Exploring the Potential of Compritol® 888 ATO for Abuse Deterrent Sustained Release Tablets

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INTRODUCTION AND OBJECTIVE

Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem globally.
Abuse-deterrent formulations are intended to prevent, impede or discourage non therapeutic use of drugs having abuse potential (Table 1). It can be achieved by preventing physical and chemical manipulation without compromising on safe and accurate delivery of drug.
Tapentadol HCl, a centrally acting opioid analgesic belongs to BCS Class-I is chosen as model drug.

Compritol® 888 ATO has pronounced hydrophobic property attributed to longer fatty acid chain length in behenic acid (C22) and higher melting point. It is insoluble in majority of commonly used solvents, which makes it a suitable excipient for abuse deterrent formulations[1].

The objective of the present work is to prepare abuse deterrent tablets of Tapentadol HCl 50 mg using Compritol® 888 ATO as sustained release matrix former in combination with Polyox™ by wet and melt granulation and to evaluate the tablets as per USFDA guidance for abuse deterrent formulations[2].

Drug Abuse	Drug Deterrence
Swallowing Multiple Pills	Physical/Chemical Barriers
Crushing and Swallowing	Agonist/Antagonist Combinations
Crushing and Snorting	Aversion
Crushing and Smoking	Delivery System
Crushing and Dissolving	New Molecular Entities and Prodrugs
Dissolving and Injecting	Combination - Two or More Techniques

Table 1. Ways of drug abuse and abuse deterrent techniques.

METHODS

Formulation Development:
Step 1: Wet Granulation and Melt Granulation (Fig. 1)
Wet granulation was performed in RMG using PVP K30 solution as binder followed by drying of granules in FBD at 50 °C. Melt granulation was performed by melting the Compritol® 888 ATO at 95 °C in RMG with heating provision followed by addition of Tapentadol HCl and mixing to obtain homogenous mixture followed by cooling until room temperature under kneading.
Step 2: Sizing of Granules
The granules from wet granulation and melt granulation were passed through sieve no. ASTM # 25.
Step 3: Blending and Lubrication
The granules were blended with extra-granular material in an octagonal blender at 25 rpm for 5 min.
Step 4: Compression
The tablet blend was compressed using 9.5 mm round shaped concave punch of type D tooling on Eliza press.
Evaluation of Formulations:
The granules prepared by wet granulation and melt granulation were evaluated for flow properties and the tablets were evaluated for IPQC parameters and *in vitro* dissolution test in 900 mL phosphate buffer pH 6.8 using USP type II apparatus with speed of 100 rpm at 37 °C, the sample were collected up to 12h at predetermined time points. Alcohol induced dose dumping (AIDD) study was also carried out in various concentrations of ethanol in 900 mL of 0.1N HCl i.e. 0%, 10%, 20% and 40% using USP type II apparatus at 50 rpm at 37 °C, with sample collection every 15 min up to 2 hours. The samples of both the studies were analysed using an HPLC method.

Evaluation of abuse deterrent properties: The developed tablets were examined for abuse deterrent potential as per USFDA guidance which includes physical manipulation and parameters like cutting, grating, milling, solution injectability, particle size and extraction in various solvents.
Stability study: The developed tablets were kept for stability study at 30°C/65% RH, 40°C/75% RH and room temperature in sealed HDPE bottles with 1g desiccant canister. The samples were analyzed for tablet parameters, drug content and *in vitro* dissolution profile.

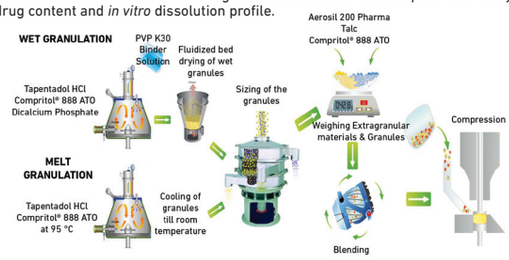

Figure 1. Development of tablets by wet and melt granulation process.

RESULTS

The granules prepared by both the techniques showed good flow properties which is suitable for tableting (Table 2).
Tablet parameters showed in Table 3 were found to be in range according to specifications.
In vitro dissolution in phosphate buffer pH 6.8 showed similar release profile in both the formulations of wet and melt granulations up to 12h (Fig. 2).
Alcohol induced dose dumping study showed good protection of the tablets in the presence of alcohol at 10%, 20% and 40% (Fig. 3).

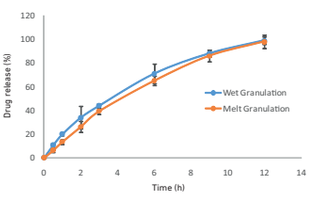

Figure 2. *In vitro* dissolution of tablets.

Table 2. Flow properties of granules.

Evaluation Parameters	Wet Granulation	Melt Granulation
Bulk Density (g/ml)	0.62	0.42
Tap Density (g/ml)	0.69	0.50
Hausner's Ratio	1.11	1.20
Compressibility Index (%)	11.29	16.67

Table 3. Tablet parameters.

Parameters	Wet Granulation	Melt Granulation
Description	White coloured round shape tablets plain on both the sides	
Weight (mg)	385-395	395-407
Dimensions (mm)	Diameter: 9.5 Thickness: 5.2-5.4	Diameter: 9.5 Thickness: 6.10-6.15
Hardness (N; n=10)	80-95	75-85
Friability (%)	0.044	0.029

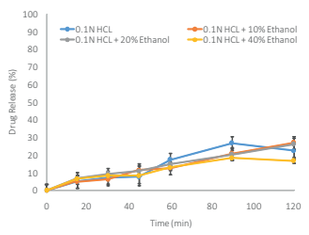

Figure 3. AIDD study of tablets of melt granulation.

