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Application of the Biopharmaceutical Classification System to Complementary and Alternative Medicines – A Systematic Review

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KEYWORDS

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ABSTRACT:

The Biopharmaceutical Classification System (BCS) has become a valuable tool in drug regulation around the world. Not only synthetic entities, but also herbal medicines (HMP) intended for oral and systemic use should fit into BCS. In the case of HMPs, the BCS is often missing due to the complex composition of their ingredients, the extensive metabolism of their chemical constituents, and analytical estimation problems that have led to adverse effects, toxicity, and interactions. It is therefore essential to regulate pharmaceutical standards for HMPs. Currently; research is focused on the integration of HMPs into BCS to determine the legal status of medicinal plants. With this in mind, several scientists have preliminarily installed HMPs in the BCS to overcome the solubility and permeability issues associated with HMPs, to establish quality standards for maximum therapeutic benefits. Our review article critically highlights relevant information for HMPs included in BCS and explained different formulation strategies.

Introduction

Herbal medicines (HMP), the oldest health care products known to have various therapeutic uses for hundreds of years. The World Health Organization estimates that about 80% of the world's population belonging to developing countries rely on HMPs for their primary health care, believing them to be more compatible with the body and associated with fewer side effects [1]. In fact, HMPs are not free of side effects. Randomized controlled trials have shown that HMPs often have adverse side effects. Some examples of these adverse side effects include the use of ephedra which causes cardiovascular problems, the consumption of kava kava led to hepatotoxicity, Datura metel as an asthma drug which causes decreased visceral activity and the use of licorice caused water retention [2,3]. In 1993, the American Herbal Products Association (AHPA) issued a warning to limit comfrey external application with pyrazolidine alkaloids resulted in hepatotoxicity. Due to the increase in side effects, regulatory authorities in many countries have issued warnings about HMPs [4]. Despite the increased use of HMPs by the public and the major health concerns that have been raised, concern among plant scientists has grown about these products to provide scientific evidence regarding the quality, safety and efficacy of their many chemical compounds responsible for the therapeutic action of HMPs.

History of Biopharmaceutical Classification System (BCS)

In 1995, the BCS was introduced to classify drugs based on their rate and extent of absorption, water solubility and gastrointestinal permeability [5]. For more than a decade, the World Health Organization (WHO), the US Food and Drug Administration (US

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FDA), and the European Medicines Agency (EMA) have implemented BCSs to set standards for market approval of medicines, with a particular focus on immediate release (IR) oral dosage forms. For in vivo testing of IR solid oral dosage forms, the FDA and EMEA have assigned BCS class I, i.e. high solubility and permeability, and the EMA has provided class III for drugs with high solubility and low permeability [6]. 123 IR drugs are tentatively classified according to BCS are included in the WHO Essential Medicines List 200 drugs from US, UK, Spain, Japan and 135 national essential drugs from Pakistan [7, 8].

(1) Biopharmaceutical Classification System (BCS)

To classify drugs according to the BCS, the solubility and permeability of the drug must be known. IR dosage forms must show > 85% release in 30 minutes, have the highest solubility over the pH range of 1-7.5 (dose/solubility ratio < 250 ml), higher permeability (absorbed fraction > 90%) and excipients must not exceed the rate of absorption. Drugs with a narrow therapeutic window and drugs that are absorbed into the oral cavity are not considered for the biowaiver. The BCS classifies drugs into 4 different classes.

Class I - drugs with high solubility and high permeability

Class II - drugs with low solubility and high permeability

Class III - drugs with high solubility and low permeability

Class IV - drugs with low solubility and low permeability

The FDA has modified BCS for regulatory purposes. The medicine integrated in the BCS provides information about changes after approval of a generic product without in vivo studies. Based on the BCS exemptions for in vivo testing of IR oral solid dosage forms, Class I can be granted if in vitro dissolution testing for two products can be comparable. According to WHO guidelines, the term biowaiver refers to a generic drug based on Active Pharmaceutical Ingredient (API) dissolution criteria as a surrogate for in vivo bioequivalence testing [9]. Now there is more attention for biowaivers for fast-dissolving, poorly permeable class III drugs [10] and the procedure has been included in European EMA guidelines [11]. For weakly acidic medicines, the WHO has included a biological release procedure if they dissolve quickly at pH 6.8.

