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In-Vitro Test Characterization of an Immediate Release Product with Abuse Deterrent Features.

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Purpose

Abuse deterrent formulations (ADF) offer significant improvements for the safety of drug products containing active pharmaceutical ingredients (API) susceptible to abuse and misuse. The clinical relevance of abuse deterrent features has to be demonstrated e.g. in pharmacokinetic (PK) and human abuse liability (HAL) studies. However, in-vitro characterization tests are required for the design of these clinical studies and the sample preparation of the clinical trial material.

Currently there are no immediate release opioid products with abuse-deterrent labeling according to FDA guidance in the market. However, in addition to the existing abuse and misuse of immediate release formulations, it is expected that a shift in the abuse patterns might occur and more un-protected formulations will be abused independently of their intended release profiles[1].

The purpose of this paper is to summarize the results from the in-vitro-characterization of a novel INTAC® immediate release Hydrocodone/APAP ADF pellet tablet[2] developed by Grünenthal GmbH, Aachen (Germany) in comparison to a marketed drug product without abuse deterrent features (Norco™, "Norco"). Different in-vitro characterization tests according to the FDA guideline[3] were performed at DrugScan, Horsham, PA (USA). Goal of the study was to investigate general formulation characteristics that might be relevant for different routes of abuse. For IR formulations, the assessment of the mechanical resistance, e.g. in terms of particle size reduction and syringeability studies are mandatory. These tests can be used for the assessment of intranasal and intravenous abuse. To make intranasal abuse less attractive and unpleasant particles should exceed a limit of 500 µm based on literature data[4,5].

Methods

Manufacturing

The INTAC® manufacturing process is based on hot-melt extrusion and pelletization, which embeds the active opioid into a homogenous pellet matrix formulation based on polyethylene-oxide of high molecular weight. A Leistritz twin-screw extruder with pelletizer in commercial scale (Fig. 1) was used to manufacture IR Hydrocodone (HC) pellets with an average diamet of 1 mm. ADF pellets were blended with a mixture of APAP granules, disintegrant and lubricant. The final blend was compressed into tablets using a rotary tablet press (Korsch XL400).

ADF properties testing

Norco tablets, HC pellets ("ADF pellets") and HC/APAP pellet tablets ("ADF tablets") were tested. Physical manipulation: For physical manipulation tests pre-trials including thermal pretreatment (microwaving; 60 seconds, 1200 W) were conducted using several tools in order to identify the best method for particle size reduction. Cut-offs (e.g. max time for treatment) were defined beforehand. Particle size distribution was determined and API content tested in sieve fractions using HPLC method. Syringe-ability: For syringe-ability studies materials were incubated with 5 mL of tap water in a 20 mL scintillation vial at RT and at 90°C while shaking at 200 RPM and tested afterwards analyzed by drawing attempts into syringes using cannulas of various gauge sizes of pretreated material and Q-tip as filter. If material was able to be drawn into syringe API content was determined using HPLC method. Liquid-liquid extractions (LLE): LLE were performed using various organic and polar media (EtOH, NaOH, water, chloroform) in separatory funnels. Organic phases were reconstituted and API content in various fractions was tested by HPLC. Three phases were analyzed and overall extraction determined (1st and 2nd organic phase summarized as organic phase and an aqueous phase).

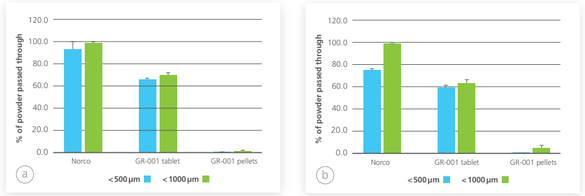
Figure 1: Commercial scale extrusion and pelletization process for manufacturing of INTAC® IR pellets

Results

Physical manipulation

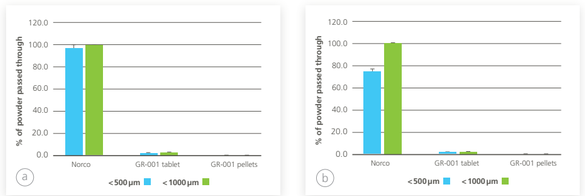
The average grinding times for untreated and preheated Norco tablets with a Krups® coffee grinder was 45 seconds. The average grinding times for ADF tablets and pellets were set at up to 5 times the amount of time required for Norco tablets. The majority of the post manipulation powder from Norco tablets passed through 500 µm sieve while a significant amount of powder from ADF tablets and pellets was retained by the 1000 µm and the 500 µm sieves (Fig. 2 a and b).

Figure 2a and b: Powder fractions of pre-heated test products manipulated afterwards by mortar and pestle (a) and Krups® coffee grinder (b)



In terms of HC distribution within the different particle populations, most of the API from ADF tablets or pellets was recovered from the powder fraction retained on the 1000 µm sieve, while almost all HC was recovered in the Norco fractions that passed through the 1000 µm or even the 500 µm sieve (Fig. 3 a and b).

Figure 3a and b: HC recovery of powder fractions of pre-heated test products manipulated afterwards by mortar and pestle (a) and Krups® coffee grinder (b)



Syringeability

Extracts from ground ADF tablets and pellets were highly viscous and non-syringeable (Fig. 4 a and b), even with the 18G needle (table 1 a). Pretreatment did not change the hard-to-syringe behavior of tested ADF formulations (table 1 b). Extracts from Norco were significantly less viscous and syringe-able with 27G or 25G needles in all attempts (Fig. 5 a and b).

