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Development of propranolol hydrochloride extended-release lipid matrix tablets for pediatric use

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ABSTRACT

Although solid oral dosage forms are widely used in adult drug therapy, age-appropriate formulations for pediatric patients remain limited. The development of suitable dosage forms is challenged by specific requirements regarding excipient safety, tablet size, and dose flexibility, as well as the need to improve therapy adherence in the context of frequent dosing. This study aimed to develop a pediatric-appropriate extended-release matrix tablet based on lipid matrix formers, with particular attention to the use of safe excipients and the selection of excipients based on sustainability considerations. Lipid-based excipients, selected due to their natural origin and similarity to dietary fats, were investigated and compared with conventional matrix formers. A formulation screening approach was applied to identify promising candidates based on drug release after one hour, followed by further evaluation of manufacturability, tablet hardness, and extended-release performance. In addition, the influence of a physiological pH-gradient, bile salts, and long-term storage on drug release was assessed. The selected formulations showed good manufacturability, uniformity, and sustained drug release. Overall, several lipid-based matrix formulations suitable for pediatric use were identified, providing a promising basis for the development of solid oral extended-release dosage forms for children.

1. Introduction

Solid oral dosage forms, such as tablets, are the most commonly used dosage forms in adult pharmacotherapy. However, conventional tablet sizes are often too large for pediatric patients to swallow, particularly in young children, who may have difficulty or are unable to swallow tablets designed for adults (Lopez et al., 2015; Ranmal et al., 2016; Walsh et al., 2018; Zuccari et al., 2022). For this reason, liquid formulations are frequently used in pediatric drug therapy due to their ease of administration (Walsh et al., 2018). However, liquid dosage forms present several disadvantages compared to solid oral dosage forms, including poor palatability and reduced physical, microbial and chemical stability. As a result, they often require special storage conditions and/or the addition of multiple excipients, despite limited safety data on excipient use in pediatric populations (Meyers, 2020; Münch et al., 2023a; Rouaz et al., 2021; Walsh et al., 2018). Therefore, there is a clear need for solid oral dosage forms tailored to pediatric patients, particularly in the form of smaller tablets, to improve safe and effective treatment and adherence.

In the development of solid oral dosage forms for pediatric use, minitablets (MTs) have gained increasing attention in recent years (Aleksovski et al., 2015; Lura et al., 2025; Meruva et al., 2024; Meyers, 2024; Zuccari et al., 2022). Although no formal definition currently exists, MTs are commonly defined as tablets with a diameter of $\leq$ 4 mm (Lennartz and Mielck, 1998; Lura et al., 2025; Meruva et al., 2024; van Riet-Nales et al., 2016). Owing to their small size and flexible dosing, MTs are considered easier for children to swallow (Aleksovski et al., 2015; Meruva et al., 2024; Zuccari et al., 2022). Several studies have investigated the acceptability of small tablets in pediatric populations, with some reporting a preference for MTs over liquid formulations. In particular, it has been shown that MTs can be given to very young children. Münch *et al.* reported that children as young as 6 months are able to swallow 2 mm tablets, whereas 3 mm tablets can be administered from the age of 3 years (Münch et al., 2023a, Münch et al., 2023b). Furthermore other studies have reported that children of pre-school age (3–5 years) are able to swallow tablets with a diameter up to 5 mm, while tablets with a diameter up to 10 mm are also accepted from the age of 6 years (Bracken et al., 2020; Spomer et al., 2012). These findings

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suggest that a reduction in tablet size may be beneficial, as it increases the potential to cover a wider range of pediatric age groups, even with only a slight increase beyond the typical MT size range.

In addition to appropriate tablet size, dosing frequency is another important factor for the safe and effective treatment of pediatric patients, as repeated administration of medication throughout the day can impose a considerable burden on children and their caregivers (Alessandrini et al., 2021; Lopalco and Denora, 2020; Meyers, 2024). Many commonly used pediatric medicines require multiple daily doses, often necessitating administration outside the child's familiar home environment. This can be a significant source of stress for both children and caregivers (Meyers, 2024). Accordingly, there is a clear need for extended-release (ER) oral dosage forms for pediatric use. Only a limited number of such formulations are currently available on the market (Lura et al., 2025).

Various strategies can be employed to achieve sustained drug release of oral dosage forms. One common approach is the application of ER coatings. However, pediatric patients may chew solid dosage forms, potentially compromising the integrity of functional coatings (Aleksovski et al., 2015; Kluk et al., 2015). Defects in the coating can result in dose dumping, particularly in formulations containing high drug loads, which may increase the risk of adverse drug reactions. An alternative approach is the use of matrix tablets, in which the drug release is controlled by the tablet core itself. In contrast to coating-based systems, matrix systems are generally less susceptible to surface defects. While conventional hydrophilic matrix systems, based on swelling and erosion mechanisms, have shown limited robustness under gastrointestinal hydrodynamic and mechanical stress conditions, non-swelling and non-erodible lipid-based matrix systems represent an interesting alternative for pediatric applications (Garbacz and Klein, 2012; Shameem et al., 1995).

A number of approaches for the preparation of lipid-based tablets using Compritol® 888 ATO as a matrix former have been reported in the literature. In addition to its role as a matrix-forming agent, Compritol® 888 ATO has been widely used as a lubricant, for hot-melt coating, and for taste masking applications (Aburahma and Badr-Eldin, 2014; Roberts et al., 2015). Its suitability for direct compression has also been investigated in multiple studies using different concentrations in the respective formulations. For example, Dzajkowska *et al.* developed 3 mm MTs containing carbamazepine with 40% Compritol® 888 ATO (Dzajkowska et al., 2017), whereas Roberts *et al.* prepared 2–4 mm MTs containing theophylline with 15–45% of the same lipid (Roberts et al., 2012). Comparable drug release behavior has also been reported for Precirol® ATO 5-based formulations highlighting its potential as an alternative to Compritol® 888 (Gu et al., 2004). Furthermore, glycerol monostearate (GMS) has also been investigated as a lipid matrix former for directy compressed matrix systems. For example, Nyavanandi *et al.* developed 10 mm matrix tablets containing either 10% GMS in combination with 5% hydroxypropyl methylcellulose (HPMC) or 20% GMS with 5% polyvinylpyrrolidone (PVP) (Nyavanandi et al., 2021). While these studies demonstrate the feasibility of direct compression, lipid-based matrix formers are still predominantly used in ER formulations produced via melt-based techniques, such as melt extrusion or melt granulation (Aburahma and Badr-Eldin, 2014; Reitz et al., 2008; Roberts et al., 2015, Roberts et al., 2012).

In addition to the selection of a suitable matrix polymer, the safety of the excipients is a key aspect in the development of pediatric dosage forms. Children require special attention with regard to excipients safety, as physiological characteristics can vary considerably between different age groups, potentially increasing the risk of excipient-related adverse effects. Therefore, a clear definition of the target age group(s) is essential. According to the ICH-Guideline '*Clinical Investigation of Medicinal Products in the Pediatric Population*', pediatric patients are classified into preterm- and term newborn infants (0 to 27 days), infants and toddlers (28 days to 23 months), children (2 to 11 years) and adolescents (12 to 16–18 years (dependent on region)) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2017). Additional subdivisions within these categories are sometimes applied. Particular caution is required when developing medicinal products for infants and young children, as in these age groups rapid developmental changes and immature physiological functions, especially in metabolism, elimination, and blood–brain barrier integrity, may affect the safety profile of excipients (Rouaz et al., 2021). Consequently, excipients considered safe in adults or older pediatric populations may pose risks in younger age groups. To support excipient risk assessment in pediatric formulations, several tools are available, including the '*The Safety and Toxicity of Excipients for Paediatrics*' (STEP) database, and the more recently developed '*Paediatric Excipient Risk Assessment*' (PERA) tool (Agrawal et al., 2024; Rouaz et al., 2021; Salunke et al., 2013).

Beyond the safety of the excipients, sustainability has become an increasingly important consideration in pharmaceutical development. In addition to resource-efficient manufacturing processes, the use of environmentally friendly excipients and active pharmaceutical ingredients (APIs) is gaining attention (Bading et al., 2024a, 2024b; Kümmerer, 2019; Milanesi et al., 2020). Biodegradability and biocompatibility are particularly relevant for polymer-based dosage forms, as many polymers used in the pharmaceutical industry are not biodegradable (Bading et al., 2024b). Non-biodegradable polymers may contribute to microplastic pollution in the environment, thereby posing a potential long-term threat to ecosystems (Ardila-Fierro and Hernández, 2021). Methacrylate-based polymers, for example, are non-biodegradable and are also applied in the development of pediatric matrix tablets (Lura et al., 2025).

