Ex-vivo Permeation Studies to Facilitate the Development of a Buccal Child-Appropriate Dosage Form by Using Lidocaine Minitablets

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Background

Lidocaine hydrochloride (BCS class III) is a local anaesthetic and a class-1b antiarrhythmic drug, which acts as a sodium channel blocker from the amino-amide type [Fig. 1]. Due to the short and rapid local anaesthetic effect, lidocaine is also used commonly for paediatric oral diseases.

Accidental intoxications of children by oral viscous lidocaine formulations had been reported regularly. About 40% of reported cases in children between 5 months and 3.5 years of age resulted in life-threatening and death situations, as a FDA warning letter reported in 2014 [1]. According to the latter, the application of available viscous formulations for treating oral diseases (e.g. pain during teething, aphthae) are not recommended and emphasizes the need of appropriate dosage forms for safe drug therapy in the vulnerable paediatric population.

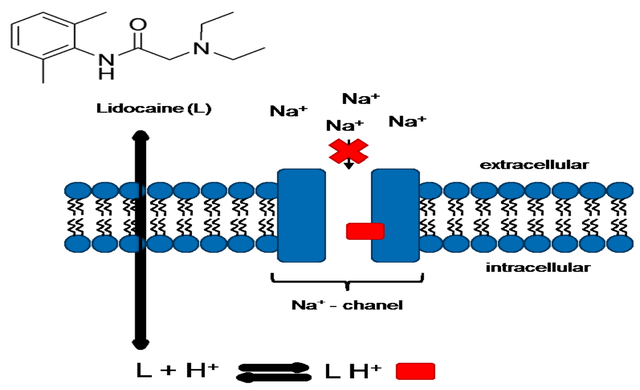

Figure 1. *Mechanism of action of lidocaine hydrochloride.*

Aim

(1) Development of a single-dosed formulation containing lidocaine hydrochloride aiming to reduce the risk of accidental intoxications.

(2) The permeability properties of the single-dosed formulation should be investigated by focusing on a clinically relevant period of application.

(3) The usefulness of the single-dosed formulation should be compared with commercial available and an alternative dosage form.

Material and Methods

Minitablets of 2 mm diameter were directly compressed by rotary press IMA (Kilian), using the powder mixture displayed in Tab.1. The mucoadhesive buccal films with an area of 3 cm² were produced using solvent casting method [Tab. 2].

Permeation investigations [Fig. 2] occurred with a fully automated permeation apparatus (Kerski cells) with a permeation area of 0.82 cm² by applying esophageal porcine membrane [2] with 300 µm thickness. To mimic physiological condition phosphate buffer of pH 6.9 was used at donor side, while pH 7.4 was applied on acceptor side with constant stirring (350 rpm) at 34 °C.

Subsequently the samples were quantified by high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) utilizing the mass transition 235.2 to 86.0 m/z for lidocaine in multiple reaction monitoring mode.

Table 1 *Composition of minitablet.*

Composition of minitablet [%]	
Lidocaine hydrochloride	30.0
Magnesium stearate	3.0
Aerosil 200	1.0
Flowlac 100	ad 100.0

Table 2 *Composition of buccal film.*

Composition of buccal film [%]	
Lidocaine hydrochloride	1.33
Hydroxypropyl methyl-cellulose	6.0
Chitosan	2.5
Glycerol 85%	2.0
0.1M Hydrochloric acid	ad 100.0

The permeation studies included the investigation of pure active pharmaceutical ingredient solutions followed by evaluation of different dosage forms (minitablet vs. Dynexan Mundgel® and minitablet vs. mucoadhesive buccal film) and the comparison between freshly prepared and frozen membranes.

LC-ESI-MS/MS	
Devices	Shimadzu LC 20 AD AB SCIEX API 2000
Column	Atlantis T3 (3.00 x 100 mm, 3 µm)
Mobile Phases	A: Water + 0.1% FA B: ACN + 0.1% FA
Flowrate	450 µL/ min
Ion Source	ESI (+)
Detection	MRM
Mass transition	235.2 to 86.0 m/z

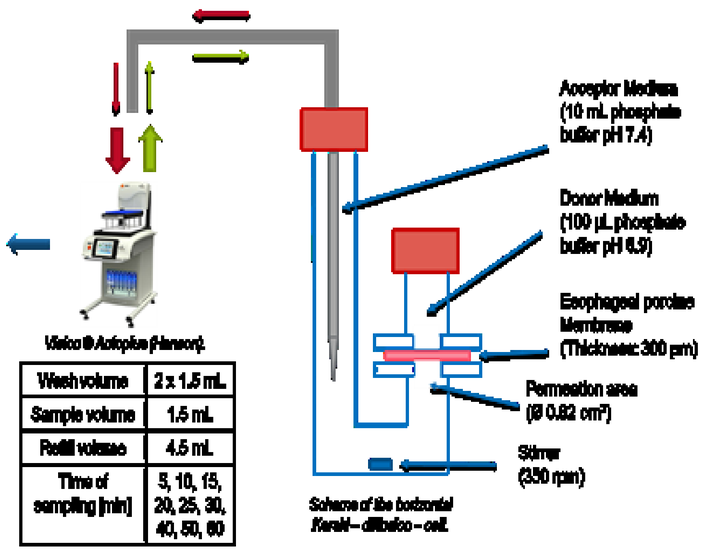

Figure 2. *Permeation and quantfication method (ESI: electrospray ionization, MRM: multiple reaction monitoring, m/z: mass-to –charge ratio, ACN: acetonitrile, FA: formic acid).*

Results

Applying LC-MS/MS offered new insight by timely close-meshed evaluation of permeability and provided a precise description of the early permeation phase. Furthermore, the lidocaine permeation profile of the minitablet can be explained by an initial disintegration process up to 4 min.

