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Production and *in vitro* evaluation of a lamotrigine extended release tablet based on a controlled-porosity osmotic pump system

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Osmotic pump delivery systems have made significant advances in the past decades for controlled drug release over a long period of time. Usually, osmotic pump products require sophisticated and expensive laser drill technology resulting in increase in production cost and decrease in production efficiency. In this study, a lamotrigine extended release tablet based on a controlled-porosity osmotic pump (CPOP) system was developed to circumvent laser drill technology in reference, Lamictal XR®. The tablet core was coated by a polymer blend of Acryl-EZE® and HPMC E5. Lactose and HPMC were added in the CPOP core to adjust the release profile. An orthogonal design was employed to optimize the formulation from factors, i.e., core composition, coating materials ratio and coating levels. Comparisons of *in vitro* drug release profiles were also conducted. The optimized formulation showed a satisfactory zero-order release profile (R^2 = 0.9912). Similarity factor, f_2 of 77 was obtained in larger scale. The lamotrigine extended release tablets based on the CPOP system showed ideal reproducibility and stability. The developed system has the ability to be an alternative production method for Lamictal XR®, which could circumvent the laser drill technology and promote the osmotic pump generalization.

1. Introduction

The osmotic pump system used for drug delivery has been developed as early as 1950s (Rose and Nelson 1955). Osmotic pump systems can deliver drug in a controlled pattern for a long period employing osmotic pressure as a driving force and maintain the drug plasma concentration in the therapeutic range. Various types of osmotic pump systems were developed and approved since their introduction (Santus and Baker 1995).

The elementary osmotic pump (EOP) was introduced by Theeuwes in the 1970s (Theeuwes 1975), which can release drug through the orifice driven by osmotic pressure. The EOP had advantages of releasing drug in a zero-order kinetic at that time, and was applied on several marketed products (Santus and Baker 1995). The EOP system consists of an osmotic core and a semipermeable coating membrane with an orifice. However, the drug release can be hampered after blockage of its sole orifice and the release of drug may be influenced, which can decrease the drug efficacy.

In order to overcome this issue, attention was devoted to drill more orifices on the surface of tablets (Liu et al. 2000). Many products based on analogous thought have been marketed, e.g., Lamictal XR®. As an extended release tablet of water-insoluble drug, lamotrigine (LTG), this product was developed and commercialized by GlaxoSmithKline plc. for adjunctive therapy of primary generalized onset seizures and focal seizures (Anderson and Saneto 2015). As Fig. 1 A shows, Lamictal XR® tablets contain a modified-release eroding matric core coated with a semipermeable coating. The core could be eroded to generate the osmotic pressure and promote the LTG release. However, the coating can retard the release of the LTG from the core. Two orifices were drilled by laser in the coating to maintain the release rate of the LTG throughout the entire gastrointestinal (GI) tract (Altria and Taylor 2012). Lamictal XR® can successfully release LTG in GI tract with a zero-order pattern, reduce seizure frequency and decrease adverse effects of Lamictal IR® (Anderson and Saneto 2015).

However, all of these osmotic pump systems face the common limitation to require sophisticated and expensive laser drill technology to produce the delivery orifice (Bhanushali et al. 2009). It is a challenge to produce a precise and reliable hole with the laser drill technology when moving under the laser head rapidly in order to obtain adequate production efficiency (Santus and Baker 1995). The laser drill requires a certain period of time to drill a hole on the coating, which severely limits the production efficiency. In order to increase production efficiency, a rapid moving speed was required but increased the risk to prepare failed orifice on the tablets at same time. Moreover, the expensive laser drill technology and poor production efficiency increase the cost of osmotic pump tablets. The requirement for a high-precision laser drill also limited the generalization of the osmotic pump production technology.