The aim of this study was to develop pediatric ER lipid matrix tablet formulations using propranolol hydrochloride (HCl) as a model drug. Propranolol HCl was selected because of its established use in pediatric patients, its relatively short elimination half-life, and its high aqueous solubility, representing a challenging model compound for evaluating the feasibility of small ER matrix tablets. The study addresses the need for age-appropriate solid oral dosage forms that combine improved swallowability through miniaturized tablet size with sustained drug release with the long-term goal of reducing dosing frequency and improving treatment adherence in pediatric patients, while also considering sustainability aspects in excipient selection. Accordingly, this proof-of-concept study focused on evaluating the feasibility of developing small-diameter lipid matrix tablets capable of providing sustained drug release over clinically relevant time periods. Rather than optimizing the formulation towards a predefined quantitative dissolution profile, the objective was to investigate whether formulation-dependent release profiles suitable for either twice-daily or, ideally, once-daily administration could be achieved.

2. Materials and methods

2.1. Materials

Propranolol HCl (Selectchemie China, Ningbo, China) was used as a model drug. The lipid matrix formers Compritol® 888 ATO and Precirol® ATO 5 were kindly provided by Gattefossé (Saint-Priest Cedex, France). Glyceryl monostearate (GMS) was purchased from Caesar & Loretz (Hilden, Germany) and Dynasan® 114 was kindly provided by IOI Oleo (Hamburg, Germany). Ethylcellulose (EC) 10 cp (Sigma-Aldrich Chemie, Taufkirchen) was used as an alternative hydrophobic matrix polymer. Hydrophilic matrix polymers included hydroxypropyl cellulose (HPC H FP-grade, kindly donated by NISSO CHEMICAL EUROPE, Düsseldorf, Germany) and hydroxypropyl methylcellulose (HPMC, Methocel K100M, kindly provided by DuPont de Nemours, Wilmington, USA). Emcompress® Premium (calcium hydrogen phosphate dihydrate, kindly provided by JRS Pharma, Rosenberg, Germany) and microcrystalline cellulose (MCC, Ceolus™ UF-711, KG-802 and KG-1000, kindly provided by Asahi-Kasei, Tokyo, Japan) were used as fillers. Colloidal

silicon dioxide (Fagron, Glinde, Germany) and magnesium stearate (Sigma-Aldrich Chemie, Taufkirchen, Germany) were purchased from the respective suppliers and used as glidant and lubricant, respectively. All other chemicals were of analytical grade and obtained from commercial suppliers.

2.2. Study design and formulation strategy

The formulation strategy aimed to balance miniaturized tablet size with sustained drug release to achieve reduced dosing frequency in pediatric therapy. The formulation was primarily intended for preschool and young school-aged children, for whom both swallowability and flexible dose adjustment are particularly important. A tablet diameter of 5 mm was selected as a compromise between acceptable swallowability, sufficient drug loading, and minimizing the number of tablets required per administration. This choice was supported by published evidence indicating that preschool children (3–5 years of age) are able to swallow tablets with diameters of up to 5 mm, whereas children from 6 years of age can also swallow tablets with diameters of up to 10 mm (Bracken et al., 2020; Spomer et al., 2012). Ideally, a flexible dosing regimen should be enabled by administering an age- or weight-adjusted number of tablet units, allowing once- or at most twice-daily administration. Formulation development involved the preparation of matrix tablets using different lipophilic and hydrophilic matrix formers. In addition, the influence of key formulation variables, including drug load, filler type, and combinations of matrix formers, was investigated to identify suitable compositions for controlling drug release of the highly water-soluble model drug. Excipient selection was guided by considerations of pediatric safety as well as sustainability aspects.

2.3. Formulation development and screening

A stepwise formulation development strategy was applied, as described in the following subsections. Initially, different matrix formers were screened to evaluate their influence on tablet characteristics and drug release behavior. Subsequently, the effect of drug loading was investigated. Then, the influence of different fillers and filler grades on manufacturability, tablet characteristics, and drug release behavior was assessed. Finally, the potential of combining selected matrix formers was evaluated with respect to achieving the desired drug release profile.

Powder blends (25 g) of the different formulations were prepared using a stainless-steel mortar and pestle. Propranolol HCl, glidant, and lubricant were sieved through a 500 μm mesh screen prior to processing. All components except the lubricant were mixed for 9 min, followed by an additional 60 s mixing step after addition of the lubricant to ensure uniform distribution.

Tablets were compressed using an EK0 eccentric tablet press (Korsch, Berlin, Germany) equipped with a 5 mm round biconcave single-tip punch. For preliminary screening of powder compaction behavior, the tablet press was operated in hand-wheel mode to assess blend robustness under low-control compaction conditions. A target tablet mass of 60 mg was used for all formulations, and the highest feasible compression force was applied to obtain tablets with maximal mechanical strength.

Table 2
Composition of matrix tablet formulations [% w/w] used to investigate the influence of reduced drug loading on tablet characteristics and drug release behavior.

	C2	P2	HPMC2	HPMC6	HPC6
Propranolol HCl	19.8	19.8	19.8	19.8	19.8
Compritol® 888 ATO	64.3	–	–	–	–
Precirol® ATO 5	–	64.3	–	–	–
HPMC K 100 M	–	–	64.3	77.7	
HPC H-FP	–	–	–	–	77.7
Emcompress® Premium	13.4	13.4	13.4	–	–
Magnesium stearate	1.5	1.5	1.5	1.5	1.5
Colloidal silicon dioxide	1.0	1.0	1.0	1.0	1.0

The composition of the different formulations is provided in Tables 1–5. During formulation development, tablet quality was monitored by basic in-process control and a preliminary assessment of the finished tablets, as follows: Weight uniformity was determined using 10 tablets (Sartorius AX124 balance, Sartorius, Göttingen, Germany), tablet hardness was measured on five tablets per formulation using a hardness tester (ZBH30, Erweka, Langen, Germany), and a preliminary *in vitro* drug release test was performed to assess the initial drug release within 1 h using a simple *in vitro* setup.

2.3.1. Evaluation of different matrix formers

In the initial screening step, the influence of different matrix former types on tablet characteristics and drug release behavior was evaluated. For this purpose, at constant proportions of API, filler, glidant, and lubricant, different matrix formers were comparatively evaluated as detailed in Table 1. Lipid-based matrix formers, namely Compritol® 888 ATO (glyceryl dibehenate), Precirol® ATO 5 (glyceryl distearate), glyceryl monostearate (GMS), and Dynasan® 114 (glyceryl trimyristate), were investigated and compared with the hydrophobic polymer EC and the hydrophilic polymers HPMC and HPC.

2.3.2. Effect of drug loading

In the second screening step, the influence of drug load on tablet characteristics and drug release behavior was evaluated. For this purpose, the amount of active pharmaceutical ingredient in selected formulations was reduced by half and replaced by additional matrix former or filler, depending on the formulation type (Table 2).

2.3.3. Effect of filler type and grade

In the third screening step, the influence of filler type and filler grade on tablet characteristics and drug release behavior of lipid-based matrix tablets was evaluated at constant drug load as used in the first screening step. In the initial sets of experiments, Emcompress® Premium was selected as the reference filler due to its GRAS (generally recognized as safe) status (Food and Drug, 2023), its ability to produce hard tablets with high density, and its suitability as identified in preliminary

Table 1
Composition of matrix tablet formulations [% w/w] used to investigate the influence of different matrix formers on tablet characteristics and drug release behavior.

	C1	P1	GMS1	Dyn1	EC1	HPMC1	HPC1
Propranolol HCl	39.6	39.6	39.6	39.6	39.6	39.6	39.6
Compritol® 888 ATO	44.5	–	–	–	–	–	–
Precirol® ATO 5	–	44.5	–	–	–	–	–
Glyceryl monostearate	–	–	44.5	–	–	–	–
Dynasan® 114	–	–	–	44.5	–	–	–
Ethylcellulose 10 cp	–	–	–	–	44.5	–	–
HPMC K 100 M	–	–	–	–	–	44.5	–
HPC H-FP	–	–	–	–	–	–	44.5
Emcompress® Premium	13.4	13.4	13.4	13.4	13.4	13.4	13.4
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Colloidal silicon dioxide	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Table 3
Composition of matrix tablet formulations [% w/w] used to investigate the influence of the grade of microcrystalline cellulose on tablet characteristics and drug release behavior.

	C1 [711]	C1 [802]	C1 [1000]	P1 [711]	P1 [802]	P1 [1000]
Propranolol HCl	39.6	39.6	39.6	39.6	39.6	39.6
Compritol® 888 ATO	44.5	44.5	44.5	–	–	–
Precirol® ATO 5	–	–	–	44.5	44.5	44.5
Ceolus™ UF-711	13.4	–	–	13.4	–	–
Ceolus™ KG-802	–	13.4	–	–	13.4	–
Ceolus™ KG-1000	–	–	13.4	–	–	13.4
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Colloidal silicon dioxide	1.0	1.0	1.0	1.0	1.0	1.0

Table 4
Composition of matrix tablet formulations [% w/w] used to investigate the influence of combining Compritol® 888 ATO with additional matrix formers on tablet characteristics and drug release behavior.

