enhancers

Type	Examples	Mechanism of action
Synthetic surfactants	Sodium lauryl sulfate, Polysorbate 20 and 80, PEG-8 laurate, sorbitan laurate, glyceryl monolaurate	Membrane interaction, extraction of membrane proteins, and lipid solubilization of peptides
Bile salts	sodium deoxycholate, sodium glycocholate, sodium fusidate, sod. taurodihydrofusidate	Decrease of mucus viscosity, decrease of peptidase activity, solubilization of peptides, and formation of reversed micelles
Fatty acids and derivatives	Oleic acid, capryilic acid, lauric acid, palmitoylcarnitine	Phospholipid acyl chain disruption.
Chelators	Na_2EDTA, citric acid, Salicylates	Ca^{++} complexation (influencing tight junctions)
Inclusion complexes	Cyclodextrins and derivatives	Increasing peptide stability, increasing solubility, enzyme inhibition
Mucoadhesive polymers	Polycarbophil Chitosan	Mucoadhesion

of permeability. It was tentatively concluded that these models would be useful for early indication with regard to the absorption profiles of the compound during the early stages of drug discovery so that the necessary modifications can be made to optimize the pharmacokinetic parameters.

APPLICATION OF BCS IN ORAL DRUG DELIVERY TECHNOLOGY[13,18,19]

Once the solubility and permeability characteristics of a drug are known, the formulation scientist can then, based on BCS, easily decide which drug delivery technology will best help in getting the optimum pharmacokinetic characteristics. The major challenge in the development of drug delivery systems for a class I drug is to achieve a targeted release profile associated with the particular pharmacokinetic and pharmacodynamic properties. Formulation approaches include both the control of release rate and physiochemical properties of drugs like the pH-solubility profile of the drug.

The systems that are developed for class II drugs are based on the micronization, lyophilization, addition of surfactants, formulation as emulsions and microemulsion systems, use of complexing agents like cyclodextrins, and so on.

Class III drugs are required for technologies that address the fundamental limitations of absolute or regional permeability. Peptides and proteins constitute, solely, the class III drugs; these are now the center of focus for research in drug delivery.

The class IV drugs present a major challenge for the development of drug delivery systems and the route of choice, due to their poor solubility and permeability characteristics. These are often administered by parenteral route with the formulation containing solubility enhancers.

BCS AS A FRAMEWORK FOR OPTIMIZATION OF A NEW CHEMICAL ENTITY

The BCS provides a clue about the pharmacokinetics of the drug (NCE), any newly synthesized or identified chemical molecule that is proved to be therapeutically active, but is still under investigation for formulation development and final approval, which provides an opportunity to the synthetic chemist or the drug designer to manipulate in the chemical structure of the drug entity so as to optimize the physicochemical parameters of the lead molecule for desired drug delivery and targeting characteristics.[20,21] The synthetic chemist and formulation scientists act together to achieve better 'deliverability' directed toward the desired pharmacokinetics and therapeutic efficiency right from the initial stages of drug design, to fulfill the propelled need for "High Throughput Pharmaceutics (HTP)".

Lipinski *et al*. has suggested a 'rule of 5,' which has been widely adopted by the pharmaceutical industry as a yard stick for screening out compounds that are likely to have poor absorption profiles. According to this rule the poor absorption or permeation is more likely when:[22]

- There are more than five H-bond donors (expressed as a sum of hydroxyl and N-H linkage).
- The molecular weight of the drug moiety is more than 500
- The log P is over %
- There are more than 10 H-bond acceptors

Compounds that are substrates for the biological transporters are an exception to the rule.

Pharmaceutical drug discovery and delivery groups and companies are increasingly using Human Drug Absorption (HDA) Studies to better understand the biopharmaceutical properties of early drug candidates and establish Life Cycle Management (LCM) strategies for marketed drugs.[23]

The proactive adoption of HDA studies provides a significant guidance to pharmaceutical formulation scientists when planning and selecting a route of experimentation, out of a wide array of possibilities, that is, having a higher probability for successful formulation development. In addition, results from the HDA studies undertaken early in the clinical development give an indication of problem compounds and provide a reliable "route-map" for subsequent developments. If the drug is absorbed from the selective area of the intestine, an appropriate bioadhesive system may be developed to improve bioavailability.