Table 4. Physical manipulation tests for both the tablets.

Test	Method	Limit	Results
Cutting	Cut tablet with knife 5 min at RT If not possible: subject it to thermal pretreatment and follow the same procedure	NMT 10 small pieces	Both Fail Further Testing for Extraction
Grating	Grate tablet within 5 min with household grater at RT If not possible: subject it to thermal pretreatment and follow the same procedure	NMT 50 wt% of particles should be less than 1 mm	
Milling	Mill tablet with coffee grinder within 5 min at RT If not possible: subject it to thermal pretreatment and follow the same procedure	NMT 50 wt% of particles should be less than 1 mm	
Syringeability	Manipulate test product. Add 10 mL of solvent at RT or ET for 5 to 60 min as per extraction study, use needle gauge 21 or finer	If not parenterally administered or evaporated	Both Pass
Powder for Insufflation	Reduce the tablet to fine particles (<500 µm) using physical manipulation within 5 min If not reduced with manipulation (with or without thermal pre t/t) then crushing, hammering or grating after thermal pre t/t to generate (<500 µm)	Mass percent of fine particles should be less than or equal to 10%	Both Pass

The developed tablets from wet granulation and melt granulation were evaluated for physical and chemical manipulation (Table 4).
The tablets prepared by wet and melt granulation could be manipulated by cutting, grating and milling challenge and produced more than 50% particles finer than 1 mm.
The solution of both the manipulated tablets were not syringeable to avoid injection and fine powder for both tablets were less than 10% to avoid insufflation.
The intact and manipulated tablets of both the formulations were taken for extraction study using various solvents at room temperature and elevated temperature.
Extractability test for intact tablet of both the formulations in all the solvents was found to be within the limit. However, the intact tablets of wet granulation at elevated temperature were found to be out of limit (>50%) in all the solvents except IPA and 0.1N HCl, and the intact tablets by melt granulation could resist the extraction in all the solvents even at elevated temperature (Fig. 4).

Extractability test for manipulated tablets of wet granulation were found to be out of limit (>50%) in all the solvents except for Acetone, Vinegar and Isopropyl alcohol (<50%) at room temperature. However, the manipulated tablets from wet granulation could not resist extraction at elevated temperature.
Extractability test for manipulated tablets of melt granulation were found to be in limit (<50%) in all the solvents except for Vinegar and 40% ethanol (<50%) at room temperature. However, the manipulated tablets could not resist extraction at elevated temperature in Vinegar, Acetone, absolute and 40% Ethanol and 0.2% baking soda.

The 6 months accelerated stability study showed no change in the tablet parameter except hardness of tablets. However, there was no visible change in dissolution profiles evident in the samples stored at 30°C/65% RH, 40°C/75% RH and room temperature compared to initial dissolution profiles.

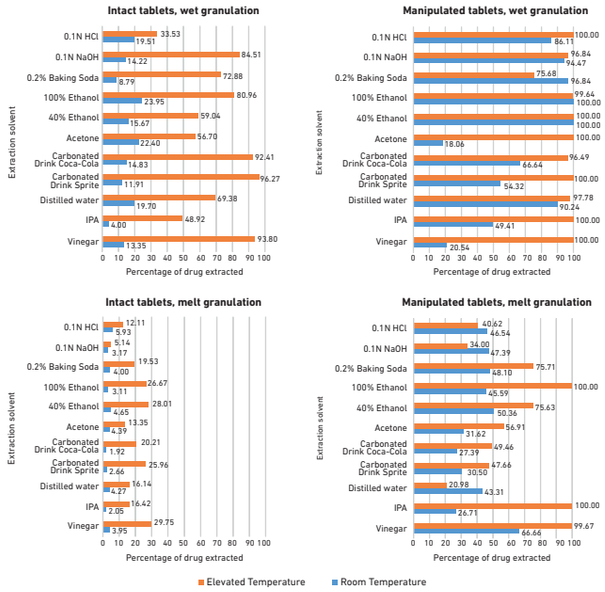

Figure 4. Extraction study of tablets prepared by wet or melt granulation.

CONCLUSION

Tapentadol HCl 50 mg abuse deterrent tablets were successfully prepared using Compritol® 888 ATO as matrix forming agent in combination with Polyox™. A comparable *in vitro* drug release profile of 12h was achieved for both the tablets using wet and melt granulation. Compritol® 888 ATO matrix also protected the formulations from dose dumping in the presence of alcohol. In the evaluation of abuse deterrent potential both the tablets were found to be sensitive to cutting grating and milling. However, the syringeablity and fine powder portion was found to be in limit to prevent injection and insufflation respectively. The tablets prepared by wet granulation were found to be sensitive when manipulated compared to tablets prepared by melt granulation which showed good resistance to extraction in various solvents even at elevated temperature. Moreover, the formulation was found to be stable in accelerated stability study over the period of 6 months. Therefore, we can conclude that the Compritol® 888 ATO has the potential to form a robust sustained release matrix in combination with Polyox™ by hot melt granulation technique from abuse deterrent formulation perspectives. Moreover, the observation of release profiles doesn't anticipate any compromise in therapeutic efficacy which makes it a suitable lipid matrix forming agent for sustained release abuse deterrent formulations.

REFERENCES AND ACKNOWLEDGEMENTS

[1] www.gattefosse.com
[2] FDA's Guidance for Industry: General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products.
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