	C1EC	C1HPMC	C3EC	C3HPMC	C3HPC	C5P
Propranolol HCl	39.6	39.6	19.8	19.8	19.8	19.8
Compritol® 888 ATO	44.5	44.5	44.5	44.5	44.5	33.2
Precirol® ATO 5	–	–	–	–	–	24.7
Ethylcellulose 10 cp	13.4	–	33.2	–	–	–
HPMC K 100 M	–	13.4	–	33.2	–	–
HPC H-FP	–	–	–	–	33.2	–
Emcompress® Premium	–	–	–	–	–	19.8
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Colloidal silicon dioxide	1.0	1.0	1.0	1.0	1.0	1.0

Table 5
Composition of matrix tablet formulations [% w/w] used to investigate the influence of combining Precirol® ATO 5 with additional matrix formers on tablet characteristics and drug release behavior.

	P3C	P3EC	P3HPMC	P3HPC	P4EC	P4HPMC	P4HPC
Propranolol HCl	19.8	19.8	19.8	19.8	19.8	19.8	19.8
Precirol® ATO 5	44.5	44.5	44.5	44.5	57.9	57.9	57.9
Compritol® 888 ATO	33.2	–	–	–	–	–	–
Ethylcellulose 10 cp	–	33.2	–	–	19.8	–	–
HPMC K 100 M	–	–	33.2	–	–	19.8	–
HPC H-FP	–	–	–	33.2	–	–	19.8
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Colloidal silicon dioxide	1.0	1.0	1.0	1.0	1.0	1.0	1.0

experiments (Tables 1 and 2). In this set of experiments, three different grades of microcrystalline cellulose (MCC; Ceolus™ UF-711, KG-802, and KG-1000) were investigated (Table 3). These grades were selected based on their differing flowability and compactibility characteristics, since a balance between sufficient powder flow for small die filling and high tablet hardness was required.

2.3.4. Evaluation of combined matrix former systems

In the final screening step, the potential of combining selected lipid and polymeric matrix formers was evaluated with the aim of achieving sustained drug release while limiting excessive initial drug release. In addition, the formulations were designed to maintain a sufficiently high drug load to ensure a practical number of tablet units per administration despite the miniaturized tablet size, while preserving the flexibility of age- and weight-adjusted dosing. For this purpose, binary mixtures of Compritol® 888 ATO or Precirol® ATO 5 with selected hydrophobic and hydrophilic polymers were prepared and compared, while keeping all other formulation components constant (Tables 4 and 5). Depending on the specific matrix former combination, formulations were prepared either with full or reduced API content, corresponding to the designs described in Sections 2.3.1 (Table 1) and 2.3.2 (Table 2), respectively. When a second matrix former was introduced, the filler proportion used in the previous experiments was replaced by the second matrix former. Correspondingly, in formulations with reduced API content, the decrease in API content was compensated for by the second matrix former. An exception was the C5P formulation, in which the proportion of Emcompress® Premium was increased to improve tabletability instead of being replaced by the second matrix former.

2.3.5. Preliminary in vitro drug release testing for extended-release screening

To obtain an initial indication of the ER performance of the individual tablet formulations and to assess their ability to limit early drug release within the first hour, a preliminary *in vitro* drug release test was performed using a simplified *in vitro* setup. Drug release after 1 h was selected as an early screening parameter because formulations exhibiting pronounced initial drug release were considered less likely to provide the sustained-release characteristics intended for the developed ER matrix tablets. The experimental procedure was as follows: A single tablet was weighed and incubated per replicate ($n = 5$) in 10.0 mL phosphate buffer (PB, pH 6.8) under continuous shaking using an incubator shaker (IKA KS 3000i control, IKA, Staufen, Germany) at 120 rpm and 37.0 ± 0.5 °C. After 1 h of incubation, an aliquot of the medium was withdrawn and analyzed spectrophotometrically with respect to the amount of propranolol HCl released (U-2900, Hitachi, Schwäbisch Gmünd, Germany) at 289 nm.

2.4. Manufacture and evaluation of selected formulations

Based on the results of the preliminary screening tests, seven formulations representing different matrix former systems (C3EC, C5P, P3EC, HPMC1, HPMC6 and HPC1, HPC6) were selected for further evaluation (Tables 1 and 2, 4 and 5). The selected formulations were subsequently manufactured under standardized and reproducible conditions. All powder components except the lubricant (50 g) were mixed in a Turbula mixer (Turbula, Willy A. Bachofen, Muttenz, Switzerland) for 9 min, followed by an additional 1 min mixing step after addition of magnesium stearate. The mixtures were compressed using an EK0 eccentric tablet press equipped with a 5 mm round, biconcave single-tip punch. In contrast to the preliminary experiments, tablet compression was performed in fully automated (motorized) mode to minimize process variability and to evaluate the suitability of the formulations for automated manufacturing. To verify the comparability between manually and automatically compressed tablets, tablet weight uniformity and hardness were evaluated as in-process control. In addition, the preliminary *in vitro* drug release test described above was repeated for all seven formulations.

2.4.1. Physical characterization

All selected formulations were tested for uniformity of dosage units by evaluating content uniformity according to Ph. Eur. monograph 2.9.40 (Directorate, 2026a). Ten tablets were individually weighed and incubated for 24 h in 25.0 mL of PB pH 6.8 under continuous shaking at 120 rpm using an incubator shaker (IKA KS 3000i control, IKA, Staufen, Germany). At predefined time points (1, 6 and 24 h), the individual incubated tablets were sonicated for 30 min to ensure complete disintegration of the matrix. Aliquots were then withdrawn using 10 mL glass syringes (Fortuna Optima, Poulten & Graf, Wertheim, Germany), filtered through 0.45 μm PVDF-syringe filters (polyvinylidene difluoride; 25 mm diameter, Millex-HV Durapore®, Merck Millipore, Cork, Ireland), and analyzed spectrophotometrically (U-2900, Hitachi, Schwäbisch Gmünd Germany) at a wavelength of 289 nm. Tablet Hardness was determined according to Ph. Eur. monograph 2.9.8 (Directorate, 2026b) using a hardness tester (ZBH30, Erweka, Langen, Germany). In addition, the formulations used for stability assessment (C3EC, P3EC, and HPMC1), the drug substance (propranolol HCl), and the corresponding matrix formers (Compritol® 888 ATO, Precirol® ATO 5, and HPMC) were characterized by differential scanning calorimetry (DSC). DSC measurements were performed using a Discovery DSC 25 Auto (TA Instruments, Waters, Eschborn, Germany). Approximately 5 mg of sample were placed in aluminum pans with a perforated lid and heated from 5 °C to 200 °C or 220 °C at a heating rate of 5 °C/min under a nitrogen atmosphere. Thermograms were analyzed using the manufacturer's software.

2.4.2. In vitro drug release testing

A first set of *in vitro* drug release studies of the selected formulations was performed in triplicate (n = 3) using the Mini-Paddle apparatus (USP Apparatus 2, DT 720, Erweka, Langen, Germany). Experiments were performed in phosphate buffer (PB, pH 6.8) at 37 ± 0.5 °C and an agitation speed of 75 rpm over 18 h using 250 mL for formulations containing 19.8% propranolol HCl and 400 mL for formulations containing 39.6% propranolol HCl to maintain sink conditions. Samples were withdrawn automatically at predetermined time points through a 10 μm poroplast cannula filter (Erweka, Langen, Germany), and drug release was quantified online at 289 nm using a Cary 8454 UV-spectrophotometer (Agilent Technologies, Santa Clara, USA).

In addition, a second set of *in vitro* drug release studies was performed to evaluate drug release under physiologically relevant gastrointestinal (GI) pH conditions by applying a pH-gradient ranging from pH 1.8 to pH 7.5. The experimental setup comprised a simulated gastric phase (60 min, Simulated Gastric Fluid without pepsin - SGF*sp* pH 1.8), small intestinal transit (240 min, consisting of 60 min each in PB pH 6.5, 6.8, 7.2 and 7.5), proximal colonic conditions (300 min, Simulated Colonic Fluid - SCoF pH 5.8), and colonic conditions (480 min, PB pH 6.5). Experiments were performed in triplicate (n = 3) using a Reciprocating Cylinder apparatus 3 (USP Apparatus 3, RRT 10, Erweka, Langen, Germany) at an agitation speed of 10 dips per minute (dpm) with 200 mL of dissolution medium per vessel across 10 vessels in series over a total duration of 18 h Klein et al., 2008. Samples were withdrawn at predefined time points via a sampling probe equipped with a 10 μm poroplast cannula filter (Erweka, Langen, Germany) into 5 mL glass syringes (Fortuna Optima, Poulten & Graf, Wertheim, Germany), and drug release was quantified at 289 nm using a UV–Vis spectrophotometer (U-2900, Hitachi, Schwäbisch Gmünd Germany).