CONCLUSION

In conclusion, the *in vivo* pharmacokinetics of drugs depends largely on the solubility and permeability. The BCS has proven to be an extremely useful guiding tool for the prediction of the *in vivo* performance of drug substance and development of new drug delivery systems to suit the performance of the drug in the body, as also for the regulation of bioequivalence of the drug product during scale-up and post approval. In the future, the BCS concept will probably be used increasingly in the early development of new drugs, including for analog selection as well as for initial formulation approaches.

REFERENCES

1. Khan GM. Controlled release oral dosage forms: Some recent advances in matrix type drug delivery systems. The Science 2001;1:350-54.
2. Sachan NK, Singh D. Evaluation of dried pulp from Carica papaya fruits as disintegrating agents in the formulation of metformin hydrochloride dispersible tablets. Journal of Assam Science Society 2006;46:20-2.
3. Amidon GL, Lennerlas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 1995;12:413-20.
4. Dressman J, Butler J, Hempenstall J, Reppas C. The BCS: Where Do We Go from Here? Pharmaceutical Technology 2001; 7:68-76. Available: www.pharmaportal.com

5. Center for drug evaluation, FDA "Guidance for Industry on Dissolution Testing of Immediate Release Solid Oral Dosage forms" 1997.
6. Center for drug evaluation, FDA "Guidance for Industry on the Waiver of *in vivo* Bioavailability and Bioequivalence for Immediate Release Solid Oral Dosage forms based on Biopharmaceutical Classification system" 2000.
7. Johnson SR, Zheng Weifan. Recent progress in computational prediction of aqueous solubility and absorption. AAPS J 2006;8 :E27-40.
8. Sharma, J.L. Dictionary of Chemistry. New Delhi India: CBS Publishers and Distributors; 1997. p. 558-60.
9. Ahuja, A., Khar, R.K. and Ali, J. Dosage Form Design. 1st ed. N.D. India: Birla Publications Pvt. Ltd.; 2004. p. 3-11.
10. Yu LX, Carlin AS, Hussain AS. Feasibility study of intrinsic dissolution rate as an alternative method to determine BCS solubility membership. AAPS annual meeting 2000.
11. Draft Guidance for Industry, "Waiver of *in vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms containing certain Active Moieties/Active Ingredients based on a Biopharmaceutic Classification System". CDER/FDA 1999.
12. British Pharmacopoeia Electronic version: Appendix I D. Buffer Solutions. London: The Stationary Office; 2003.
13. Devane J. Oral drug delivery technology: Addressing the solubility/ permeability paradigm, Pharmaceutical Technology. 1998; 11:68-74.
14. Dressman J.B. Physiological aspects of the design of dissolution tests, in: Amidon G, Robinson J. Williams R. (eds.), Scientific foundation for regulating drug product quality. Alexandria, VA: AAPS Press. 1997;155-65.
15. Lobenberg R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. Eur J Pharm Biopharm 2000; 50:3-12.
16. Rinaki E, Valsami G, Macheras P. Quantitative biopharmaceutics classification system: The central role of dose/solubility ratio. Pharm Res 2003;20:1917-25.
17. Bergström CA, Strafford M, Lazorova L, Avdeef A, Luthman K, Artursson P. Absorption classification of oral drugs based on molecular surface properties. J Med Chem 2003;46:558-70.
18. Mirja, T. and Gray V.A. Meeting report: Conference on Dissolution, Bioequivalence and Bioavailability. Dissolution Technology 2004;11:25-8.
19. Verma RK, Garg S. Current status of drug delivery technologies and future directions. Pharmaceutical Technology (online) 2001; 25(2):1-14.
20. Jorgensen WL, Duffy EM. Prediction of drug solubility from structure. Adv Drug Deliv Rev 2002;54:355-66.
21. LobelL M, Sivrajah V. In silico prediction of aqueous solubility, human plasma protein binding and volume of distribution of compounds from calculated pKa and AlogP98 values. Mol Divers 2003;7:69-87.
22. Lipinsky CA, Lombordo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 1997;23:3-26.
23. Wikling IR, Prior DV. Remote controlled capsules in human drug absorption (HAD) studies. Crit Rev Ther Drug Carrier Syst 2003;20:405-31.

Source of Support: Nil, **Conflict of Interest:** None declared.