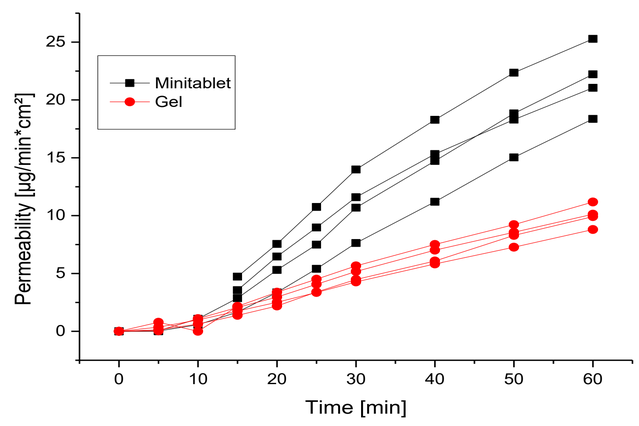

Figure 3. *Comparison of permeation of minitablet (MT) vs. Dynexan® Mundgel (Gel), both formulations containing 1.6 mg lidocaine, n = 4 each.*

The direct comparison of minitablet (1.6 mg pure base) vs. Dynexan Mundgel® (1.6 mg pure base) obtained approximately twice as high permeation rate in minitablet compared to the commercial available oral lidocaine gel Dynexan Mundgel® (by Kreussler Pharma) although comparable dose was applied [Fig. 4]. Subsequently a dose halving is feasible if compared to the mouth gel. This enables the same effect by reducing the potentially risk triggered by ingestion.

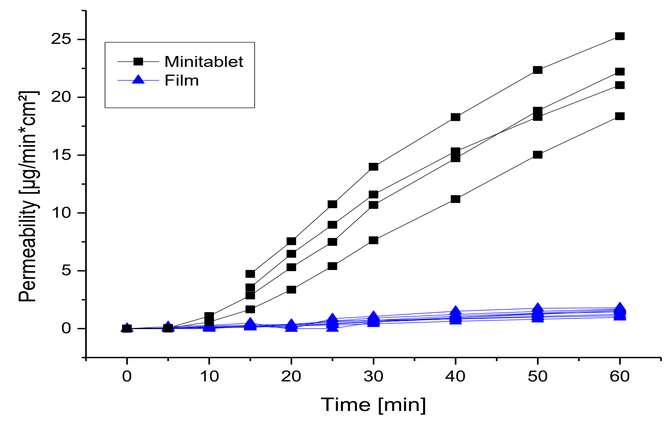

Figure 4. *Comparison of permeation of minitablet (MT) vs. mucoadhesive buccal film (Film) normalized to an amount of 1.6 mg lidocaine, MT: n = 4, Film: n = 8.*

The evaluation of permeability using minitablet (1.6 mg pure base) vs. an in-house developed drug loaded mucoadhesive buccal film (normalized to 1.6 mg of pure base) resulted in four times higher permeation rate of the minitablet [Fig. 5]. This finding emphasized the suitability of the minitablet as a single-dosed and appropriate formulation in paediatrics. Moreover, it justified the development of a composite drug dosage form as a combination of minitablet and a drug free mucoadhesive buccal film.

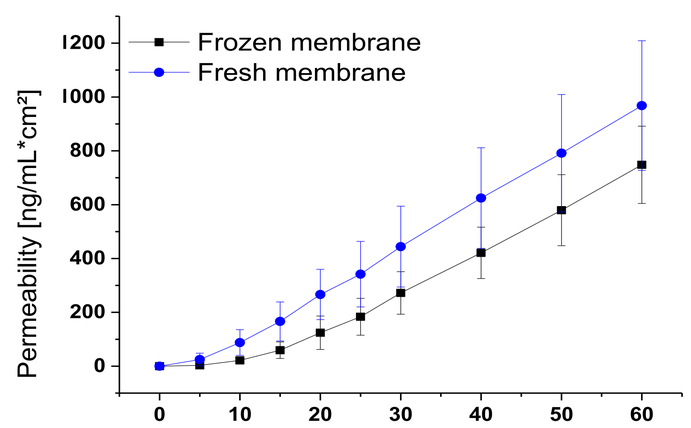

Figure 5. *Comparison of permeation profiles (mean ± sd) using lidocaine hydrochloride solution (0.2 mg/mL) through fresh prepared vs. frozen membrane, fresh: n = 4, frozen: n = 8.*

By applying lidocaine hydrochloride solution, no substantial impact on the permeation profile could be observed if freshly prepared vs. frozen membrane were assessed [Fig. 6].

Conclusion

The LC-MS/MS as quantification method allowed the reliable determination of lidocaine with focus on a clinically relevant period of application. The successful developed minitablet as a single-dosed formulation, showed higher permeability of lidocaine compared to Dynexan Mundgel® and to a lidocaine loaded mucoadhesive buccal film. This supports the approach of a dose reduction and the combination of minitablet and a drug free mucoadhesive buccal film with a backing layer, which allows a unidirectional drug release and further reduces the risk of accidental ingestion of drug substance and accounts for better patient safety.

References

1. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA recommends not using lidocaine to treat teething pain and requires new Boxed Warning 2014. https://www.fda.gov/Drugs/DrugSafety/ucm402240.htm Last accessed: 28/05/2018.

2. Consuelo I. D., Comparison of the lipid composition of porcine buccal and esophageal permeability barriers. Archives of Oral Biology (2005) 50, 981-987.