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Interplay of extended clearance and salivary excretion classification systems

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ABSTRACT: The aim of this commentary is to investigate the interplay of Extended Clearance Classification System (ECCS) and Salivary Excretion Classification System (SECS). ECCS utilized the involvement of transporters to classify drugs based on permeability, ionization and molecular weight for the purpose of predicting rate determining clearance. On the other hand, SECS classified drugs based on permeability and protein binding for the purpose of predicting salivary excretion of drugs. The proposed Salivary Excretion Classification System (SECS) can be used as a guide for drug salivary excretion based on permeability and protein binding, but not transporters involved.

KEYWORDS: SECS; ECCS; transporters; BCS; ADMIT Predictor

1. INTRODUCTION

Drug effective permeability is major key factor in its transport across all body membranes such as membranes in the intestine, liver, blood capillaries, blood brain barrier and salivary mucosa. An interesting finding was noted that when drug effective permeability is high in the intestinal mucosa, it will undergo high metabolism in liver [1]. Similarly, when drug effective permeability is high in the intestinal mucosa, it will undergo salivary excretion in salivary mucosa [2].

Biopharmaceutics Classification System (BCS) first classified drugs based on permeability and solubility for the purpose of predicting oral drug absorption as shown in Table 1 [3], where high intestinal permeability corresponds to fraction absorption Fa > 0.9 and high solubility corresponds to the highest oral dose being soluble in 250 ml water.

Table 1. Biopharmaceutics Classification System (BCS) according to drug permeability (P_{eff}) and solubility (C_s).

Parameter Class	P_{eff}	C_s
Class I	High	High
Class II	High	Low
Class III	Low	High
Class IV	Low	Low

Then Bioharmaceutics Drug Disposition Classification System (BDDCS) linked permeability with hepatic metabolism and classified drugs based on metabolism and solubility for the purpose of predicting oral drug disposition as shown in Table 2 [1]. BDDCS uses liver metabolism instead of permeability, since drug metabolism data is more available and consistent than permeability data, where high metabolism drugs have extraction ratio > 70 % and low metabolism drugs have extraction ratio < 30 %. It was found that 27 out of 29 drugs (93.1 %) of the high permeability drugs were highly metabolized in the liver, with few unexplained exceptions [4].

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Table 2. Biopharmaceutics Drug Disposition Classification System (BDDCS) according to drug metabolism and and solubility (Cs).

Parameter Class	Metabolism	C_s
Class I	High	High
Class II	High	Low
Class III	Low	High
Class IV	Low	Low

2. RESULTS

Salivary Excretion Classification System (SECS) classified drugs based on permeability and protein binding for the purpose of predicting salivary excretion of drugs as shown in Table 3 [2]. Similar to Biopharmaceutics Classification System BCS, Salivary Excretion Classification System (SECS) high intestinal permeability corresponds to fraction absorption Fa > 0.9. On the other hand, high protein binding corresponds to low fraction unbound fu of < 0.1 [2]. The salivary excretion is possible only for SECS classes I, II & III. Indeed, saliva can be used instead of plasma for therapeutic drug monitoring but need high sensitive instruments for the drug assay in saliva.

Table 3. Salivary Excretion Classification System (SECS) according to drug permeability (P_{eff}) and fraction unbound to plasma proteins (fu).

Parameter Class	P_{eff}	Fu	Salivary excretion
Class I	High	High	Yes
Class II	Low	High	Yes
Class III	High	Low	Yes
Class IV	Low	Low	No

Extended Clearance Classification System (ECCS) was proposed [6]. ECCS utilized the involvement of transporters to classify drugs based on permeability, ionization and molecular weight for the purpose of predicting rate determining clearance. Drugs were classified into these classes: 1A, 1B, 2, 3A, 3B, 4 (Figure 1). Class 1A & 1B determining clearance is metabolism for high permeability (more than $5X10^{-6}$ cm/sec) acids/zwitterions of molecular weights less than or equal 400, and hepatic uptake for molecular weights more than 400. Class 2 determining clearance is mainly metabolism for high permeability bases/neutrals. Classes 3A & 3B determining clearance is renal for low permeability (less than $5X10^{-6}$ cm/sec) acids/zwitterions of molecular weights less than 400, and renal/hepatic uptake for molecular weights more than 400. Class 4 determining clearance is mainly renal for low permeability bases/neutrals. Specific different enzymes and transporters control drug clearance according to ECCS [6]. SECS permeability is classified as high (H) is absorption is equal or more than 90%, while fraction unbound is classified as high (H) if protein binding is less than 90% (2). ECCS permeability is classified as high (H) when it is more than $5X10^{-6}$ cm/sec, while molecular weight is classified as high (H) if it is more than 400 daltons.

