New Abuse Deterrent Formulation (ADF) Technology for Immediate-Release Opioids

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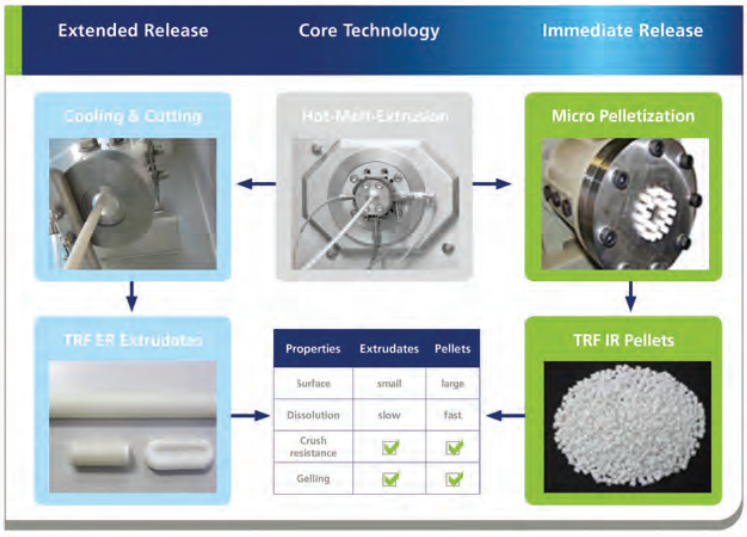
INTRODUCTION

Despite the recent introduction to the market of extended release (ER) opioid analgesics (re-)formulated with abuse deterrent (AD) properties, prescription opioid abuse in the US is an ongoing epidemic.[1] In reaction to these abuse deterrent formulation (ADF) products, abusers "are shifting away from the new tamper-resistant formulations to non-tamper-resistant formulations of other opioids," thus the need to turn more opioid analgesics into ADFs remains high.[2] Meanwhile, the FDA has issued the "Draft Guidance for Industry Abuse-Deterrent Opioids – Evaluation and Labeling" to define a framework for development, characterization, premarketing, and post-marketing studies for assessment of AD features.[3] In addition, the document suggests examples of labeling that may eventually be assigned to new AD formulations. The first ADFs to come to the market have concentrated on ER products as these contain significantly more active ingredient per tablet than immediate-release (IR) forms. These new ADFs predominantly apply crush-resistance technology for enhanced physicochemical properties. With reformulated OxyContin® CR (ORF in 2010), Nucynta® ER (2011), and reformulated

FIGURE 1



INTAC® manufacturing concept for ER and IR products.

FIGURE 2

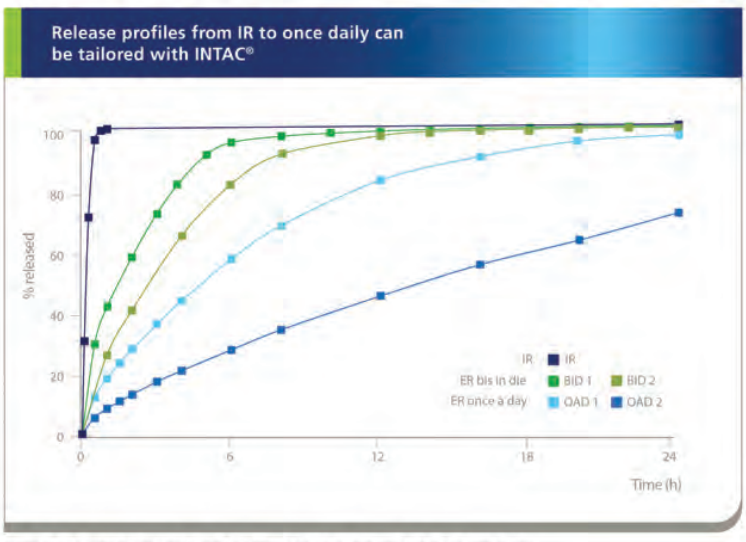


Figure 2: In vitro release profiles of INTAC® ER bid/oad and INTAC® IR formulations

In vitro profiles of INTAC® ER bid/oad and INTAC® IR formulations.

