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In Vivo and *In Vitro* Performance of a Novel Self-Correcting 600mg 12-hour Controlled Release Formulation of Ibuprofen

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Summary

The release characteristics of a novel 600mg controlled release tablet formulation of ibuprofen were evaluated using in vitro dissolution studies and in vivo human pharmacokinetic studies. In vitro analysis showed the formulation was capable of releasing ibuprofen in a controlled manner over 12 hours. In vivo analysis showed the formulation performed in a manner similar to that demonstrated by dissolution studies, resulting in a biphasic profile of ibuprofen release. The available literature of ibuprofen suggests that such a biphasic profile is an appropriate rate of release for achieving the desired onset of action and prevention of breakthrough symptoms in vivo.

Introduction

The objective of this work was to evaluate the in vivo and in vitro performance of a novel 600mg, 12-hour controlled release formulation of ibuprofen within a monolithic self-correcting matrix tablet. Ibuprofen is a prototype of non-steroidal anti-inflammatory drugs (NSAIDs) containing an arylpropionic acid structure, which is used for its anti-inflammatory, antipyretic, and analgesic effects. Ibuprofen is rapidly and extensively absorbed following oral administration, and possesses a plasma half-life of 1.5-2 hours and 80% of the administered dose is excreted in urine as parent drug, metabolites, or their conjugates. The OTC immediate-release dose of ibuprofen is 200mg every 4-6 hours, with a maximum dose of 1200mg over 24 hours. There is currently no controlled release formulation of ibuprofen approved in the US. With its short half-life and good permeability throughout the GI tract, ibuprofen is an excellent candidate for controlled release formulation. Given ibuprofen's physiochemical characteristics however, formulation of a controlled release ibuprofen within a monolithic tablet preparation presents numerous difficulties. The large dose necessitates either dispersion of the poorly-compressible drug within a matrix of more compressible materials or physical processing of the drug, such as granulation, to improve compression characteristics of the drug. Achieving a desirable *in vivo* release profile also presents many obstacles to controlled-release formulation, requiring the ability to deliver an efficacious dose of ibuprofen immediately, while also controlling the release of the remainder of the dose over the entire 12-hour period.

Experimental Methods

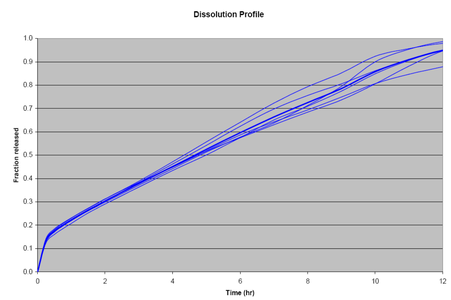
Tablets were manufactured on a high speed rotary press under GMP conditions. In vitro dissolution studies were conducted using a USP Type II apparatus with 900mL pH 7.2 phosphate buffer media at 37 degrees C and 50 rpm paddle speed. Tablets were weighted with a helix of wire to prevent flotation. Samples were removed and UV-Vis analyzed at 264nm.

A randomized, five-way crossover, open label, single dose fasted *in vivo* human pharmacokinetic study was also conducted. The study evaluated the rate and extent of absorption of single doses of three self-correcting controlled release formulations and Motrin® 600mg immediate-release tablets, and 3 x 200mg of the immediate-release OTC reference listed drug Motrin® IB, dosed at 0, 4 and 8 hours. Ten healthy, non-smoking male subjects received each test article separated by wash-out intervals of at least one week. Drug plasma levels were measured for each subject over a 24-hour period using a validated assay method. Cmax, Tmax and AUC were calculated for each subject. Using SAS, statistical analysis was conducted; ANOVA was performed on Ln-transformed AUC(o-t), AUC(0-inf) and Cmax.

Results and Discussion

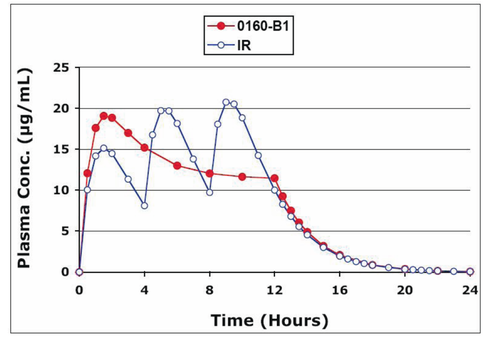
In vitro dissolution showed the novel monolithic tablet controlled the release of ibuprofen over 12 hours.

Figure 1. *In vitro* dissolution profile



The release profile may be described as biphasic: 100-120 mg is delivered in the first hour, and the remainder of the dose delivered in a near-linear fashion for the remainder of the dissolution period.

Figure 2. In vitro PK modeling further illlustrates the applicability of a bimodal characteristic..



In vivo pharmacokinetic studies also showed ibuprofen release from the monolithic tablet was well controlled. The plasma profile obtained from subjects receiving the self-correcting formulations was essentially biphasic in nature, reaching 10ng/mL within the first 2 hours and remaining at or above 6-10ng/mL through 12 hours. All of the self-correcting formulations displayed comparable AUC(0-inf) values to both the 200mg and 600mg Motrin®.

Figure 3. Plasma levels from a representative subject in the study.

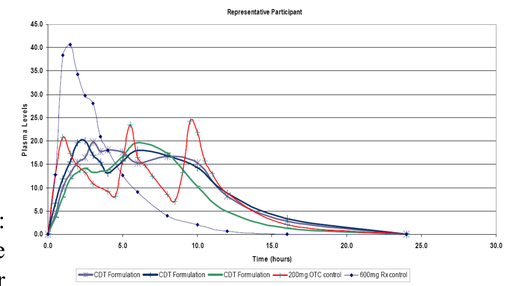
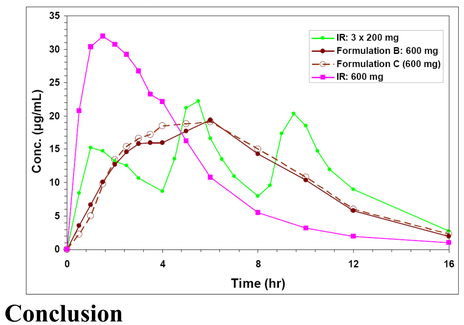


Figure 4. Mean (Geometric) plasma levels for the entire study.



Conclusion

The combined *in vivo* and *in vitro* performance of this formulation indicates that this novel monolithic tablet technology is capable of effectively controlling the release of ibuprofen in a biphasic manner.

Table 1. Summary of PK results, 90% Confidence Interval.

Summary of 90% CI

Formulation	Reference: D (1 x 600 mg)			Reference: E (3 x 200 mg)		
	C_{max}	$AUC_{0\text{-last}}$	$AUC_{0\text{-}\infty}$	C_{max}	$AUC_{0\text{-last}}$	$AUC_{0\text{-}\infty}$
CDT-B	40.2-51.0	93.3-112	95.4-114	63.6-80.6	84.3-101	84.9-102
CDT-B	42.4-53.8	96.2-115	97.0-116	67.0-85.0	86.9-104	86.3-103
CDT-C	44.7-57.0	96.9-116	98.7-119	70.7-90.3	87.5-105	87.7-106
D	–	–	–	140-179	82.3-99.2	80.9-97.7
E	55.9-71.5	101-122	102-124	–	–	–

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