A further series of *in vitro* drug release studies was performed in pediatric FaSSIF (pFaSSIF) pH 6.8 (Freerks et al., 2023) to investigate the influence of physiologically relevant bile salt and phospholipid concentrations on drug release. Experiments were performed using the same Reciprocating Cylinder apparatus 3 at an agitation speed of 10 dpm with 200 mL of dissolution medium over 18 h. In contrast to the GI transit simulation, the experiments were conducted in a single vessel. Samples were taken at predefined time points via a sample probe equipped with a 10 μm poroplast cannula filter (Erweka, Langen, Germany) into a 5 mL glass syringe (Fortuna Optima, Poulten & Graf, Wertheim, Germany). For analysis, 500 μL of each sample was diluted with 250 μL acetonitrile, 200 μL 20 mM PB pH 3.0, and 50 μL 200 mM PB pH 3.0. Drug quantification was performed using a Waters HPLC system consisting of a 1525 binary pump, a 2707 autosampler, and a 2998 photodiode array (PDA) detector (Waters, Milford, MA, USA). Separation was achieved on a Chromolith performance RP-18e column (4.6 × 100 mm, 2 μm; Merck, Darmstadt, Germany), protected by a LiChrospher 100 RP-18 (4 × 4 mm, 5 μm; Merck, Darmstadt, Germany) guard (pre-) column. Data acquisition and processing were performed using Waters Breeze™ 2 software. The mobile phase consisted of a 20 mM PB pH 3.0 and acetonitrile (65:35, *v:v*) at a flow rate of 1.2 mL/min and a column temperature of 40 °C. The injection volume was 50 μL and propranolol HCl was detected at a wavelength of 294 nm. Calibration curves were linear in the range of 2 to 50 μg/mL ($r^2 > 0.999$), with accuracy and precision of quality control samples within ± 5% of nominal values. To ensure sink conditions, saturation solubility was determined in all media at 37 °C prior to the experiments. No significant differences in solubility were observed across the tested pH range (pH 1.8–7.5), with values exceeding 200 mg/mL.

To assess the influence of dissolution conditions on drug release, the drug release profiles obtained under pH-gradient conditions and in pFaSSIF pH 6.8 were compared with those obtained in PB pH 6.8 using the similarity factor (f_2) (Moore and Flanner, 1996). For this comparison, mean drug release profiles were calculated based on three individual release profiles per condition. Although the number of units did not meet the recommendation provided in the EMA guideline, all remaining requirements for the calculation of the similarity factor (f_2) were fulfilled (Committee, 2010). Consequently, the similarity factor (f_2) was used as a supportive tool to compare dissolution profiles obtained under different experimental conditions, rather than as a basis for regulatory assessment.

2.4.3. Stability assessment

Stability studies were conducted on formulations C3EC, P3EC and HPMC1 in accordance with the storage conditions specified in the ICH Guideline *'Stability testing of new drug substances and products'* (Committee, 2003) . These formulations were selected at an early stage of formulation development based on the results available from the preceding formulation screening and initial *in vitro* drug release studies in the Mini-Paddle apparatus as described in **Section 2.4.2**. At the time

of selection, they represented the most promising formulations of the three matrix former systems that formed the primary focus of the subsequent formulation development. Samples were stored at 5 ± 3 °C and 25 ± 2 °C / 60 ± 5% relative humidity (RH) for up to 12 months. After 0, 1, 3, 6 and 12 months, samples were tested for their *in vitro* drug release behavior in PB pH 6.8 using the Mini-Paddle apparatus as described above, with a test duration of 22 h. In addition, DSC measurements were performed on these three formulations immediately after manufacture (0 months) and after each storage interval under both storage conditions to assess potential changes in their solid-state characteristics, as indicated by their thermal behavior during storage. To compare drug release profiles during stability testing, the similarity factor (f_2) was calculated using the same approach and acceptance criteria as described for the comparison of dissolution profiles obtained under different experimental conditions. The drug release profile obtained immediately after manufacture was compared with the corresponding profiles after each specified storage period under the defined storage conditions. As the Mini-Paddle experiment in PB pH 6.8 served as the standardized quality control method throughout formulation development, profile comparisons during stability testing were limited to dissolution profiles obtained under these conditions.

3. Results

3.1. Formulation development and screening

This study aimed to develop formulations capable of sustaining the release of a highly water-soluble drug. Lipid-based matrix formers were primarily investigated, while cellulose-based matrix formers served as comparators. A broad range of formulations was prepared, varying in matrix former type, drug load, and combinations of matrix formers. Most formulations could be manufactured without major issues. However, formulations C3HPMC, P2, P3HPMC, P3C and P4HPMC exhibited pronounced sticking to the upper punch, resulting in defects on the tablet and were therefore excluded from further investigations. The Dyn1 formulation based on Dynasan® 114 could not be manufactured at all due to insufficient die filling and severe sticking during compression.

To enable rapid screening of formulation performance, a simplified *in vitro* test was applied by incubating the tablets in PB pH 6.8 for 1 h. Drug release after 1 h served as an early screening parameter to identify formulations with the greatest potential for further evaluation as ER matrix tablets. The corresponding drug release results are summarized in Fig. 1. As shown in Fig. 1a, the type of matrix former strongly

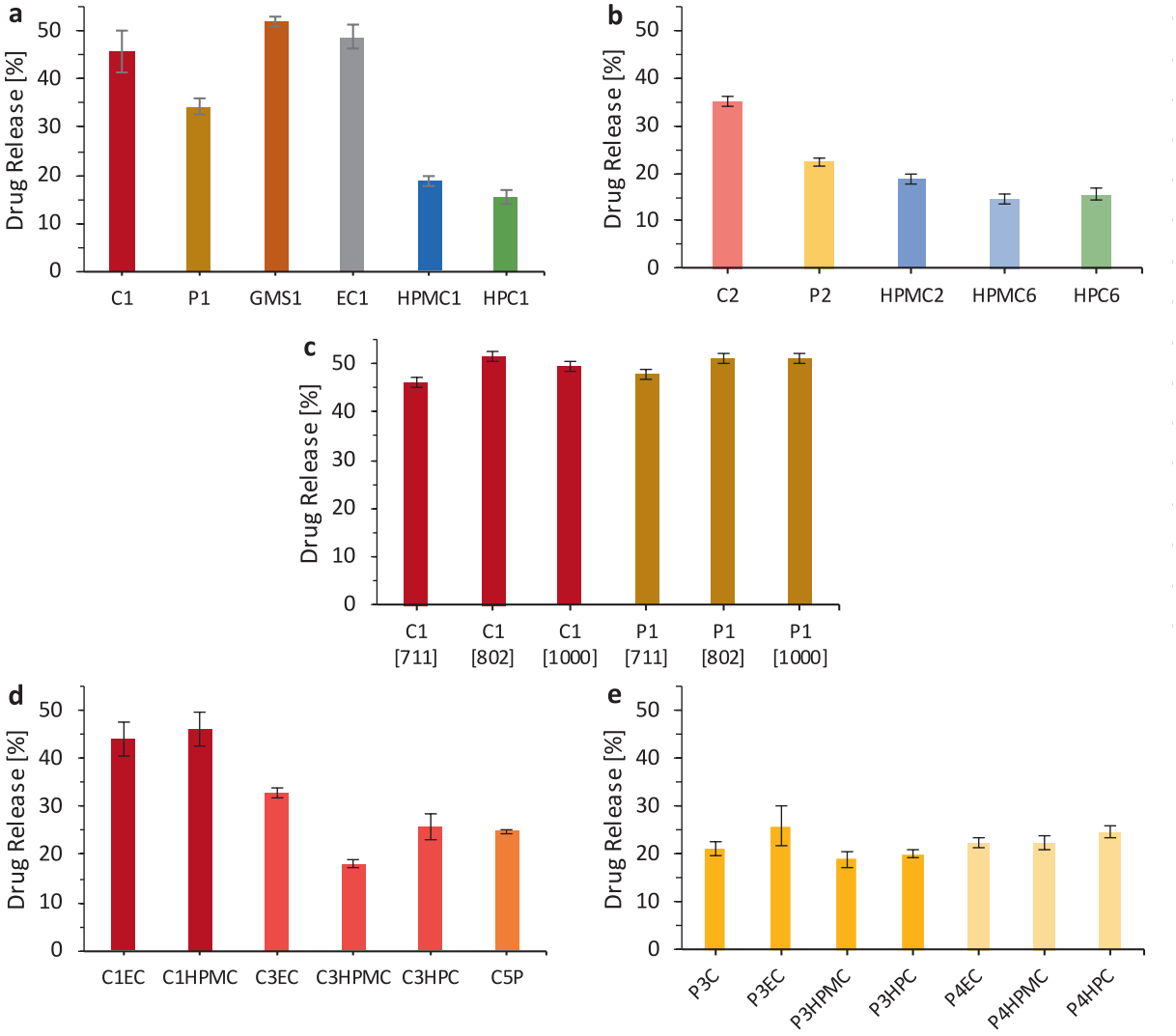

Fig. 1. Drug release of the pre-screened formulations after 1 h of incubation in 10 mL phosphate buffer pH 6.8 (37 ± 0.5 °C, 120 rpm) to evaluate the influence of (a) matrix former type, (b) reduced drug load, (c) filler type (different MCC grades), (d) combinations of Compritol® with other matrix formers and (e) the combinations of Precirol® with other matrix formers (n = 3; mean ± S.D.).

influenced drug release after 1 h. The amount of drug released after 1 h decreased in the following order: GMS > EC > Compritol® > Precirol® > HPMC > HPC. The Dyn1 formulation was not further evaluated due to its lack of manufacturability. Formulations based on EC and GMS showed comparatively high drug release and were therefore not considered for further studies. In the second screening step (Fig. 1b), the effect of reducing the drug load by half was investigated. For the lipid-based formulations C2 and P2, a reduction in drug release of approximately 10% was observed compared to the corresponding formulations C1 and P1. In contrast, no difference was detected between HPMC1 and HPMC2. Consequently, the filler in the HPMC formulation was replaced by the matrix former (HPMC6), resulting in a further reduction in drug release of approximately 4%. A comparable approach was applied to the HPC formulations (HPC1 to HPC6), although no relevant differences in drug release were observed. The influence of filler type was evaluated by replacing Emcompress® with different grades of MCC (Fig. 1c). All MCC-based formulations resulted in turbidity of the dissolution medium during the 1 h incubation and exhibited higher drug release compared to formulations containing Emcompress®.

