T4013

DEVELOPMENT OF MECHANISTIC IN VITRO IN VIVO CORRELATION (IVIVC) OF ABUSE-DETERRENT HYDROCODONE BITARTRATE EXTENDED RELEASE TABLETS

Satish Sharan[1], Anna Externbrink[2], Dajun Sun[1], Xinyuan Zhang[1], Jianghong Fan[1], Wenlei Jiang[1], Zongming Gao[2], David Keire[2], Robert Lionberger[1] and Liang Zhao[1]

[1]Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, CDER, FDA

[2]Division of Pharmaceutical Analysis, Office of Translational Research, Office of Pharmaceutical Quality, CDER, FDA

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PURPOSE

Hydrocodone bitartrate extended-release (ER) tablets are indicated for the management of severe pain that requires daily, around the clock, long-term opioid treatment for which alternative treatment options are inadequate. Abuse of opioids is a serious public health threat. Hydrocodone bitartrate ER tablet has been approved by FDA as having abuse-deterrent properties that are expected to deter misuse and abuse via chewing followed by oral ingestion in addition to intranasal and intravenous abuse deterrence claims. The aim of this work was to develop an in vitro-in vivo correlation (IVIVC) model based on physiologically based pharmacokinetic absorption modeling. The established relationship may be used for predicting the in vivo behavior of hydrocodone bitartrate ER tablets after chewing followed by oral ingestion, using modeling and simulation approaches. The in vitro chewing method may be further developed into an alternative to the in vivo PK studies evaluating comparative abuse deterrence between reference and test products.

METHODS

Mean plasma PK data for solution, intact, chewed and milled forms of hydrocodone bitartrate ER tablets were collected from published FDA reviews. The PK study results used in this analysis were conducted in healthy nondependent recreational drug users with moderate experience with opioids using a double blind, randomized, crossover study design. In vitro dissolution method for chewing study was developed and optimized in-house using Erweka DRT 3 chewing apparatus and was used in conjunction with the FDA recommended dissolution method for hydrocodone bitartrate ER tablet. Dissolution data for intact and crushed tablets were generated in-house using the FDA recommended dissolution method with slight modification for milled tablets. GastroPlus (version 9.0, Simulations Plus Inc. Lancaster, CA) based on ACAT (Advanced Compartmental Absorption and Transit) model was used to perform physiologically based pharmacokinetic (PBPK) modeling to predict the mean plasma profiles of healthy volunteers orally administered with intact, chewed and milled forms of hydrocodone bitartrate ER tablets. The PK parameters used in the PBPK model were estimated using oral solution mean PK data of hydrocodone bitartrate ER tablet. .

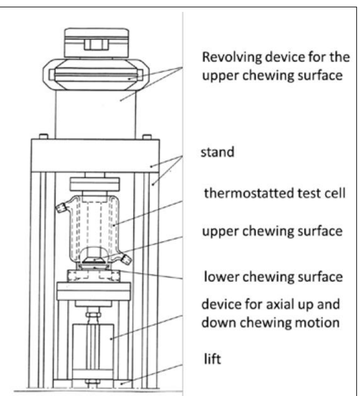

Figure 1: Erweka DRT 3 Chewing Apparatus (Image courtesy of Erweka)

RESULTS

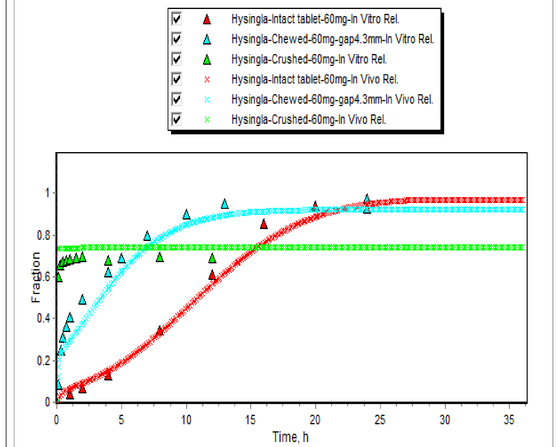

Figure 2: Comparison between observed in vitro and PBPK model deconvoluted in vivo dissolution profile for intact, chewed and crushed forms of hydrocodone.

