



The development of a link model consisting of *in vitro* drug release and tablets gastric emptying time: Application to diclofenac enteric coated tablets

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Gastric emptying (GE) of tablets under fasting conditions

Tablets gastric emptying times were gathered from 19 studies during the literature search. Tablets of round and capsule shape of various sizes were administered to healthy subjects together with 50 – 250 mL of water under fasting conditions. The gastric emptying of tablets was evaluated by gamma-scintigraphy or magnetic marker monitoring. In total 153 tablets gastric emptying times were obtained [1].

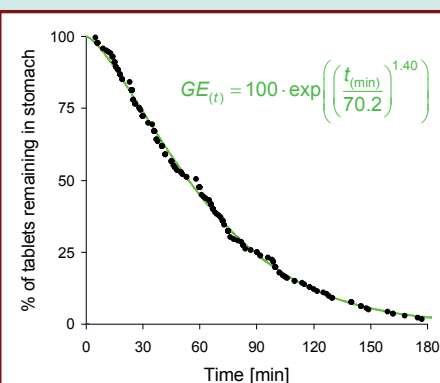


Figure 1.
Cumulative distribution function of tablets gastric emptying (GE) times.
Weibull function fit.

Simulation of diclofenac *in vivo* release profiles

A vector of 100 individual tablets gastric emptying times was generated in R environment using the Weibull function (Figure 1). On the basis of these values and *in vitro* diclofenac release model (Table 1), 100 individual predicted *in vivo* diclofenac release profiles were obtained using NONMEM simulation step (Figure 3).

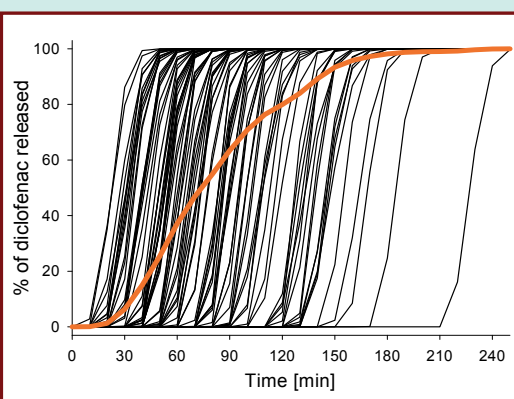


Figure 3.
Individual predicted *in vivo* diclofenac release from enteric coated Voltaren tablets (n = 100).
Mean *in vivo* release profile.

Modelling of *in vitro* diclofenac release data

Diclofenac release from 50 mg enteric coated Voltaren tablets was tested using simulated gastric fluid (pH = 1.2), which was replaced by simulated intestinal fluid (pH = 6.8) after 2, 10, 30, 50, 70, 90, 110, 130, 150, and 200 minutes in order to mimic tablets several gastric residence times (GRT). Each *in vitro* experiment was performed in triplicates. Modelling of diclofenac release (DR) data was performed in NONMEM using lag time (t_{lag}) Weibull model:

$$DR_{(t)} = 100 \cdot \left(1 - \exp \left(- \left(\frac{t - \theta_{lag} - GRT \cdot \theta_{GRT}}{\theta_{\eta}} \right)^{\theta_{\beta}} \right) \right)$$

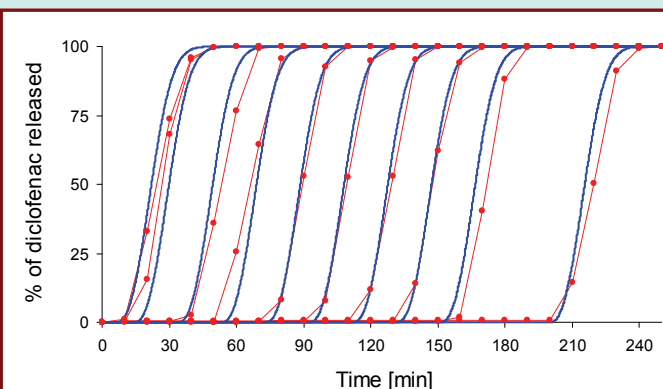


Table 1. *In vitro* diclofenac release model.

Parameter	Estimate	RSE
θ_{β}	2.45	3.9%
θ_{η} [min]	18.2	3.4%
θ_{lag} [min]	4.39	14%
θ_{GRT}	0.978	1.3%
ω_{lag} (proportional)	6.0%	38%
ω_{η} (exponential)	0.17	50%
Residual error	4.1%	17%

Figure 2.

Mean *in vitro* dissolution profiles (n = 3) obtained at several residence times in simulated gastric fluid.
Population predicted values for diclofenac released (DR).

Figure 4.

Mean diclofenac plasma concentrations after administration of enteric coated Voltaren tablets (reference) under fasting conditions [2]. Decovolution of the mean profile was performed using Wagner-Nelson method. *In vitro* – *in vivo* correlation: %_{abs} = 0.934%_{diss} + 1.40 (R² = 0.992).

CONCLUSION

The link between diclofenac release from enteric coated Voltaren tablets and tablets GE times was estimated allowing adequate prediction of *in vivo* diclofenac release profiles.

REFERENCES

- [1] Locatelli I, et al. Statistical evaluation of gastric emptying of tablets under fasting conditions: Application to diclofenac *in vivo* release profiles. *In preparation*.
- [2] Drugs@FDA: Diclofenac sodium bioequivalence reviews for ANDA No. 074986 (1998). http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/74986_Diclofenec%20Sodium_bioeqr.pdf, p.43 (4/6/2010).