In a final series of formulation screening experiments, combinations of lipid matrix formers with selected polymeric matrix formers were investigated based on the results of the preceding screening steps. The corresponding drug release data are presented in Fig. 1d and e. For Compritol®-based formulations, combining Compritol® with EC or HPMC at high drug load (39.6% API, C1) did not reduce the amount of drug released after 1 h compared with the corresponding reference formulation. Consequently, subsequent investigations focused on formulations containing 19.8% API.

At reduced drug load, combinations of Compritol® with EC, HPMC, and HPC resulted in lower drug release after 1 h compared with C2. The combination of Compritol® with Precirol® was also feasible, provided that Emcompress® was retained in the formulation, and showed reduced drug release compared to C2. In contrast, binary lipid formulations without filler (P3C) could not be manufactured due to pronounced sticking (Fig. 1e). For Precirol®-based formulations, combinations with cellulose-based matrix formers also resulted in lower drug release compared with P2 (Fig. 1e). However, no relevant differences between the individual combinations were observed. Notably, formulations containing EC or HPC exhibited improved manufacturability, as no significant sticking occurred during compression.

3.2. Manufacture and evaluation of selected formulations

3.2.1. Physical characterization

Based on the preliminary 1 h *in vitro* drug release screening, seven formulations were selected as promising due to their low drug release and acceptable manufacturability. These formulations were reproduced under automated conditions using an eccentric tablet press. All formulations could be manufactured without relevant process-related defects such as sticking or capping and were therefore subjected to further characterization. Uniformity of dosage units was assessed for all batches (n = 10) in accordance with Ph. Eur. monograph 2.9.40. The drug content ranged from 95.5 to 100.9%, with a maximum acceptance value (AV) of 7.6 (Table 6). All formulations complied with Ph. Eur. specifications and were considered suitable for further characterization.

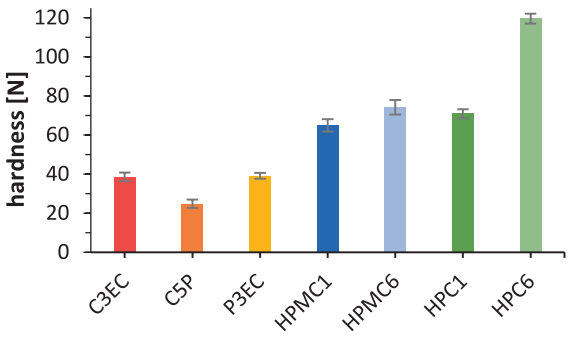

Fig. 2. Hardness of selected of tablet formulations produced by automatic compression; mean ± S.D. (n = 10).

Subsequently, tablet hardness was determined in accordance with Ph. Eur. monograph 2.9.8. As shown in Fig. 2, lipid-based formulations exhibited lower hardness compared with cellulose ether-based formulations. A reduction in drug load was associated with increased tablet hardness (HPC1 vs HPC6). Furthermore, the incorporation of EC in formulations C3EC and P3EC resulted in higher hardness compared with formulations containing lipid matrix formers and Emcompress® alone. In addition, the tablet formulations produced by automatic compression were evaluated for drug release after 1 h to assess their comparability with the manually compressed tablets. All formulations showed comparable drug release to their manually produced counterparts.

3.2.2. In vitro drug release testing

Drug release behavior of the seven selected formulations was evaluated under three different experimental scenarios. The mean drug release profiles are shown in Fig. 3.

In the first series of tests, drug release was investigated using the Mini-Paddle apparatus in 250 mL or 400 mL PB pH 6.8 for formulations containing 19.8% propranolol HCl (C3EC, C5P, P3EC, HPMC6, and HPC6) and 39.6% propranolol HCl (HPMC1 and HPC1), respectively (Fig. 3a and b). Drug release from C3EC and P3EC was comparable with that of the cellulose ether-based formulations, with P3EC showing slightly lower release compared to C3EC. The Compritol®/Precirol® formulation C5P exhibited the fastest drug release among the lipid-based systems, while still remaining comparable with the other formulations. No relevant differences were observed between the cellulose ether-based formulations. As expected, the hydrophilic cellulose ether-based tablets exhibited swelling during the test, whereas lipid-based formulations did not show swelling and exhibited no visible erosion over the test period.

In the second series of experiments, drug release was assessed using a pH gradient (pH 1.8–7.5) with the Reciprocating Cylinder apparatus (Fig. 3c and d). Compared with the first setup, more pronounced

Table 6
Absolute (mg) and relative (%) drug content (mean ± SD), together with the corresponding acceptance values (AV), of tablet formulations produced by automatic compression (n = 10).

	C3EC	C5P	P3EC	HPMC1	HPMC6	HPC1	HPC6
Mean [mg]	11.40	12.68	11.90	24.40	12.80	24.60	12.30
S.D. [mg]	0.14	0.23	0.29	0.49	0.24	0.47	0.20
Mean [%]	97.6	100.9	98.3	100.6	97.6	95.6	95.5
S.D. [%]	1.1	1.9	2.4	1.8	2.0	1.9	1.6
AV	3.5	2.1	6.1	4.3	5.8	7.6	6.8