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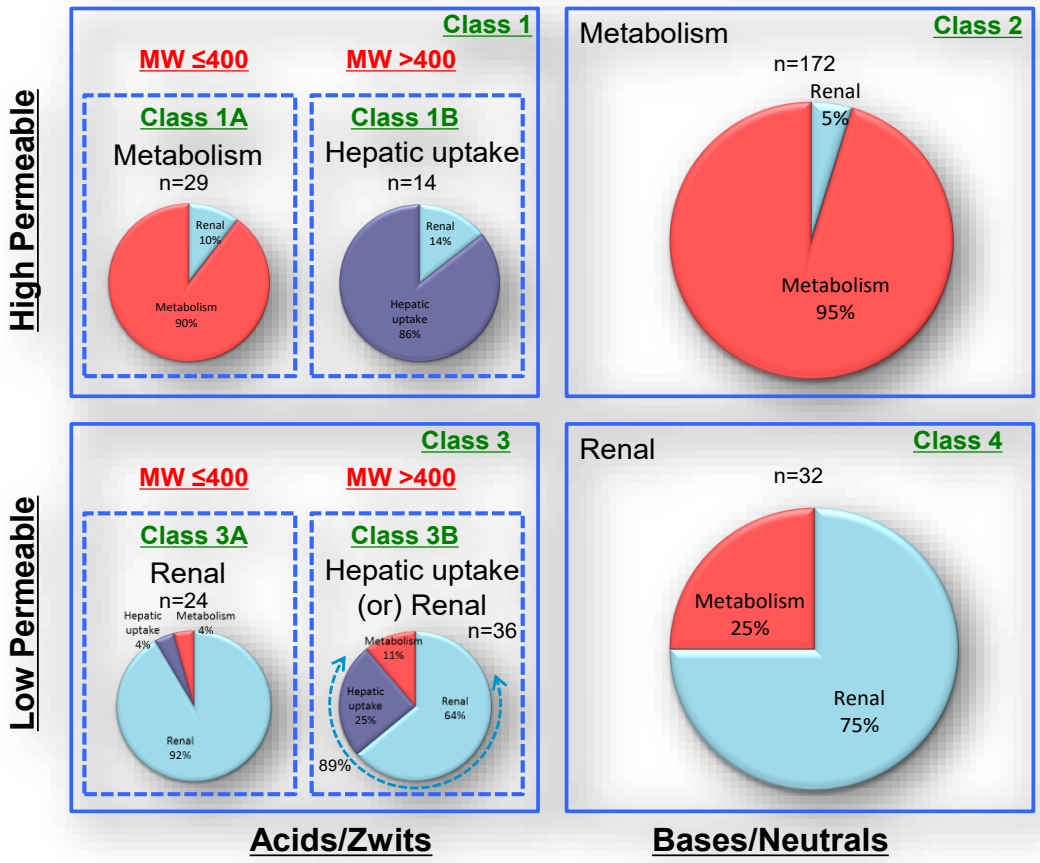

Figure 1. ECCS classification [6]

3. DISCUSSION

Results did not show any correlation between SECS and ECCS. It was found that drug salivary excretion does not depend on transporters. For example, Breast Cancer Resistant Protein (BCRP) was detected in salivary mucosa (7). However, salivary excretion does not depend on BCRP since some drugs of class 4 SECS are substrates to BCRP but are not excreted in saliva as shown in Table 4.

Table 4. SECS and ECCS interplay

Drug	Rate determining clearance*	BCRP Substrate*	ECCS Class*	SECS Class	Salivary Excretion
Azithromycin	Hepatic Uptake	No	4	I	Yes
Sitagliptin	Metabolism	Yes	4	I	Yes
Tolterodine	Metabolism	No	2	I	Yes
Carbamazepine	Metabolism	No	2	I	Yes
Erythromycin	Hepatic Uptake	No	4	I	Yes
Fluconazole	Metabolism	No	2	I	Yes

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Norfloxacin	Renal	Yes	1A	I	Yes
Paracetamol	Renal	Yes	2	I	Yes
Metformin	Renal	No	4	II	Yes
HCT	Renal	Yes	4	II	Yes
Cinacalcet	Metabolism	Yes	2	III	Yes
Cloxacillin	Metabolism	No	3B	III	Yes
Rosuvastatin	Hepatic Uptake	Yes	3B	III	Yes
Phenytoin	Metabolism	No	2	III	Yes
Tamsulosin	Metabolism	No	4	IV	No
Montelukast	Hepatic Uptake	No	1B	IV	No
Lornoxicam	Metabolism	Yes	1A	IV	No
Losartan	Hepatic Uptake	Yes	3B	IV	No
Diacerhein	Metabolism	Yes	1B	IV	No
Ibuprofen	Metabolism	No	1A	IV	No

* predicted by ADMIT predictor V12.

4. CONCLUSION

The proposed Salivary Excretion Classification System (SECS) can be used as a guide for drug salivary excretion based on permeability and protein binding, but not transporters involved. There is no correlation between the two classification systems.

5. MATERIALS AND METHODS

The role of transporters on salivary excretion is investigated. ADMIT predictor V12 program (Simulation Plus, CA, USA) was used for ECCS classification and transporter finding. This was done by using Med Chem Designer to draw the chemical stucture of each drug. Then molecular properties were calculated. Finaly, the involved transporters and ECCS class were obtained directly from the ADMIT predictor program. Correlartion analysis between SECS and ECCS was done using Excell program. This was done by corrlating all drugs SECS classes versus ECCS classes.

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Concept – NI.; Design – NI.; Supervision – NI.; Resources – NI.; Materials – NI.; Data Collection and/or Processing – NI, EI.; Analysis and/or Interpretation – NI, EI.; Literature Search – NI.; Writing – NI.; Critical Reviews – NI

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