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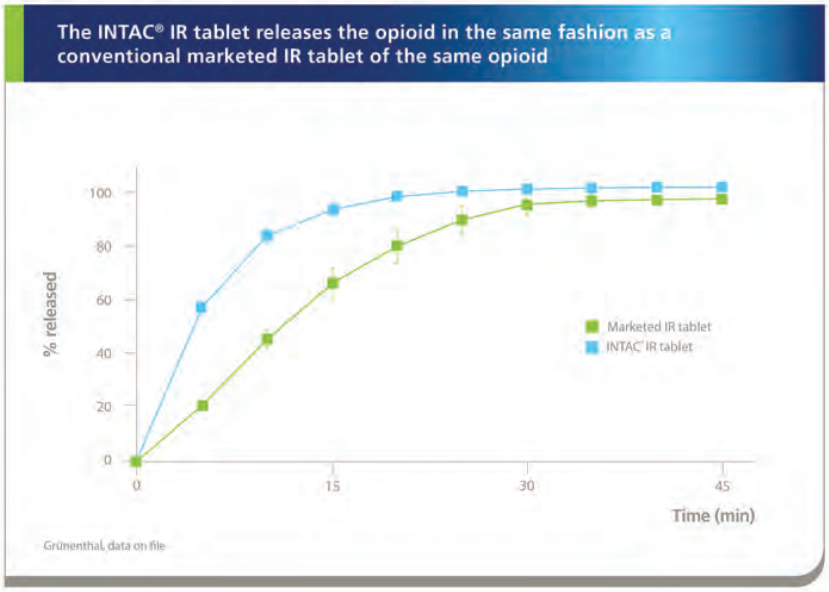
Opana® ER (CRF in 2012), three products using such technology are currently available in the US market. Significant reduction in abuse after introduction of the reformulation has been demonstrated by post-marketing surveillance data for OxyContin CR and Opana ER mainly for non-oral routes of abuse such as nasal abuse (snorting, for both products) and intravenous injections (predominantly for OxyContin CR because Opana ER intravenous abuse rates were already low).[4,5] For Nucynta ER on the other hand, such comparisons with earlier non-ADFs are not possible because this product was launched for the first time already as a crush-resistant formulation. In accordance with the aforementioned "Draft Guidance for Industry Abuse-Deterrent Opioids – Evaluation and Labeling", the FDA very recently approved the first AD labeling, which was granted for reformulated OxyContin.[6,7] This was based on the results of laboratory manipulation and extraction studies, abuse liability studies comparing drug liking of manipulated reformulated OxyContin ORF with original OxyContin and oxycodone HCl powder, and post-marketing surveillance data. "The new labeling indicates that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)."[6] The FDA determined further that the original formulation of OxyContin was withdrawn for reasons of safety or effectiveness and, thus, ANDAs relying on original OxyContin will not be accepted or approved. This case underpins the FDA's positive position on ADFs and sets the stage for regulatory endorsement and labeling options of future ADFs for opioid products.

After introduction of the first crush-resistant opioid ER products, abuse has been redirected to both unprotected ER formulations (initially also including Opana ER, which was still available in the non-crush resistant form at the time reformulated Oxycontin CR was launched) as well as to IR opioid products.[8] Consequently, IR formulations should also become a greater focus in ADF concepts. A first concept using nasal irritants was introduced to the market in form of the oxycodone IR product Oxecta®, although no post-marketing surveillance data on this product have so far been published. The next logical step would therefore be to investigate whether the crush-resistance technology that has proven its merits for ER opioid products can be applied to IR forms.

FIGURE 3



In vitro release of a marketed model opioid from INTAC® IR tablet and conventional IR tablet.