Herbal BCS regulations across the world

HMPs were unregulated in several parts of the world and considered dietary supplements in the United States. Only Europe and Canada have regulations requiring approval [12]. In China, the registration of Chinese herbal medicines was in accordance with the Medicines Administration Law of the People's Republic of China. But in the approval process, the traditional bioavailability/bioequivalence has not been achieved for traditional Chinese medicine compared to Western medicines [13]. In case of inconsistency of HMP during production, content uniformity, different pesticide use, heavy metal contamination, excipient inconsistency, time and place of harvest, other contaminants, and mislabeled herbal medicines were different in different countries, which ultimately led to adverse effects. , toxicity and interactions between herbal medicines. It is therefore essential to regulate pharmaceutical standards for HMPs [14]. BCS for herb markers has different implications in many parts of the world. Due to fewer establishments of reference products, the concept of phytoequivalence has become theoretical to a certain extent. The basic principles of BCS for HMPs can be used to gain knowledge and are useful for establishing in vitro quality standards for HMPs.

Application of BCS to HMP's

The BCS concept should be valid for herbal medicines containing more than one ingredient and for herbal products containing more than one herb. The application of BCS to HMPs is more complex compared to synthetic drugs with one or few combinations of APIs with a defined excipient matrix.

Today, BCS applied to HMPs in which herbal marker compounds were classified based on BCS principles [15] to establish dissolution standards, ensure consistency of orally used HMPs at minimum cost, establish in vitro quality standards to maximize global therapeutic achieve benefit. The biopharmaceutical quality of herbal medicinal products (PMH) intended for systemic action should be assessed in terms of quality, efficacy and safety in accordance with regulatory guidelines. HMPs should be characterized

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by appropriate in vitro and in vivo experiments. But mostly the biopharmaceutical characterization of HMPs has been difficult due to the complex composition of the extensive metabolism of their chemical constituents and led to analytical difficulties, such information is not available at this stage. The BCS concept is useful for HMPs with known therapeutic activity based on their dissolution, solubility and permeability data [16]. BCS characterization for multi-ingredient HMPs would be more complex compared to synthetic chemical entities due to the lack of proper regulation worldwide. The small number of herbal reference product establishments to some extent drives the concept of theoretical phytoequivalence. But the concept of BCS can be used to gain biopharmaceutical knowledge about herbal markers. BCS characterization of herbal markers can be useful in setting quality standards for HMPs, especially in designing disintegration tests for herbal formulations with highly soluble ingredients (classes I and III) may only be required to meet disintegration specifications, but with poorly soluble components (classes II and IV) must pass a batch-to-batch consistency dissolution test demonstrating estimated content. It is very difficult and expensive to obtain clinical data on safety and efficacy and batch to batch consistency for HMPs. Compared to synthetic drugs, the quality of HMP was not well documented, which is very essential [17]. However, there is currently a need for an assessment of the biopharmaceutical quality of herbal medicinal products intended for oral use. Therefore, a classification system for herbal medicines has been developed based on information on herbal extracts by the European Pharmacopoeia and the International Pharmaceutical Federation (FIP). Based on this classification system, herbal extracts can be classified into three categories.

Class A: Standardized extracts containing components solely responsible for therapeutic activity. (Milk thistle, Senna)

Class B: quantified extracts whose components contain active markers. (St John's Wort, Ginkgo)

Class C: Other extracts without ingredients documented to be relevant to efficacy or have pharmacological or clinical relevance. (Valerian) Again, these categories can be divided into extracts with negative marker substances that should be restricted due to their toxicity or phytoequivalence markers that can be used to establish bioequivalence between products (Ginkgobiloba flavonoid glycosides). In Europe, type A or B extracts, BCS and biowaivers could be used to establish pharmaceutical equivalence for markers and modifications of HMPs after approval to demonstrate in vitro stability, but type C extracts are not due to the absence of known active ingredients (18). The BCS concept can be useful for sorting extracts from category C to category B or A.

The main purpose of our review article is to provide relevant information about HMPs and herbal components provisionally included in the BCS system. All herbal ingredients incorporated in BCS are listed in Table 1.

Methods

Important parameters required to classify drugs in BCS include number of doses, solubility, permeability, and dissolution. According to FDA guidelines for biologic release, lack of evidence suggests gastrointestinal instability, a drug is considered highly permeable when the rate of absorption is 90% or more than the administered dose in humans [18].

Dose

The dose used for the calculation of the dose: solubility (D:S) in mg/ml is the maximum recommended dose for this medicinal product. The dose may differ from the prescription specifications given in different countries.

