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Investigation of the Drug Dose, Alongside the Solubility, the Permeability, and their Interplay, as Key Factors in Formulation Development for Oral Lipophilic Drugs

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1. Introduction

Two main key factors that govern oral drug absorption are the solubility the drug in the aqueous intestinal milieu, and its permeability throughout the gastrointestinal (GI) membrane[1]. Many pharmacologically active substances fail to become drugs because of insufficient solubility. Although various formulations allow tackling this obstacle, the bioavailability of the drug often remains unchanged or even decreases with these formulations. We have previously revealed that while the solubility of the drug may be significantly increased, its permeability may concomitantly decrease; this solubility-permeability tradeoff may be the reason for the failure of many formulations[2]. In our previous study, such tradeoff was evident with the cosolvent PEG-400[3]. In the current study, we aimed to investigate the dose, the solubility, and the permeability, as key factors in oral formulation development for lipophilic drugs formulated with 100% cosolvent PEG-400. We used carbamazepine (CBZ) as a drug model.

2. Materials and methods

The solubility of the lipophilic drug CBZ was studied in water and 100% PEG-400, at 25 °C and at 37 °C. Then, PEG-400 based formulation was studied for five CBZ doses (10, 25, 50, 100 and 200 mg/kg) accounting for the biorelevant dissolution of the dose in the gastro intestinal tract and the in-vivo bioavailability in rats.

3. Results

PEG-400 allowed a substantial solubility increase of CBZ, compared to its solubility in water; the drugs' solubility increased ~700% and ~300%-fold at room temperature and at 37 °C, respectively (***Figure 1***). The biorelevant pH-dilution dissolution studies allow to evaluate the ability of the formulation to achieve and maintain drug dose dissolution while its travel along the rat intestinal tract (Figure 2). According to this experiment, 100% PEG-400 formulation succeeded to achieve and maintain complete in-vitro dissolution throughout the experiment of three lower doses of CBZ (10, 25 and 50 mg/kg), however

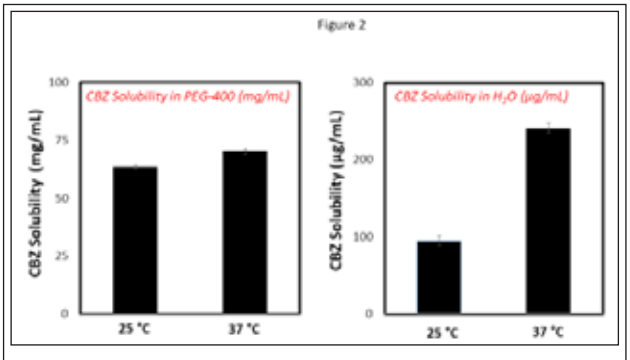

Figure 1 *C solubility in PEG-400 (left panel) and in water (right panel), at room temperature (25 °C) and at 37 °C.*

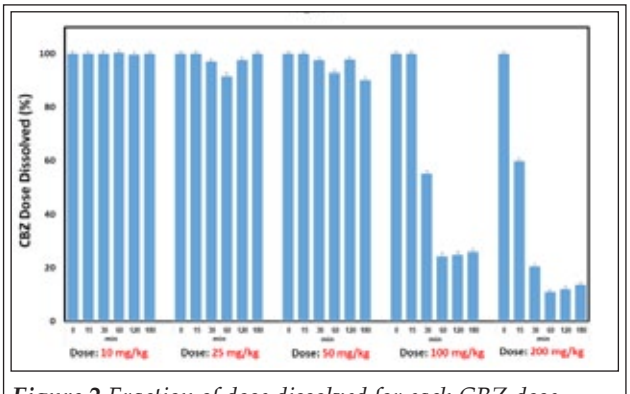

Figure 2 *Fraction of dose dissolved for each CBZ dose throughout the time course of the dissolution experiment.*

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Table I *CBZ PK parameters following oral administration of the different doses to rats (n=5). Similar formulation (100% PEG-400) was administered to all experimental groups. Data presented as average (SD). AUC following i.v. administration of 5 mg/kg CBZ (n=3) was 162 (6) μg/mL×min, and this value was used for bioavailability (F) calculations.*