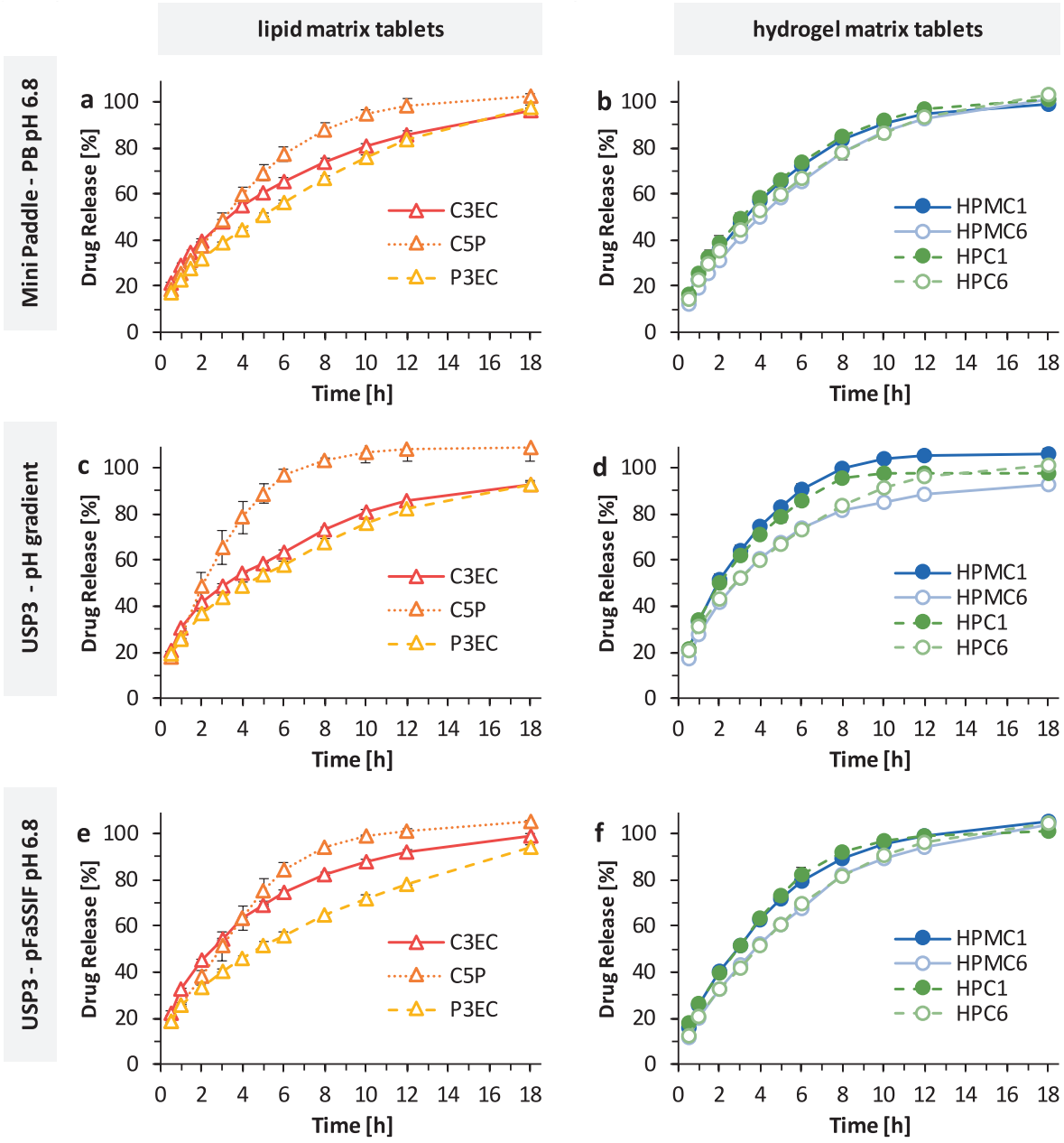

Fig. 3. Drug release from (a, c, e) lipid matrix tablets and (b, d, f) hydrogel matrix tablets (a and b) in the Mini-Paddle apparatus (250 or 400 mL phosphate buffer -PB pH 6.8, 37 ± 0.5 °C, 75 rpm), (c and d) in the Reciprocating Cylinder apparatus (200 mL Simulated Gastric Fluid without pepsin - SGF*sp*, phosphate buffer or Simulated Colonic Fluid - SCoF, pH 1.8–7.5, 37 ± 0.5 °C, 10 dpm) and (e and f) in the Reciprocating Cylinder apparatus (200 mL pediatric FaSSIF - pFaSSIF pH 6.8, 37 ± 0.5 °C, 10 dpm); n = 3; mean ± S.D..

differences between formulations were observed. C5P again showed the fastest drug release among the lipid-based formulations, with a more distinct separation from the other lipid systems. In this setup, C5P also exhibited a release profile similar to that of HPMC1. C3EC and P3EC again showed comparable release behavior over the entire test period. Overall, cellulose ether-based formulations exhibited intermediate release profiles between C5P and the C3EC and P3EC formulations. As expected, formulations containing 39.6% propranolol HCl showed a slight tendency towards faster drug release than those containing 19.8% propranolol HCl.

In the third series of experiments, a more biorelevant dissolution setup using pFaSSIF pH 6.8 was applied (Fig. 3e and f). Under these conditions, C3EC exhibited slightly faster drug release compared with P3EC, with a profile similar to that of the cellulose ether-based formulations. All other formulations showed comparable release behavior to that observed in the pH-gradient study.

The trends observed by visual comparison of the release profiles were largely reflected by the similarity factor (f_2) analysis. For most formulations, f_2 values above 50 were obtained. However, for C5P, HPMC1, and HPC1, f_2 values between 40 and 50 were calculated when comparing drug release in PB pH 6.8 and the pH-gradient (Table 7).

Table 7
Similarity factors (f_2) comparing drug release profiles obtained in the Mini-Paddle apparatus (USP 2, 250 or 400 mL phosphate buffer - PB pH 6.8, 37 ± 0.5 °C, 75 rpm), in the Reciprocating Cylinder apparatus (200 mL Simulated Gastric Fluid without pepsin - SGF*sp*, phosphate buffer or Simulated Colonic Fluid - SCoF, pH 1.8–7.5, 37 ± 0.5 °C, 10 dpm), and in the Reciprocating Cylinder apparatus (USP 3, 200 mL pediatric FaSSIF - pFaSSIF pH 6.8, 37 ± 0.5 °C, 10 dpm) (n = 3).

USP 2 – PB pH 6.8							
	C3EC	**C5P**	**P3EC**	**HPMC1**	**HPMC6**	**HPC1**	**HPC6**
USP 3 – pH-gradient	88.64	43.00	73.43	41.00	54.83	47.86	59.20
USP 3 – pFaSSIF pH 6.8	57.98	67.73	75.87	65.23	80.50	64.43	76.76

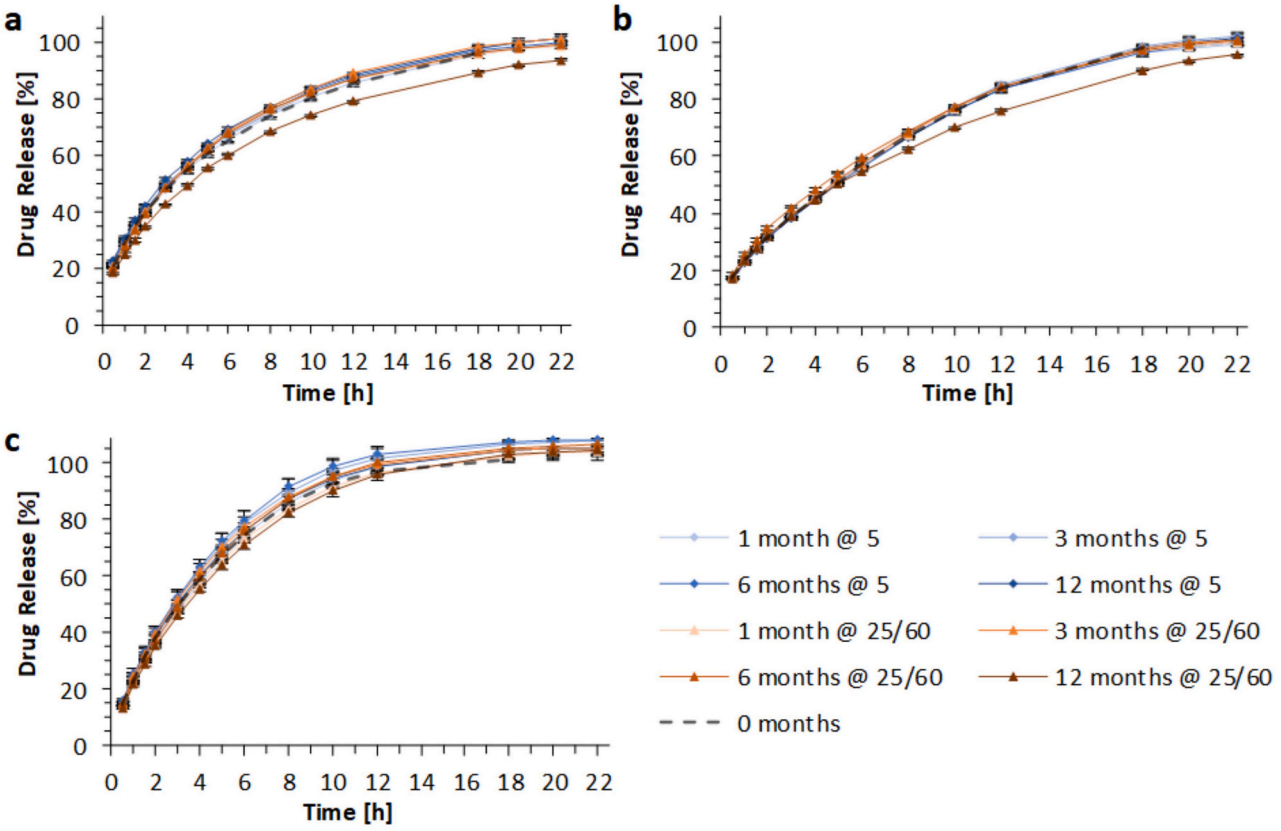

Fig. 4. Drug release from (a) C3EC, (b) P3EC and (c) HPMC1 in the Mini-Paddle apparatus (250 or 400 mL phosphate buffer - PB pH 6.8, 37 ± 0.5 °C, 75 rpm), after storage for 1, 3, 6 or 12 months under ICH conditions: refrigerated (5 °C ± 3 °C,) and long term (RT; 25 °C ± 2 °C/60% RH ± 5% RH;); (n = 3; mean ± S.D.).

3.2.3. *Stability assessment*

Stability of formulations C3EC, P3EC, and HPMC1 was evaluated under the storage conditions specified in ICH guideline Q1A (R2) '*Stability testing of new drug substances and drug products*' (Committee, 2003).

Table 8
Similarity factors (f_2) comparing drug release profiles of freshly prepared ER and stored tablets under different conditions, determined using the Mini-Paddle apparatus in phosphate buffer - PB pH 6.8 (n = 3).

		Freshly prepared		
		C3EC	**P3EC**	**HPMC1**
5 °C	**1 month**	98.64	97.69	88.71
	3 months	89.17	97.09	97.66
	6 months	91.17	93.04	65.86
	12 months	80.64	95.61	68.66
25 °C / 60% R.H.	**1 month**	87.20	97.39	61.89
	3 months	87.10	78.17	79.37
	6 months	75.86	99.43	74.08
	12 months	63.16	69.42	91.75

Drug release profiles obtained immediately after manufacture and after storage are shown in Fig. 4. The three formulations maintained comparable drug release profiles over 12 months under both investigated storage conditions, as demonstrated by f_2 values exceeding 50 for all profile comparisons. (Table 8).