Solubility

For an immediate release dosage form, solubility is defined as the highest dose. A drug molecule is considered highly soluble in the pH range of 1 to 7.5 when the highest dose is soluble in an aqueous medium of 250 ml or less at 37°C. The protocols prescribe the administration of the drug to human volunteers fasting with a glass of water. The main purpose of BCS was to determine the equilibrium solubility of the drug at a physiological pH of 1 to 7.5. The pH conditions for drug solubility were based on the ionization characteristics of the drug used for the test [19]. A minimum of three repeat solubility determinations under each pH condition is recommended. Reliable estimation of solubility may sometimes require additional repetition, depending on the variability of the

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study. Buffer solutions used for solubility studies should be prepared according to pharmacopoeial guidelines. By adding the drug to the buffer solution, the pH should be controlled. Methods such as acid/base titration are preferred with a different justification than the traditional shake flask method to predict the equilibrium solubility of the tested drug. A validated stability indication test is used to determine the drug concentration in selected buffers to differentiate the drug from other degradation products. Stability data must report whether there is any degradation of the drug, which is observed based on buffer composition or pH [20].

Permeability

Effective permeability is defined as units of molecular motion per unit time. High permeability drugs have an absorption rate greater than or equal to 90% and are not associated with problems of gastrointestinal instability. The method for determining permeability varies from simple oil/water partition coefficient to absolute bioavailability studies. The methods are given below [21].

• Extent of absorption in humans - Mass balance pharmacokinetic studies

Absolute bioavailability studies

• Intestinal Permeability Methods:

– In vivo intestinal perfusion studies in humans

– In vivo or in situ intestinal perfusion studies in animals.

– In vitro permeation experiments with excised human or animal intestinal tissue.

– In vitro permeation experiments through monolayers of epithelial cells (5)

The primary source of permeability data was the fraction included in human studies. In some cases, results from the Caco-2 cell line were considered with human trials as additional evidence (cimetidine, ciprofloxacin, furosemide, phenoxymethylpenicillin, phenytoin, and propranolol). In some exceptional cases, animal data have been considered (acetazolamide, benznidazole, furosemide and sulfadiazine). Data such as oral versus intravenous administration, urinary recovery, radiolabeled drugs and infusion studies in humans were obtained. If possible, the absorbed fraction has been localized, otherwise the absolute bioavailability has been looked at. Drugs with reduced bioavailability due to impairment of the gastrointestinal tract or first-pass metabolism were marked with an asterisk. In the case of poorly soluble drugs, it is difficult to determine the bioavailability <90% due to a problem of solubility or permeability. Sometimes when the drug is given with food, the higher bioavailability is indicative of <90% absorption and has been considered a solubility problem rather than a permeability problem [22].

Dissolution methods

The 85% of the labeled immediate release (IR) claim must dissolve within 30 minutes using United States Pharmacopeia (USP) Device I (100 rpm) or Device II (50 rpm) in a volume of 900 mL or less buffered in a medium such as 0.1 N HCl or USP simulated enzyme-free gastric fluid pH 4.5 and 6.8 or USP simulated enzyme-free intestinal fluid. The legal interest is to know the similarity between the two curves. To indicate similarity, the FDA has set the public standard f2 value between 50 and 100. A minimum of 12 units should be used for each profiling. In the case of mean solution data, the first % point of the coefficient of variance must be less than 20% and the other times must be less than 10%. Before and after dissolution, measurements and the time points of dissolution of both products should be performed under the same test conditions. For IR drugs 15, 30, 45 and 60 minutes and for extended release (ER) products 1, 2, 3, 5 and 8 hours were considered dissolution times. A single measurement should be considered after 85% dissolution, as f2 values are sensitive to the number of dissolution times [23]. Profile comparison is not necessary for fast dissolving products, i.e. more than 85% solution in 15 min or less. An F2 value greater than 50% indicates the equivalence of the two curves and additionally indicates the performance of the drugs. High variability is observed under certain conditions, after which a bootstrap approach is used for statistical evaluation to calculate the confidence interval. According to the FDA's biowaiver, the drugs were classified in BCS based on the above data.

Applications of BCS

BCS is a simple tool useful in early development for the determination of oral absorption in the drug

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development process. For IR drugs, the FDA grants an exemption for time-consuming bioequivalence studies, shortening timelines in the drug development process. For Class 1 drugs, it is essential to achieve a target release profile with a pharmacokinetic/ pharmacodynamic profile and formulation approaches such as release rate control and properties such as the pH solubility profile of the drug were essential. In the case of class II drugs, the necessary techniques are micronization, lyophilization, addition of surfactants, microemulsion systems and addition of complexing agents. Class III drugs require the fundamental limits of absolute permeability to be addressed. Class IV drugs pose major challenges in drug development and the route of administration of these drugs involves parent formulation with solubility enhancers [20].

