Drug abuse resistant, controlled release, using Egalet® dosage units

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SUMMARY

The drug release from Egalet® dosage units involves the processes of water penetration, polymer dissolution and erosion. The potential abuse has been tested by a crush test, a melting test and by extraction. It was impossible to extract the drug substance from the units by these methods.

Furthermore the potential ethanol (EtOH) induced dose dumping was evaluated by in-vitro dissolution. It was found that ethanol decreases the dissolution rate from Egalet® dosage units. In general it seems almost impossible to abuse Egalet® dosage units

INTRODUCTION

FDA is generally aware of problems related to the abuse of narcotic drugs. In some cases it has been reported that a widespread abuse and misuse of drugs occurs as it is possible to crush controlled release capsules followed by extraction and injection or by snorting, thereby increasing the release of a given drug [1].

Furthermore it has been reported that in some cases of modified release oral dosage forms concomitant consumption of alcoholic beverages along with the drug may potentially induce dose dumping [2, 3].

Egalet® dosage units offer new possibilities in controlled release drug delivery for both well-known and new chemical entities. In its basic shape Egalet® dosage units comprise a matrix partly covered by a bio-degradable shell exposing a constant surface area to dissolution.

The current study evaluates the abuse potential and risk of dose dumping of Egalet® dosage units for controlled release. It is clearly shown that Egalet® dosage units mitigate the risk of ethanol dose dumping and that it is not prone to abuse.

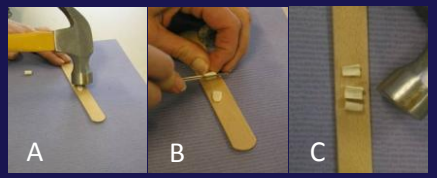


Fig. 1: A) Crushing of an Egalet® unit, B) Removal of the shell, C) Matrix and shell.

MATERIALS AND METHODS:

Batches of Egalet® dosage units containing Morphine sulphate were prepared by two component injection molding as described elsewhere [4]. Basically, both shell and matrix are formulated using thermoplastic polymers which are melted and shaped into Egalet® dosage units followed by cooling.

The abuse resistance of Egalet® dosage units was tested by three methods: i) crush test using a hammer, ii) melting test using a tablespoon and a lighter and iii) extraction of one dosage unit in 50 mL of Water, Ethanol or Methanol.

The dissolution tests were performed using an USP 2 paddle method (50 rpm, 37ºC) employing media with varying ratios of 0.05 M Phosphate buffer pH 6.8 and EtOH: i) 100: 0 v/v %, ii) 96:4 v/v %, iii) 80:20 v/v % and iv) 60:40 v/v %.

Fig. 2: Melting test of an Egalet® dosage unit matrix .

RESULTS

Hammering of Egalet® dosage units resulted in flattened units. It was not possible to obtain a fine powder for injection, even when the shell of the dosage unit was removed before the attempt (see **Fig. 1**).

For the melting test, Egalet® dosage units were placed on a tablespoon and a lighter was kept under the spoon for at least 8 minutes. The unit melted but was too viscous to be used for injection. The texture of the melted unit resembled used dried chewing gum and readily solidified again upon cooling (see **Fig. 2**). The result was the same also when the shell was removed before the melting test.

Solvent extraction of the Egalet® dosage unit was performed by dissolving the unit in Water, Ethanol and Methanol (**Table 1 and Fig. 3**). The resulting turbid solution formed over at least 24 hours. Further purification of the solution was almost impossible because of the content of polymers making the solution highly viscous.

Table 1: Extraction of Egalet® dosage units, in three different solvents.

Time (h)	Water	Ethanol	Methanol
1	insoluble	Matrix slightly dissolved	Matrix slightly dissolved
2	insoluble	Matrix slightly dissolved	Matrix slightly dissolved
4	insoluble	Matrix slightly dissolved Shell slightly dissolved	Matrix slightly dissolved Shell slightly dissolved
24	insoluble	Dissolved Turbid solution	Dissolved Turbid solution

The propensity of Egalet® dosage units to dose dumping with concomitant consumption of alcohol was tested in vitro by dissolution in media with varying alcohol content (see **Fig. 4,** below). The dissolution rate decreases with increasing EtOH content in the release media showing that controlled release using Egalet® technology mitigates the risk of Ethanol induced dose dumping. For reference the same test was used for a marketed product, which exhibits pronounced risk of Ethanol induced dose dumping.

DISCUSSION

The inability of Egalet® units to dose dump is based on the composition having a solubility in water higher than that in Ethanol. The general solubility equation (GSE) states that the solubility of a substance in water depends upon the melting entropy, the temperature difference between the melting point of the substance and the operating temperature as well as the hydrophobicity of the substance expressed as the octanol-water partition coefficient [5]. In this particular case, the ethanol-water partition coefficient is that of most interest. The GSE may be applicable to entire Egalet® dosage units.

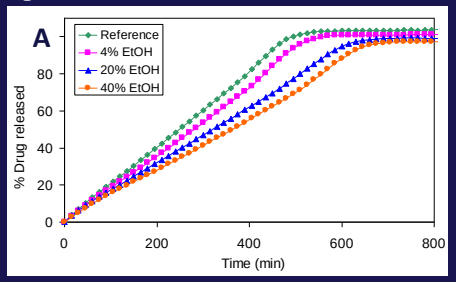
Fig. 3: Extraction of Egalet® dosage units, in three different solvents: left: Ethanol, center: Water, right Methanol.

The solubility rate of the dosage unit depends on parameters, such as, the melting temperature and the hydrophobicity of the matrix composition, the pH environment, the ion strength, the melting entropy – which relates to polymer disentanglement and the wetability of the matrix. In this way Egalet® units possess inherent properties that facilitate a lower solubility in ethanol. Accordingly, Egalet® release technology is designed to encompass a large range of drug substances with diverse chemical properties.

CONCLUSION:

- It was impossible to extract the drug substance powder either by crushing or by melting Egalet® units
- Extraction with different solvents did not lead to a solution useful for injection.
- The dissolution rate decreased in the following order: Reference > 4% EtOH > 20% EtOH > 40% EtOH.
- Ethanol does not increase the drug release rate from Egalet® dosage units.

Egalet® unit



Comparator

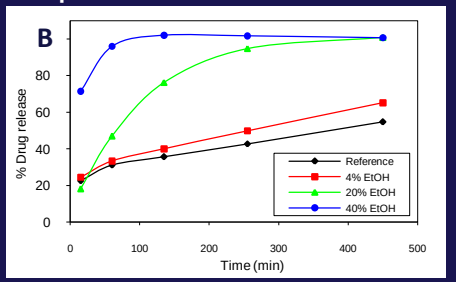


Fig. 4: Mean Morphine sulphate release profile in media with increasing content of EtOH. (50 rpm, pH 6.8, 37.5oC). A: Egalet® formulation, B: marketed formulation

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