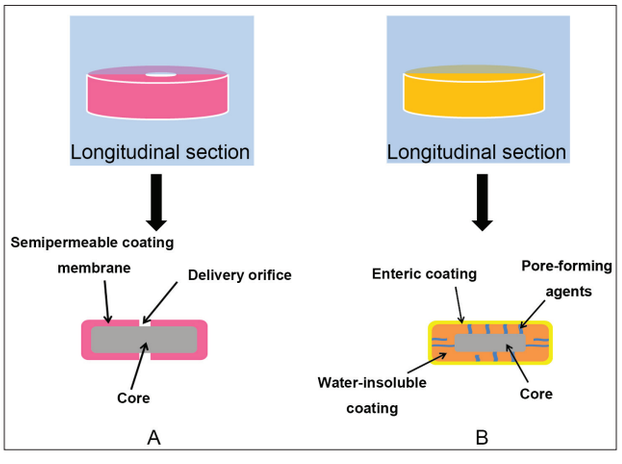

Fig. 1: Structure schemes of Lamictal XR® (A) and CPOP tablet (B) was showed in their longitudinal sections.

A controlled-porosity osmotic pump (CPOP) system prepared with traditional coating technology was designed to surmount this disadvantage. As depicted in Fig. 1 B, an osmotic core and a coating layer consisting of two types of polymers were designed to adjust

the drug release profile in the CPOP system. Some excipients were used in the osmotic core as osmagent to adjust the drug release from the core of tablets for the drug with low aqueous solubility (Verma et al. 2002). There were two types of polymers in the tablets coating: The water-soluble polymer acted as pore-forming agent and a water-insoluble polymer was used in the controlled release membrane coated on CPOP tablets (Lin and Lee 2003;He et al. 2006). Pore-forming agents could be dissolved and generate water channels to adjust and obtain a controlled drug release profile. The expensive and sophisticated laser drilling process can be excluded and cost can be reduced. The ratio of the two polymers types could have induced the different distribution of pore-forming agents and form different water channels, which played an important role in adjusting the drug release profile. The CPOP system could also achieve constant drug release by releasing drug through the pores and the inter-connected channels in coating.

In this study, the water-insoluble LTG was selected as a model drug and Lamictal XR® formulation was selected as a reference. Lactose and HPMC were used in CPOP tablet core to generate the osmotic pressure and hence promote the LTG release. A coating with Acryl-EZE® and HPMC E5 was covered on the core to adjust the LTG release and an Opadry®200 was coated as an outermost layer. The obtained release profile of CPOP tablets fitted the zero-order model to describe its release profile. The feasibility of the CPOP system applied in LTG extended delivery was verified by investigating the resistance to the dissolution media variation, reproducibility and stability.

2. Investigations and results

2.1. Saturated solubility

As shown in Fig. 2, LTG showed the highest and lowest solubility in pH 2.0 and pH 6.9 (DI water), respectively. The saturated solubility of LTG decreased with increasing pH values.

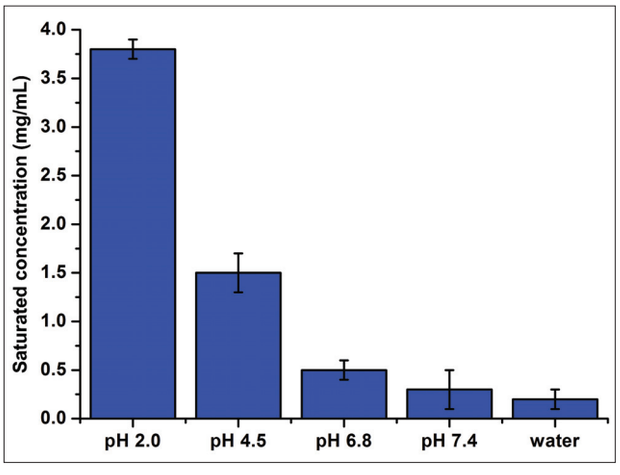

Fig. 2: Saturated solubility of LTG in different pH values media (n = 3).

2.2. Influence of tablet formulation

2.2.1. Influence of the tablet core

The amount of lactose and HPMC in the core were the two factors selected to investigate the influence of tablets osmotic core on the release profile. The CPOP tablet core was compressed with different amounts of lactose to study its effect on the LTG release profile.