Table-1: HMP's and their BCS Classification

SNO	HMP's	Constituents	BCS class	Reference
1.	Ginseng	ginsenoside Rb1	Class III	15
2.	Ginseng	ginsenoside Rb2	Class III	15
3.	Ginseng	ginsenoside Rc	Class III	15
4.	Ginseng	ginsenoside Rd	Class III	15
5.	Ginseng	ginsenoside Re	Class III	15
6.	Ginseng	ginsenoside Rf	Class III	15
7.	Ginseng	ginsenoside Rg1	Class III	15
8.	Ginseng	ginsenoside Rg2	Class IV	15
9.	Garlic	Alliin	Class III	15
10.	Garlic	Allicin	Class I	15
11.	Gensing	protopanaxadiol	Class IV	15
12.	Gensing	propanaxatriol	Class IV	15
13.	Ginger	6-gingerol	Class I	15
14.	Ginger	8-gingerol	Class I	15
15.	Ginger	10-gingerol	Class II	15
16.	Ginger	6-shogaol	Class I	15
17.	Ginger	8-shogaol	Class II	15
18.	Ginger	10-shogaol	Class II	15
19.	Ginger	6-gingerdione	Class I	15
20.	Ginger	8-gingerdione	Class I	15
21.	Gingko	bilobalide	Class III	15
22.	Gingko	ginkgolide A	Class III	15
23.	Gingko	ginkgolide B	Class III	15
24.	Gingko	ginkgolide C	Class III	15
25.	Gingko	quercetin-3-O-coumaryl-glycosyl-rhamnoside	Class III	15
26.	Milk Thistle	silybin A	Class III	15
27.	Milk Thistle	silybin B	Class III	15
28.	Red Clover	biochanin A	Class IV	15
29.	Red Clover	daidzein	Class IV	15
30.	Red Clover	formononetin	Class II	15
31.	Red Clover	genistein	Class IV	15
32.	Senna	sennoside B	Class III	15
33.	Senna	sennidin B	Class IV	15

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34.	St. John's Wort	hyperforin	Class II	15
35.	St. John's Wort	hypericin	Class IV	15
36.	St. John's Wort	pseudohypericin	Class IV	15
37.	Theophyllin		Class I	20, 38, 39, 40, 41
38.	allicin tablet	allicin	Mixed (Class III &I)	21
39.	andrographolide tablet	andrographolide	Mixed (Class III &I)	21
40.	anisodine tablet	anisodine	Class III	21
41.	asiaticosid tablet	asiaticoside	Mixed (Class IV&II)	21
42.	atractylodes	atractylodin	Class II	21
43.	Banlangen	(R,S)- goitrin	Class I	21
44.	blister beetle oral pill	cantharidin	Class III	21
45.	breviscapine	scutellarin	Class III	21
46.	butylphthalide capsule	butylphthalide	Class II	21
47.	Cascara	cascaroside A	Class III	21
48.	Cascara	cascaroside A aglycon	Class III	21
49.	Chamomile	apigenin	Class IV	21
50.	Chamomile	quercetin	Class IV	21
51.	Chinese arborvitae	quercitrin	Class I	21
52.	extract of horse chestnut seeds tablet	esculin	Class III	21
53.	Ginkgo biloba leaf extract tablet	quercetin	Class I	21
54.	Ginkgo biloba leaf extract tablet	kaempferol	Class I	21
55.	Ginkgo biloba leaf extract	isorhamnetin	Class II	21
56.	Ginkgo biloba leaf extract tablet	bilobalide	Class I	21
57.	Ginkgo biloba leaf extract tablet	ginkgolide A	Mixed(Class III &I)	21
58.	Ginkgo biloba leaf extract tablet	ginkgolide B	Class I	21
59.	Ginkgo biloba leaf extract tablet	ginkgolide C	Class I	21
60.	Gongxuening capsule	polyphyllin VI	Class II	21
61.	lappaconitine tablet	appaconitine	Class I	21
62.	Leonurus	leonurine hydrochloride	Class III	21
63.	Licorice	glycyrrhizic acid	MIXED(Class IV & II)	21
64.	Licorice	liquiritin	MIXED(Class II & IV)	21
65.	ma-huang	ephedrine hydrochloride	Class III	21
66.	ma-huang	pseudoephedrine hydrochloride	Class III	21