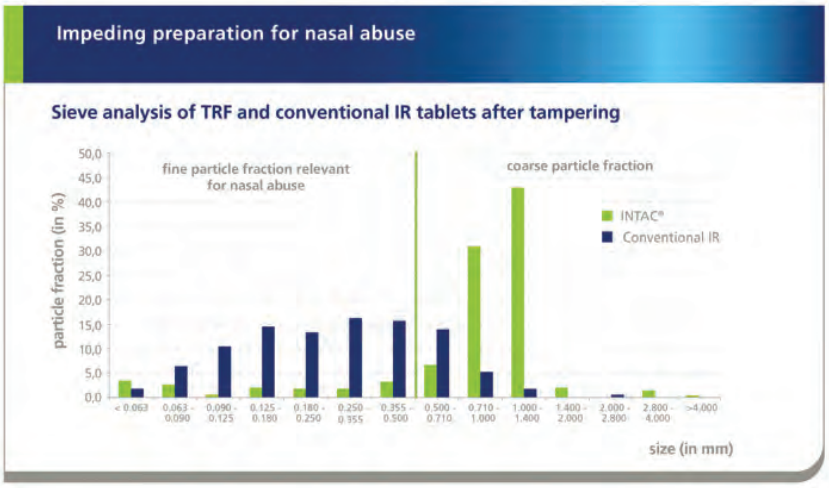
DESIGN OF INTAC® IR

INTAC® is Grünenthal's proprietary drug delivery platform of crush-resistant formulations already used in marketed opioid ER products.[9,10] Unlike with ER formulations, crushing of IR tablets for oral abuse does not

FIGURE 4

Attempt to prepare INTAC® IR tablet for intravenous abuse.

FIGURE 5



Particle sizes after tampering of tablets for preparation for nasal abuse.

significantly alter their inherent fast-release profile. Therefore the focus in extending the INTAC formulation platform is to impede preparation for non-oral abuse of IR products without impacting the IR functionality. Consequently, a multiparticulate tamper-resistant INTAC tablet has been developed that is characterized by a distinct gelling quality that leads to low extraction rates and raises the hurdles against intravenous abuse. This feature is combined with pronounced resistance to crushing of the multiparticulate drug matrix, thereby inhibiting preparation for subsequent nasal abuse. The manufacturing concept for this approach is based on creating crush-resistant material by the versatile core technology of hot melt extrusion (HME). The same first step of HME is employed as for INTAC ER, but a different downstream process using a plurality of smaller dies and cutting by a pelletizer delivers AD IR pellets or granules (Figure 1) that can be further processed into IR tablets.

With the addition of this IR concept, it is now possible to tailor release profiles from minutes up to about 1 day. Thus, INTAC becomes available as the solution for ADFs over the whole range of drug-release requirements from IR through twice-daily up to once-daily ER applications (Figure 2).

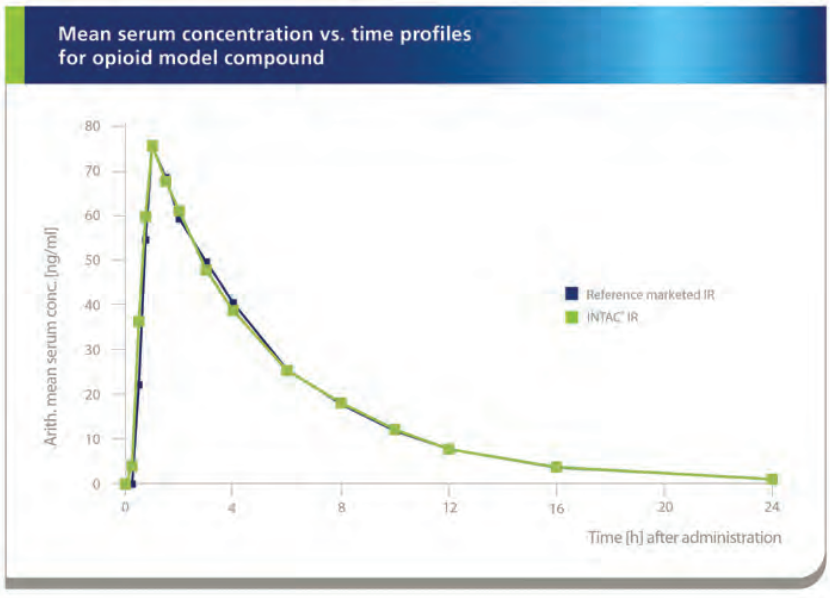
IN VITRO TAMPER-RESISTANCE TESTING

To verify the design concept for IR opioids, INTAC IR tablets were manufactured by HME of an opioid model compound together with a proprietary mix of ingredients, amongst others, a high molecular weight polyethylene oxide (PEO). The resulting crush-resistant pellets were subsequently mixed with easily compressible excipients. This blend was compressed to a tablet that releases the opioid in the same fashion as a conventional marketed IR tablet of the same opioid (Figure 3).