PK parameter	10 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg
$t_{1/2}$ (min)	116 (22)	132 (40)	312 (27)	532 (80)	730 (113)
T_{max} (min)	90	120	120	150	150
$C_{max\ (\mu g/mL)}$	2 (0.14)	4 (0.23)	5 (0.12)	11 (0.1)	12 (0.15)
$AUC_{0\text{-}t\ (\mu g/mL \times min)}$	453 (8)	1033 (64)	1943 (110)	3390 (210)	3586 (30)
F (%)	100 (14)	100 (8)	100 (6)	76 (7)	42 (3)
k_a	$8.60E^{-3}$ ($8.65E^{-4}$)	$5.5E^{-3}$ ($1.6E^{-3}$)	$2.22E^{-3}$ ($1.9E^{-4}$)	$1.32E^{-3}$ ($1.9E^{-3}$)	$1.18E^{-3}$ ($7.4E^{-4}$)

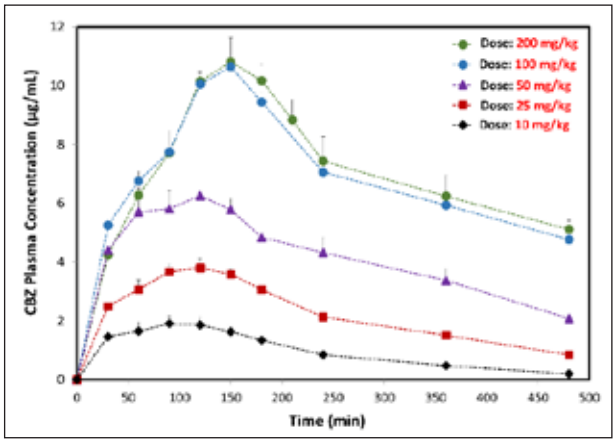

Figure 3 *CBZ rat plasma PK profiles following oral administration of the different doses in the studied formulation (100% PEG-400).*

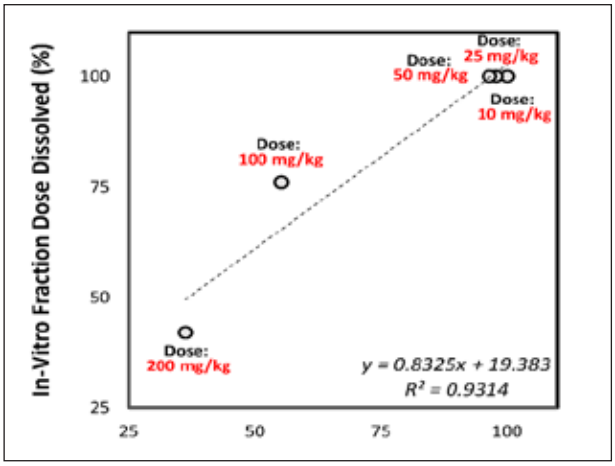

Figure 4 *CBZ rat plasma PK profiles following oral administration of the different doses in the studied formulation (100% PEG-400).*

significant precipitation occurred with higher drug doses (100 and 200 mg/kg). Likewise, the studied formulation allowed complete bioavailability (100%) in-vivo with three lower doses, while the same formulation allowed only 76% and 42% bioavailability for the 100 and 200 mg/kg doses, respectively (Figure 3, Table 1)). Good correlation was evident between the in-vitro and in-vivo results (Figure 4).

4. Conclusions

This work demonstrates that the dose is a crucial factor in the formulation development process; each formulation has limited drug capacity, drugs quantities beyond this capability will fail to reach the full drug bioavailability, may result in gastro intestinal side effects and is a waste of the drug substance. Hence, the solubility, permeability, and their interplay, in light of the drug dose intended to be administered, have to be considered for successful oral formulation development.

References

1. *Amidon, Gordon L., et al. "A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability." Pharmaceutical research, 12.3:*
2. *413-420 (1995).*
3. *Beig, Avital, et al. "Accounting for the solubility–permeability interplay in oral formulation development for poor water solubility drugs: the effect of PEG-400 on carbamazepine absorption." European journal of pharmaceutics and biopharmaceutics, 81.2: 386-391 (2012).*
4. *Beig, Avital, et al. "Striking the optimal solubility– permeability balance in oral formulation development for lipophilic drugs: maximizing carbamazepine blood levels." Molecular pharmaceutics, 14.1: 319-327 (2017).*