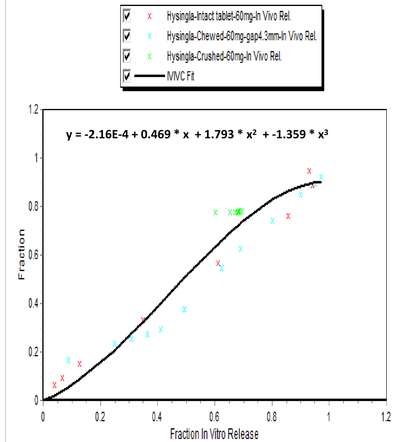

Figure 3: A third order polynomial correlation was found between in vitro dissolution and the in vivo absorption with a correlation coefficient of 0.95.

RESULTS

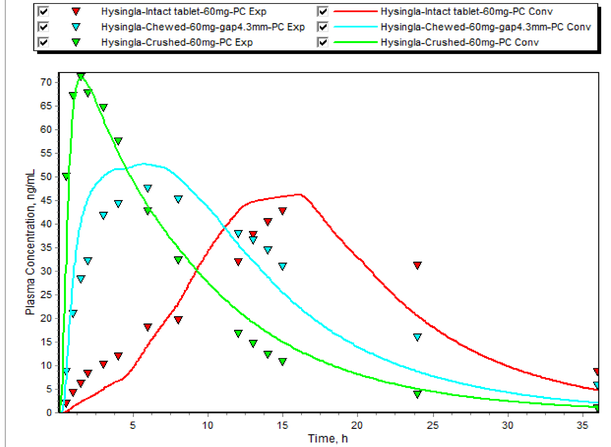

Figure 4: Observed and IVIVC model convoluted plasma concentration of hydrocodone for intact, chewed and crushed forms.

Table 1. Observed and predicted Cmax and AUC values with their respective absolute percentages of prediction error (%).

	Cmax (ng/mL)			AUC (ng/mL*h)		
Drug Record	**Obs.**	**Pred.**	**% Pred. Error**	**Obs.**	**Pred.**	**% Pred. Error**
Hysingla-Intact tablet	42.58	46.18	-8.44	854.90	779.90	8.78
Hysingla-Chewed	47.53	52.62	-10.72	895.80	815.30	8.99
Hysingla-Crushed	71.11	70.88	0.32	633.00	680.20	-7.46
Mean Prediction Error			**6.48**			**8.42**

RESULTS

- In in vitro dissolution experiments 12.8%, 61.1% and 94.1% of label claim were released after 4, 12 and 20 hours respectively for intact tablet.
- For milled tablets around 60.2% of label claim was released after 10 minutes and drug release reached a plateau of approximately 70% label claim after about one hour of dissolution. In vitro chewing study using Erweka DRT 3 apparatus with a gap size of 4.3 mm showed that 41.3% of labeled dose was released after 1 hour and the remaining drug was released with a similar rate as for intact tablet.
- Level A IVIVC was successfully developed to link in vitro dissolution data and in vivo plasma PK data after oral administration of intact, milled and chewed hydrocodone bitartrate ER tablets.
- The correlation was adequate with a correlation coefficient (R^2) above 0.9. The percentage prediction error (% PE) for Cmax and AUC for intact, chewed and crushed forms of hydrocodone bitartrate ER tablet ranged between 0.3 to 10.7 % and 7.5 to 9 % respectively.

CONCLUSION

The results suggest that the development of an IVIVC model for hydrocodone bitartrate ER tablets is feasible and the newly developed in vitro method of artificial chewing can be helpful in predicting the in vivo behavior of hydrocodone bitartrate ER tablet after chewing followed by oral ingestion..

DISCLAIMER

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