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67.	manyprinckle acanthopanax root	syringoside	Class III	21
68.	milkvetch root	astragaloside IV	MIXED(Class IV & II)	21
69.	milkvetch root	calycosin-7-glucoside	Class III	21
70.	moschus pill	muscone	Class I	21
71.	notoginseng total saponins	gensenoside Rg1	MIXED (Class IV &II)	21
72.	notoginseng total saponins	gensenoside Rb1	Class II	21
73.	notoginseng total saponins	notoginsenoside R1	MIXED (Class IV &II)	21
74.	notoginseng total saponins	gensenoside Re	Class II	21
75.	notoginseng total saponins	gensenoside Rd	Class II	21
76.	pingxiao tablet	strychnine	Class III	21
77.	qingkailing tablet	baicalin	Class III	21
78.	qingkailing tablet	cholic acid	Class II	21
79.	qingkailing tablet	geniposide	Class I	21
80.	red peony root	paeoniflorin	MIXED (Class IV & II)	21
81.	red sage	tanshinone IIA	Class II	21
82.	red sage	salvianolic acid B	MIXED (Class II	21
83.	shuanghuanglian tablet	chlorogenic acid	Class III	21
84.	shuanghuanglian tablet	baicalin	Class IV	21
85.	shuanghuanglian tablet	forsythin	Class III	21
86.	silybin meglumine tablet	silybin meglumine	Class II	21
87.	tang-kuei	ferulic acid	Class III	21
88.	Ufang danshen tablet	tanshinone IIA	Class II	21
89.	Ufang danshen tablet	salvianolic acid B	MIXED (Class I &III)	21
90.	Xueshuan xinmaining capsule	anhydrous rutin	Class III	21
91.	Chloroquine		Class I	22
92.	Codeine phosphate		Class III	22, 23,24,25
93.	Colchicine		Class III	22, 26,27
94.	Ergotamine Tartrate		Class III	22,33,34, 35,36
95.	Cinnamon	cinnamaldehyde	Class I	24
96.	Digoxine		Class I	28,29,30,31,32
97.	Fruits and vegetables	Apigenin	Class II	37

BCS Applications in formulation development

BCS is a simple tool useful in early development for determining oral absorption in the drug development process [5]. For IR drugs, the FDA grants an exemption for time-consuming bioequivalence studies, shortening timelines in the drug development process. For Class I drugs, it is essential to achieve a target release profile with a pharmacokinetic/ pharmacodynamic profile and formulation approaches

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such as release rate control and properties such as the pH solubility profile of the medication are essential. In the case of class II drugs, the necessary techniques are micronization, lyophilization, addition of surfactants, microemulsion systems and addition of complexing agents. Class III drugs require the fundamental limits of absolute permeability to be addressed. Class IV drugs pose major challenges in drug development and the route of administration of these drugs involves parent formulation with solubility enhancers. Therefore, it may be useful to extrapolate this experience to formulation development concepts, as shown in Figure 1.