Fig. 3 A shows the release profile with lactose amount of 135 mg (F1), 150 mg (F2) and 165 mg (F5) in the tablets core. The total release amount and release rate were two important indexes to investigate and evaluate the CPOP tablets release profile. The release rate and total release amount increased with lactose amount from 135 mg to 165 mg. For F1, the LTG released slowly in the initial 2 h, and the total release amount achieved less than 90% ultimately.

HPMC used to adjust the LTG release profile might have formed a different viscosity hydrogel in the system. Different HPMC types were added in the tablets core to investigate their interference with the release rates. The release profiles of tablet cores contained HPMC K100 LV CR (F3), HPMC K4M CR (F2) and HPMC K15M CR (F4) are shown in Fig. 3 B. The formulation F3 showed the slow release of LTG in pH 2.0 media in initial 2 h, and the total release amount reached about 100% in the 17 h. F2 showed less total release amount and lower release rate than F3 but performed faster when compared with F4 formulation.

2.2.2. Influence of tablet coating

In this study, the ratio of HPMC E5 in Acryl-EZE® formulation and HPMC E5 coating and the coating levels were used to investigate their effects on CPOP tablets release profiles. HPMC E5 was used as pore-forming agent to adjust the CPOP tablets release profile. Fig. 3 C revealed the release profile of CPOP tablets containing different HPMC E5 amounts. For 10:1 Acryl-EZE®: HPMC E5 ratio, LTG released slowly in pH 2.0 media in the initial 2 h. The R^2 of 2 h release profile fitted with zero order model was highest in Acryl-EZE®: HPMC E5 = 4: 1 (R^2 = 0.9848) and lowest in Acryl-EZE®: HPMC E5 = 1: 1 (R^2 = 0.9793), respectively. The zero-order release profile was obtained after replacing the pH 2.0 media with pH 6.0 PBS and the release profile was approached closer to zero order release with the increasing ratio of HPMC E5 in coating. LTG release slowed down in the last 4 h and the total release amount achieved was ~80%. LTG release rate and total release amount increased with the HPMC E5 ratio from 10:1 to 4:1 (Acryl-EZE®: HPMC E5) in the coating.

As shown in Fig. 3 D, the total release amount decreased with the increase in coating level from 3% to 10%. With the coating level of 3%, LTG released in a constant rate and total release amount reached to 100%, which was the highest total release amount among these three coating levels.

2.3. Result of orthogonal experiment

The results of orthogonal design of HPMC amount, coating levels and pore-forming agent's amount in the coating was presented in Table 1. The similarity factor f_2 helped to choose a release profile similar to the reference (Zeng et al. 2016). The optimized formulation with the highest f_2 (79) was as follows: 50 mg LTG, 70 mg HPMC K4M CR, 25 mg HPMC K100 LV CR and 150 mg flowLac®100 and 24 mg blend of Acryl-EZE and HPMC E5 with Acryl-EZE®: HPMC E5 = 5: 1 in the coating.

2.4. Resistance to dissolution media variation and reproducibility

The dissolution behavior of optimal LTG CPOP tablets and reference in different pH dissolution media is shown in Fig. 4. The f_2 value in pH 6.8, pH 7.4 and DI water with pH 6.9 after initial 2 h were 81, 78 and 82, respectively. It was revealed that the optimized CPOP tablets possessed similar release profile with Lamictal® XR in these three solutions.

Three batches of optimized CPOP tablets were produced and their release profiles are shown in Fig. 5. The f_2 values of every batch compared to Lamictal® XR were 80, 78 and 72, respectively, which showed that the optimized formulation was reproducible and possessed the identical release profile to the Lamictal® XR. The calculated f_2 values were 89 (Batch 1 to Batch 2), 87 (Batch 1 to Batch 3) and 89 (Batch 2 to Batch 3), respectively, showed the identical release profiles when compared with each other and promising reproducibility of the formulation.

Table 2 shows the results of optimized formulation release profiles fitting zero-order model, first-order model, Higuchi model and Ritger-Peppas model. It was shown that the release profile of CPOP tablets fitted best the zero-order model and the total release amount exceeded 80%.