DSC thermograms of the pure drug substance, the individual matrix formers, and the selected formulations before and during storage are shown in Fig. 5. For C3EC and P3EC, the thermal events associated with propranolol HCl and the respective lipid matrix formers remained essentially unchanged throughout storage under both conditions, indicating no relevant changes in the thermal behavior of these formulations. Similarly, the DSC thermograms of HPMC1 showed no relevant changes in the propranolol HCl melting endotherm during storage. However, an additional small thermal event was observed in HPMC1 at temperatures above the propranolol HCl melting peak.

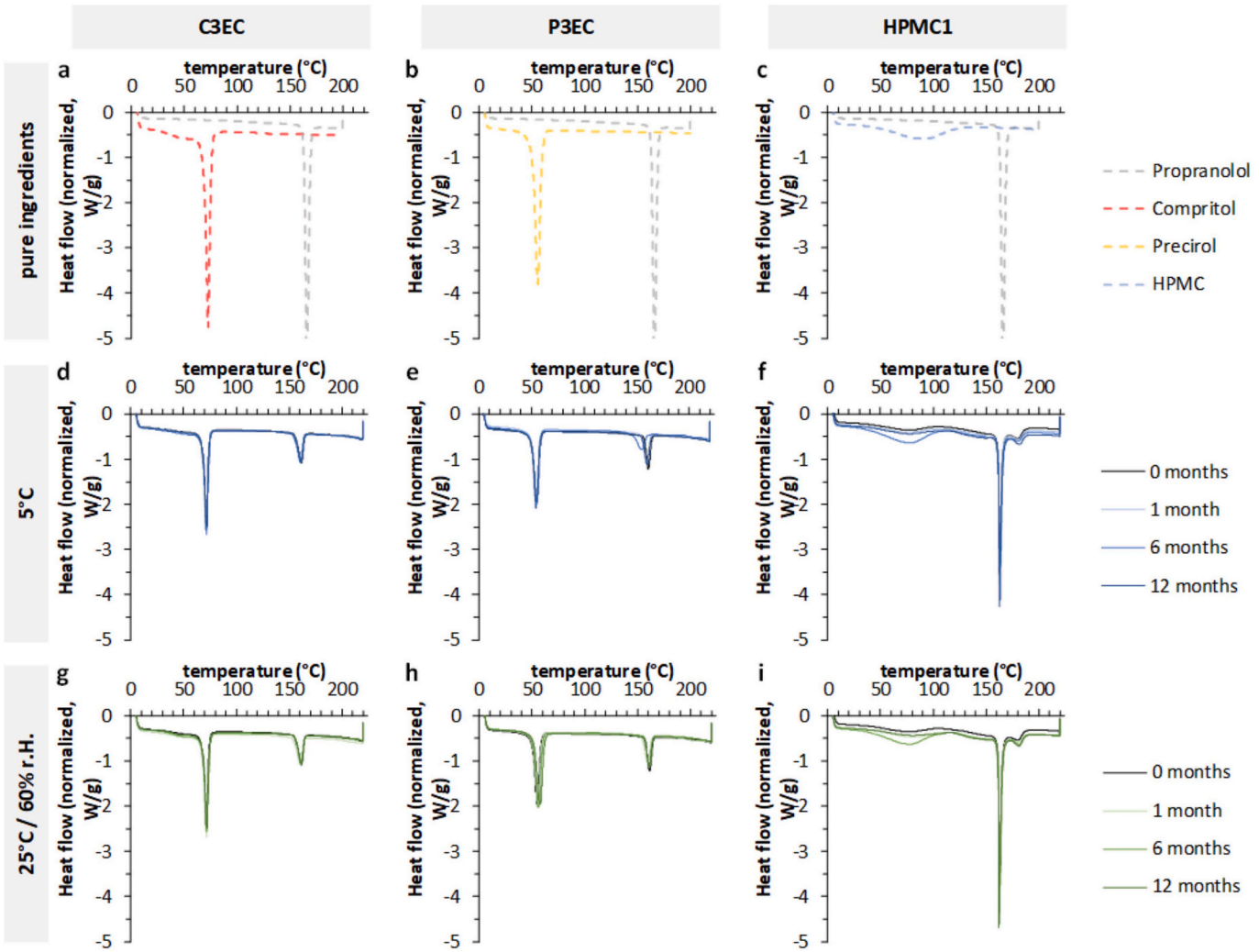

Fig. 5. Differential scanning calorimetry (DSC) thermograms of propranolol HCl, the individual matrix formers (Compritol®, Precirol® and HPMC), and the selected formulations (C3EC, P3EC, and HPMC1). The top row (a–c) shows the thermograms of propranolol HCl and the corresponding matrix former(s). The middle row (d–f) shows the formulations directly after manufacture (0 months) and following storage at 5 ± 3 °C. The bottom row (g–i) shows the formulations directly after manufacture and following storage at 25 ± 2 °C/60 ± 5% RH.

4. Discussion

The present proof-of-concept study focused on evaluating the feasibility of developing small-diameter (5 mm) lipid matrix tablets capable of providing sustained drug release over clinically relevant time periods. Propranolol HCl was selected as the model drug. In pediatric patients, it is used for various indications, including hemangiomas, tachycardic arrhythmias, hypertension, and migraine prophylaxis, and is listed in the WHO '*Essential Medicines List for Children*' (Mecklin et al., 2022; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004; Patel and Bauman, 2014; World Health Organization, 2025). Preschool- and school-aged children represent a potential target population for the 5 mm tablets. For indications such as tachycardic arrhythmias, hypertension, and migraine prophylaxis, propranolol HCl dosing regimens differ according to the indication. Overall, the recommended doses generally range from approximately 0.5–3 mg/kg/day, administered in two to four divided doses (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004; Pacifici, 2021; Patel and Bauman, 2014). Because treatment may require administration up to four times daily, depending on the indication and dosing regimen, it poses a considerable burden for both pediatric patients and their caregivers. Currently, treatment mainly relies on liquid formulations or compounded preparations, such as capsules that can be opened and administered with food or via enteral feeding tubes. The smallest commercially available propranolol HCl immediate release (IR) tablets have a diameter of 6–7 mm and are therefore unsuitable for younger children. Moreover, although some propranolol HCl ER formulations are available for adults, they are not appropriate for pediatric use. To our knowledge, there are currently no reports on pediatric-appropriate ER formulations of propranolol HCl. Thus, there is a clear unmet need for such a dosage form.

To address this unmet need, the present study investigated a lipid-based matrix tablet designed for pediatric use. The formulation was developed using safe excipients selected with sustainability considerations in mind, while aiming to provide sustained drug release and facilitate swallowing through its small size. A tablet diameter of 5 mm was selected as a compromise between swallowability and matrix size sufficient to achieve extended drug release.

4.1. Formulation development and selection

During formulation development, key factors such as manufacturability, tablet hardness, and sustained drug release were systemically investigated. Excipients were selected based on their suitability for pediatric use and sustainability aspects. A structured excipient selection

strategy was applied using information from the STEP database, where available, together with published literature, previous use in pediatric medicinal products, manufacturer information, and, where applicable, GRAS status as supportive evidence for an established safety profile. Since the tablet size was intentionally minimized, the resulting excipient exposure per dosage unit would also be low, thereby further reducing potential safety concerns. For example, assuming a 5-year-old preschool child weighing 24 kg, corresponding approximately to the 97th percentile body weight according to the WHO '*Child Growth Standards – Boys Chart*' (World Health Organization and Child Growth, 2006), and receiving the highest dose considered in this study (3 mg/kg/day), the maximum daily propranolol HCl dose would be 72 mg. This corresponds to three 24 mg tablets or six 12 mg tablets per day. Given a tablet weight of 60 mg, the resulting total daily excipient exposure would be approximately 108 mg and 288 mg, respectively. As shown in Tables 1–6, the majority of the tablet mass consists of excipients that were identified as suitable for pediatric use during the excipient selection process based on available safety information and for which no acceptable daily intake (ADI) has been established. Therefore, these estimated total daily excipient amounts are not expected to raise safety concerns.

Particular attention was given to the selection of matrix formers. Lipid-based excipients such as Compritol® 888 ATO (glyceryl dibehenate), Precirol® ATO 5 (glyceryl distearate), Dynasan® 114 (glyceryl trimyristate), and glyceryl monostearate are of vegetable origin and structurally similar to dietary lipids, supporting their suitability for pediatric formulations (Aburahma and Badr-Eldin, 2014; Corporate Headquarters Gattefosse, 2023; European Paediatric Formulation Initiative, 2017). As cellulose-based alternatives, EC, HPMC and HPC were selected. While EC is a hydrophobic, non-swellable cellulose derivate, HPMC and HPC are hydrophilic and swellable in aqueous environments. These polymers are widely used in pharmaceutical and food applications and exhibit low oral toxicity, and are already included in various oral drug products for pediatric use (Rouaz et al., 2021; Walsh et al., 2014).