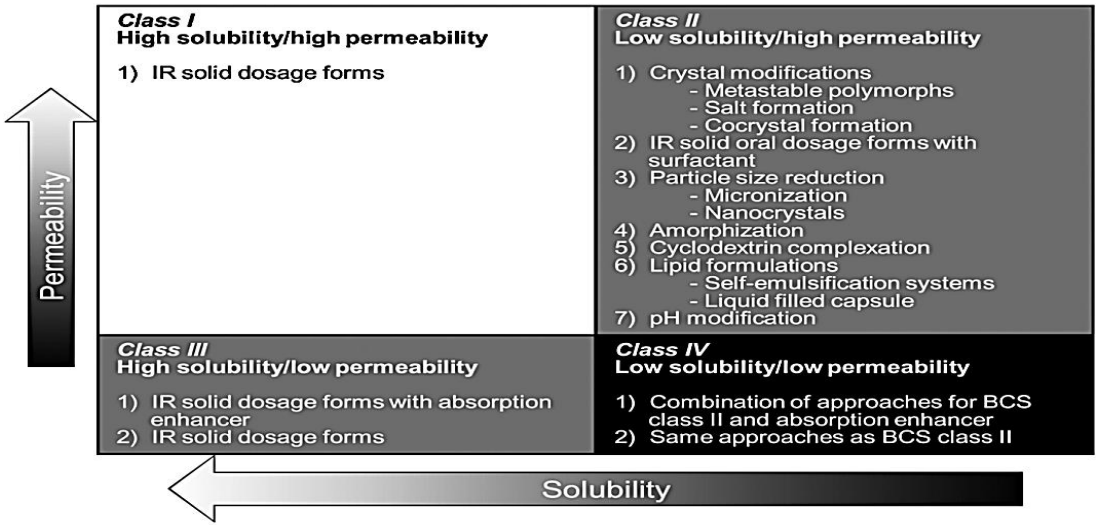

Figure 1: BCS and concepts for viable formulation options

Formulation strategies based on Biopharmaceutics classification system

Formulations for BCS class I drugs

IR solid oral dosage forms, for example conventional tablet or capsule formulations, are generally designed to dissolve rapidly in the gastrointestinal tract [42].

Formulations for BCS class II drugs

In general, the bioavailability of a BCS Class II drug is limited by its dissolution. Therefore, improving the drug dissolution rate is considered a key factor to improve the bioavailability of BCS class II drugs. Various physico-chemical factors determine the dissolution rate of drugs. Crystal modification [43], particle size reduction [44], self-emulsification [45], pHmodification [46] and amorphization [47] are considered effective in improving the dissolution behavior of BCS class II drugs, as shown in Fig. 2.

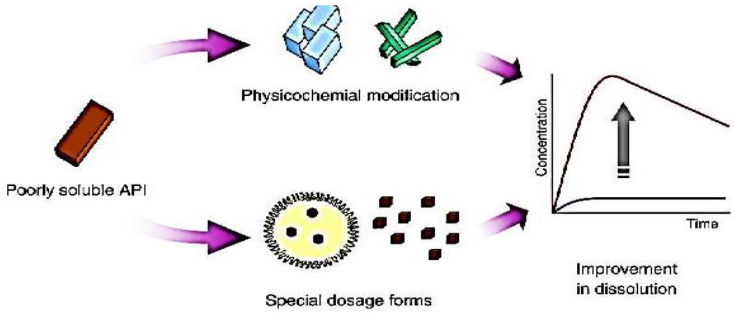

Figure 2: Different strategy for improvement of poor soluble drugs.

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Formulations for BCS class III drugs

The bioavailability of BCS class III drugs is limited by membrane permeability in the gastrointestinal tract. For BCS Class III drugs, solid IR dosage forms must be conveniently designed for clinical use, although absorption may be limited by membrane permeation. Permeation enhancers, such as fatty acids, bile salts, surfactants and polysaccharides, play a role in enhancing drug permeability through the paracellular pathway [48,49].

Formulations for BCS class IV drugs

Formulation approaches similar to BCS Class II and III can be practically applied to BCS Class IV drugs, although absorption may be limited by low permeability after dissolution in the gastrointestinal tract [50].

Delivery options for class IV drugs

In drug discovery, combinatorial chemistry and high-throughput screening often lead to new high molecular weight chemical entities with increasing lipophilicity and therefore decreasing water solubility [51,52]. It is estimated that almost 40% of drugs under development have solubility problems and 60% of new drugs are poorly soluble in water [53]. To achieve its pharmacological activity, the drug must be present in a dissolved state at the site of absorption during oral administration [54]. Many approaches have been developed to improve the solubility of drugs in the aqueous phase, such as crystal modifications, salt formation, particle size reduction, amorphization, complexes with cyclodextrin, self-emulsification, pH modification, nanocrystals and lipid formulations [55].

Conclusion

The BCS Principles in Alternative and Complementary Medicine provide a reasonable approach to testing and approving the quality of herbal products. Class 2 and 4 BCS applications are challenging and offer opportunities to reduce regulatory pressure with scientific substantiation. The current BCS classification of herbal extracts and their markers has shown that some special considerations need to be incorporated into the classification strategy, such as pharmacological knowledge of markers to categorize herbal extracts and to conduct subsequent research. vivo correlation. The application of solubility-based classification can be used in product development to choose an appropriate marker for dissolution studies. When no upper dose limit is known for a marker or when the active substances are not known, a marker classification based on solubility provides information when a marker changes from poorly soluble to highly soluble, which can help select the right marker for quality control purposes. Similarly, clinical researchers can use classification to choose markers that have the appropriate solubility and permeability properties and can be detected in vivo. Applying BCS principles to medicinal plants and their markers can help improve the quality of herbal medicines.

Conflict of Interest

Authors declared no conflicts

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