Table 1: Results of orthogonal experiment

Treatment number or result	Factors				Cumulative release (%)									f_2
	A (mg)	B (mg)	C (mg)	D (mg)	2 h	3 h	4 h	5 h	7 h	9 h	12 h	14 h	17 h	
1	50	25	12	2	12	17	22	30	47	63	80	87	98	48
2	50	30	18	3	2	7	15	24	41	55	71	80	95	61
3	50	35	24	4	1	5	13	22	40	55	71	79	92	63
4	60	25	18	4	3	7	14	23	42	58	75	84	100	62
5	60	30	24	2	1	4	11	19	36	52	72	83	96	74
6	60	35	12	3	6	10	15	21	37	56	79	88	101	65
7	70	25	24	3	1	4	10	17	32	50	72	82	96	79
8	70	30	12	4	18	23	25	28	38	50	68	78	92	47
9	70	35	18	2	6	10	15	22	39	56	72	82	91	61
k_1	57	63	53	61										
k_2	67	60	61	68										
k_3	62	63	72	57										
R	10	2	18	11										

* A: The amount of HPMC K4M CR; B: The amount of HPMC K100 LV CR; C: The amount of coating material; D: The amount of pore-forming agents, HPMC E5.
k_1, k_2 and k_3 represent the averages of the f_2 for each factor at the same level, and the R value represents the range of the average total score for the same factors between different levels.