In addition, sustainability informed the selection of excipients. In line with the principles of green chemistry, preference was given to materials of natural or renewable origin, as well as polymers with favorable biodegradation or environmental fate profiles (Kar et al., 2022; Kümmerer, 2019). The lipid-based excipients used as matrix formers are derived from renewable resources and are expected to be biodegradable due to their similarity to dietary fats (Candiani et al., 2022, 2025) Cellulose derivatives, although semi-synthetic, are generally biodegradable (Layek and Mandal, 2020; Miroshnichenko et al., 2022), whereas EC shows only limited biodegradability but does not bioaccumulate and is considered environmentally benign compared to more persistent synthetic polymers (Cetin et al., 2023; Lourenço et al., 2025; Moermond et al., 2022; Shlush and Davidovich-Pinhas, 2023).

Among the tested fillers, Emcompress® proved to be the most suitable, enabling the production of hard tablets that remained largely intact during dissolution testing, whereas the use of MCC resulted in partial tablet disintegration. From a formulation perspective, a lower drug load was advantageous, particularly for lipid-based systems, in which drug release is predominantly diffusion-controlled (Roberts et al., 2015). Increasing the matrix former content likely reduced tablet porosity, thereby contributing to the slower drug release. The combination of lipid matrix formers with swellable polymers such as HPMC or HPC was expected to further retard drug release, potentially through pore blocking; however, no significant additional effect was observed.

The selected drug loads were guided by both formulation and practical dosing considerations. An initial target drug load of approximately 40% (w/w) was selected to investigate the feasibility of manufacturing small-diameter lipid matrix tablets with a comparatively high drug loading by direct compression. Following formulation optimization, the resulting formulation contained 39.6% (w/w) propranolol HCl. A second formulation containing approximately half this drug load (19.8% (w/w)) was subsequently investigated to evaluate the influence of drug loading on tablet properties and drug release. The resulting tablet strengths of approximately 24 mg and 12 mg propranolol HCl should therefore be regarded as proof-of-concept dosage strengths rather than fixed pediatric doses.

During formulation development, manufacturing issues such as sticking and capping were observed, particularly in lipid-based formulations. The incorporation of EC into these formulations resulted in improved manufacturability and promising early drug release behavior within the first hour. Accordingly, the formulations C3EC and P3EC, were selected for further evaluation. To additionally investigate a lipid-based system without cellulose derivatives, C5P was included. This formulation combines Compritol® and Precirol® with Emcompress® as the filler and also exhibited adequate manufacturability despite the absence of EC. For comparison with conventional hydrophilic matrix systems, HPMC- and HPC-based formulations with different drug loads were included. Overall, C3EC, C5P, P3EC, HPMC1, HPMC6, HPC1, and HPC6 were identified as promising formulations for further investigation.

4.2. Formulation evaluation

The propranolol HCl content of all formulations was close to the respective target dose, resulting in AVs (n = 10) below the Ph. Eur. monograph 2.9.40 limit of 15. Thus, all selected formulations met the pharmacopoeial requirements for uniformity of dosage units, indicating homogeneous and reproducible manufacturing.

Tablet hardness is a critical quality attribute for pediatric solid oral ER dosage forms, as sustained drug release depends on maintaining matrix integrity throughout the intended release period. This is particularly relevant because young children, especially those between 2 and 3 years of age, may chew small dosage forms before swallowing them (Klingmann, 2017; Münch et al., 2023b). The cellulose ether-based formulations exhibited hardness values ranging from approximately 60 to 75 N for HPMC1, HPMC6, and HPC1 and exceeding 100 N for HPC6, whereas the incorporation of lipid matrix formers consistently resulted in lower tablet hardness. Among the lipid-based formulations, the addition of EC increased tablet hardness to approximately 40 N for C3EC and P3EC, whereas C5P, which did not contain EC, exhibited a hardness of only approximately 25 N despite application of the maximum compression force.

Beyond mechanical properties, sustained drug release was also investigated. Drug release profiles were first evaluated in PB pH 6.8 using the Mini Paddle Apparatus. In agreement with the pre-screening results, lower drug loads and higher matrix former contents resulted in more sustained release profiles. Precirol® provided a greater prolongation of drug release compared to Compritol®, whereas no relevant differences were observed between HPMC- and HPC-based formulations. Overall, approximately 80% drug release was achieved after 5 h for C5P and HPMC1, after 6 h for HPC1, after 8 h for C3EC, HPMC6, and HPC6, and after 10 h for P3EC.

To further evaluate the robustness of the investigated formulations, drug release was subsequently investigated under a physiological pH gradient and in pFaSSIF pH 6.8 using the Reciprocating Cylinder Apparatus. Overall, only minor differences in release behavior were observed between the different dissolution conditions, with slight effects noted for C5P and HPMC1. In particular, P3EC showed a consistent release profile across all test conditions. This observation was supported by similarity factor (f_2) analysis. For most formulations, f_2 values exceeded 50 despite the use of different dissolution media and two dissolution apparatuses with different hydrodynamic conditions. Only C5P, HPMC1, and HPC1 yielded f_2 values slightly below the generally accepted threshold of 50 (43–48) when comparing the release profiles obtained in PB pH 6.8 using the Mini Paddle Apparatus with those obtained under the physiological pH gradient using the Reciprocating Cylinder Apparatus. Considering the limited number of replicates (n =

3), the different hydrodynamic conditions of the two dissolution apparatuses, and the fact that all comparisons between PB pH 6.8 and pFaSSIF resulted in f_2 values above 50, these findings suggest that overall, the investigated formulations exhibited robust release characteristics under the investigated dissolution conditions. Nevertheless, additional studies under biorelevant conditions are warranted to further substantiate these observations.

To evaluate long-term performance, stability studies were conducted for C3EC, P3EC, and HPMC1 according to ICH guidelines. P3EC and HPMC1 showed comparable release profiles across all storage conditions, whereas C3EC showed a slight trend towards a decrease in release rate over time when stored at room temperature. This observation was reflected in the similarity factor (f_2) analysis of the stability samples, which indicated high similarity ($f_2 > 50$) for all formulations across all storage conditions. Although C3EC showed a slight tendency towards slower drug release after storage at room temperature, the overall similarity of the dissolution profiles indicates that no relevant changes in release behavior occurred under the investigated storage conditions. These findings demonstrate that the investigated matrix systems generally maintained their release characteristics throughout storage. The DSC thermograms obtained before and during storage did not reveal relevant changes in the thermal behavior of the investigated lipid-based formulations, supporting the dissolution results and suggesting that the formulations remained physically stable under the investigated storage conditions. Although an additional minor thermal event was observed for HPMC1, this was not further investigated, as the subsequent formulation development focused on the lipid-based systems.

Based on its favorable release characteristics across different dissolution conditions, satisfactory storage stability, and acceptable manufacturability, P3EC appears to be the most promising lipid-based formulation for further development. Nevertheless, its hardness of approximately 40 N should be interpreted in the context of this proof-of-concept study. Although the tablets could be manufactured and handled throughout the experimental work without visible mechanical failure, hardness alone does not fully reflect all aspects of mechanical robustness during packaging, transport, or patient use. The impact of tablet damage or chewing on drug release was beyond the scope of the present study. However, future studies should include further characterization of the mechanical robustness of the formulation, for example by friability and mechanical stress testing, as well as dissolution studies using deliberately damaged tablets to further evaluate its performance under conditions relevant to clinical use.

The present study demonstrates the feasibility of developing lipid-based matrix tablets for pediatric use, enabling extended drug release with acceptable manufacturability and stability. Overall, the investigated formulations establish a promising platform for further development of pediatric ER drug delivery systems.

5. Conclusion

The aim of this study was to develop a propranolol HCl matrix formulation based on lipid matrix formers. To achieve a balance between sustained drug release and a tablet size suitable for pediatric use, 5 mm tablets at two different dose levels were manufactured using safe excipients, with sustainability aspects guiding excipient selection. From a broader formulation screening, seven candidates were selected for further investigation, including three lipid-based systems. Among the investigated formulations, the Precirol®-based formulation P3EC demonstrated the most favorable overall performance, combining acceptable manufacturability with a sustained and robust release profile that was maintained after storage under different conditions. These findings demonstrate the feasibility of developing small lipid-based ER matrix tablets for pediatric use and identify P3EC as a promising starting point for further formulation optimization. Future work should focus on further reduction of tablet size, improvement of mechanical strength, and evaluation of the formulation concept with other active pharmaceutical ingredients to further advance the development of age-appropriate ER solid oral dosage forms for pediatric therapy.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used DeepL and DeepL Pro in order to improve the language of selected sentences. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Stefanie Broocks: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Melanie Gebhardt:** Investigation, Formal analysis. **Sandra Klein:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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