The INTAC IR tablet was subjected to in vitro tamper-resistance testing by manipulations reflecting preparation for intravenous and nasal abuse. In order to test for impedance of intravenous abuse, INTAC multiparticulate IR tablets were prepared simulating the typical abuser procedure for intravenous administration trying to obtain a powder that can be extracted, preferably by water. Due to the gelling properties of the excipients used in the formulation, attempts to draw the resulting extract into a syringe (typically done with a cigarette filter by the experienced intravenous abuser) were unsuccessful, and virtually no extract could be drawn up into the syringe (Figure 4).

For testing of impeding nasal abuse, INTAC multiparticulate IR tablets were

FIGURE 6



Mean serum concentration-time profiles of a model opioid administered in form of INTAC® IR tablets and as a conventional IR tablet market product.

prepared simulating a typical abuser procedure for nasal administration by comminution. Even with a sophisticated manipulation technique, obtaining particle sizes < 500 microns for nasal abuse was substantially limited for the INTAC IR formulation (about 85% ≥ 500 microns). In contrast, the conventional IR tablet could easily be broken down far below 500 microns, about 80% < 500 microns (Figure 5). 500 microns was set as a limit well above the typical particle sizes known to be suitable for nasal administration of compounds.

These results from the laboratory tamper-resistance testing support the concept based on the chosen physicochemical approach showing that INTAC IR has the potential to impede abuse of IR opioids by non-oral administration routes.

CLINICAL DEVELOPMENT

To verify that the change to an ADF formulation does not negatively impact the desired IR features of the product when patients take the product by the intended oral route, a bioavailability trial comparing the previously described INTAC IR model product to a marketed conventional IR formulation was performed. In an open, randomized, two-treatment, two-period, two-sequence cross-over design study with 24 healthy volunteers (22 completed) the relative bioavailability of the two products was evaluated.[11] The mean serum concentration curves of the model opioid from both formulations were almost superimposable over the whole investigation time (Figure 6).

The statistical evaluation of the pharmacokinetic parameters (Table 1) showed that the 90% confidence intervals (CI) for the ratios test/reference of Cmax, AUC0-t and AUC (area under the curve up to infinite time) fell within the 80% to 125% range commonly used for assessing bioequivalence.

TABLE 1

Summary of statistical analysis of pharmacokinetic parameters

PK parameter	ANOVA CVs [%]	Point estimates	90% confidence intervals [%]
C_{max} [ng/mL]	24.1	103	90 – 117
AUC_{0-t} [h*ng/mL]	13.7	102	94 – 110
AUC [h*ng/mL]	13.5	102	94 – 110

Statistical evaluation of mean pharmacokinetic parameters of a model opioid administered in form of INTAC® IR tablets and as a conventional IR tablet market product.

SUMMARY

In order to cope with the increasing abuse of IR opioids after introduction of AD formulations for ER opioid products, the INTAC technology platform has been extended to IR formulations with the intention to deter their non-oral routes of abuse. In vitro tampering tests have shown convincing results with regard to impeding nasal and intravenous abuse. Although INTAC IR's multiparticulate drug matrix is difficult to pulverize and dissolve, the in vivo performance is nonetheless entirely comparable to the marketed conventional IR product as the 90% confidence intervals for the ratios of the mean PK parameters Cmax and AUC fulfilled the conditions commonly used for assessing bioequivalence. The safety and tolerability data of the INTAC IR formulation were equally in line with the marketed IR reference product. Thus, once approved and launched, INTAC IR products may enable physicians to simply switch from conventional to reformulated tamper-resistant products. Overall, the INTAC technology has demonstrated its versatility and broad applicability to both ER formulations, already available as marketed products, and to IR formulations that are coming more into focus for prescription opioid abuse. ◆

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