Figure 4a and b: Extracts from pre-heated and ground ADF tablets (a) and pellets (b) shaking at 200 RPM at 90°C, post extraction (Extract could not be drawn into syringe)

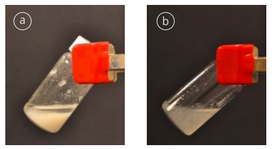


Figure 5a and b: Extracts from pre-heated and ground Norco tablets shaking at 200 RPM at 90°C, post extraction (a) and post syringe (b)

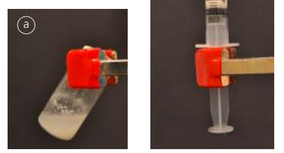


Table 1a and b: Recoveries of HC and APAP from untreated (a) and pre-heated (b) ground drug materials with incubation at 90 °C while shaking at 200RPM.

(a)

					Hydrocodene Bitartrate	Acetaminophen
Druy material	**Replicate**	**Final needle gauge**	**Volume drawn (mL)**	**Vicosity (cP)**	**Recovery of HC in drawn fractions as % of nominal content of tablet**	**Recovery of APAP in drawn fraction as % of nominal content of tablet**
Norco	1	27	2.0	3.738	30.1	20.7
	2	27	2.2	2.854	38.2	22.2
	3	27	1.4	3.318	26.4	15.2
GR-001 tablet	1	18	0	n/a	n/a	n/a
	2	18	0	n/a	n/a	n/a
	3	18	0	n/a	n/a	n/a
GR-001 pellets	1	18	0	n/a	n/a	n/a
	2	18	0	n/a	n/a	n/a
	3	18	0	n/a	n/a	n/a

n/a: no sample collected for analysis

(b)

					Hydrocodene Bitartrate	Acetaminophen
Druy material	**Replicate**	**Final needle gauge**	**Volume drawn (mL)**	**Vicosity (cP)**	**Recovery of HC in drawn fractions as % of nominal content of tablet**	**Recovery of APAP in drawn fraction as % of nominal content of tablet**
Norco	1	27	3.4	2.192	55.4	23.3
	2	27	2.4	2.160	41.1	15.8
	3	25	3.4	2.120	54.2	24.2
GR-001 tablet	1	18	0	n/a	n/a	n/a
	2	18	0	n/a	n/a	n/a
	3	18	0	n/a	n/a	n/a
GR-001 pellets	1	18	0	n/a	n/a	n/a
	2	18	0	n/a	n/a	n/a
	3	18	0	n/a	n/a	n/a

n/a: no sample collected for analysis

The percent of API recovered from nominal Norco tablet content ranged from 20.5 – 50.2 % and 9.7 – 21.1 % for HC and APAP respectively (Table 1 a). Preheating in a microwave and heated extraction seemed to enhance syringe-ability and increase recovery of HC and APAP (Table 1 b).

Liquid-Liquid Extraction

LLE: While both ADF products and Norco are IR formulations, HC recovery in the organic phase without and with pre-heating from ADF tablets (~44 % (pre-heated ~56 %)) and pellets (~37 % (pre-heated ~42 %)) was less than HC recovered from Norco (~68 % (pre-heated ~74 %)) (Fig. 6 a and b). The APAP recovery was comparable for ADF tablets and Norco with and without pre-heating (Fig. 7 a and b)

Figure 6a and b: Overall HC recovery after LLE for ground (a) and pre-heated and ground material (b)

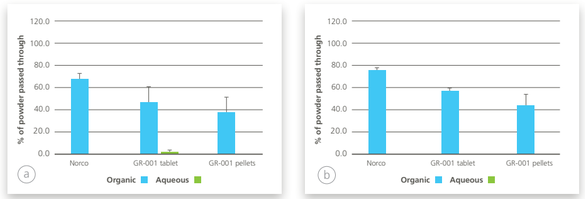
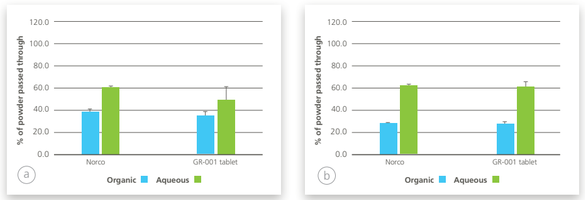


Figure 7a and b: Overall APAP recovery after LLE for ground (a) and pre-heated and ground material (b)



Conclusion

The current in-vitro characterization tests for intranasal (physical manipulation studies) or intravenous preparation (syringeability studies) indicate good abuse deterrent properties for the INTAC® based HC / APAP ADF product from Grünenthal. The ADF pellets and tablets could not be manipulated to yield particles <500 µm amenable to insufflation. No material, even after strong pretreatment in microwave could be drawn up into a syringe after boiling in 5mL water. Extraction data indicate that, although a significant amount of the HC was isolated from INTAC® and Norco™, a significant amount of APAP was co-isolated, i.e. isolated HC still impure for abuse. During later phases of the development a full test battery with additional tests and more conditions (time, temperature, and agitation) will be conducted.

References

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