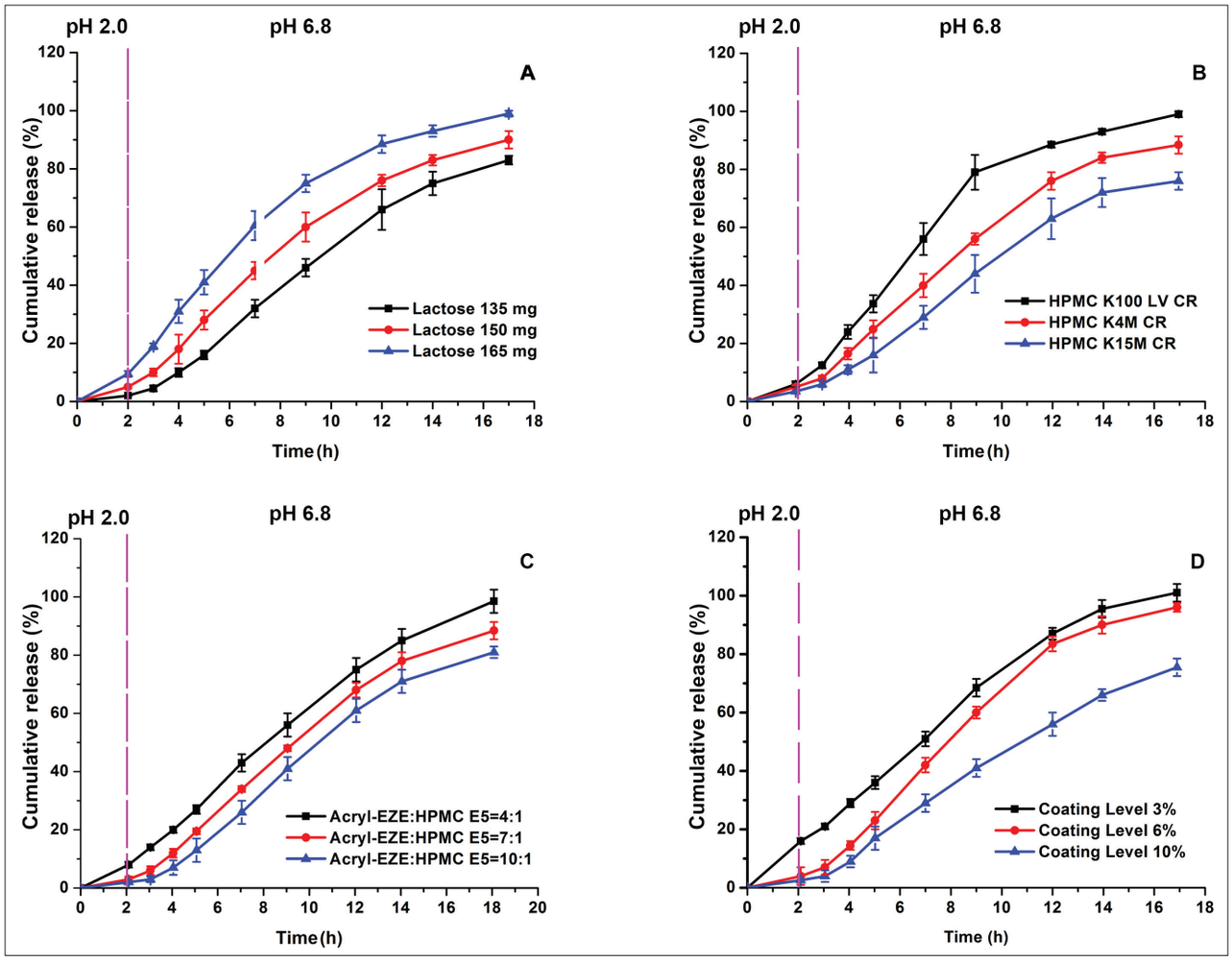

Fig. 3: Influence of CPOP tablets formulation ($n = 3$). A: Influence of the lactose amount on dissolution behavior of CPOP tablets. B: Influence of HPMC viscosity on dissolution behavior of CPOP tablets. C: Influence of different ratio of Acryl-EZE® to HPMC E5 on dissolution behavior of CPOP tablets. D: Influence of different coating levels on dissolution behavior of CPOP tablets.

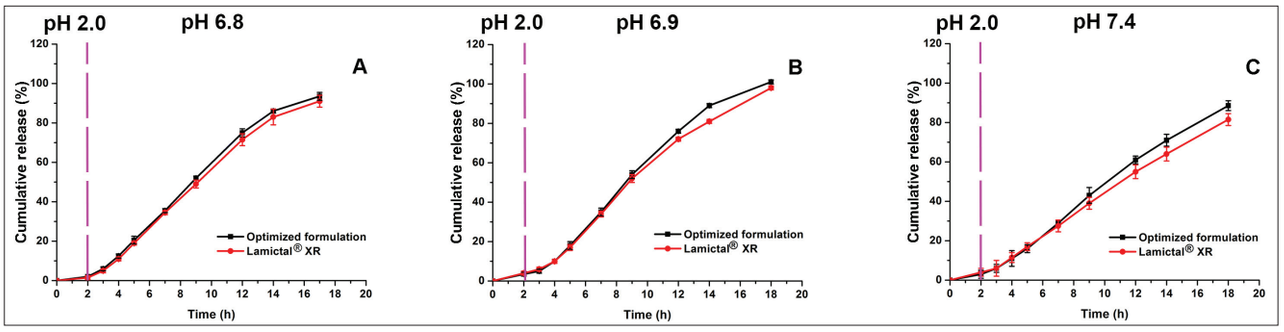

Fig. 4: *In vitro* dissolution studies of optimized formulation and reference in different pH media (n = 3). A: LTG release in pH 2.0 media (0-2 h) followed by pH 6.8 PBS (2-17 h); B: LTG release in pH 2.0 media (0-2 h) followed by water (pH 6.9) (2-17 h); C: LTG release in pH 2.0 media (0-2 h) followed by pH 7.4 PBS (2-17 h).

Table 2: Model fitting result of *in vitro* drug release profile of the optimized formulation

Model	Fitting equation	Parameters assessing model fitting				
		SSR	AIC	$R^2_{adjusted}$	r	k
First-order	$\ln(100-Q)=-0.078t+4.771$	185.098	77.2347	0.8423	0.9655	0.078
Zero-order	$Q=6.17t-1.507$	29.964	21.0366	0.9912	0.9971	6.170
Higuchi	$Q=17.062t^{1/2}$	341.65	83.3650	0.7089	0.9162	17.062
Ritger-Peppas	$Q=1.652t^{1.02}$	111.89	41.7404	0.9809	0.9929	1.652

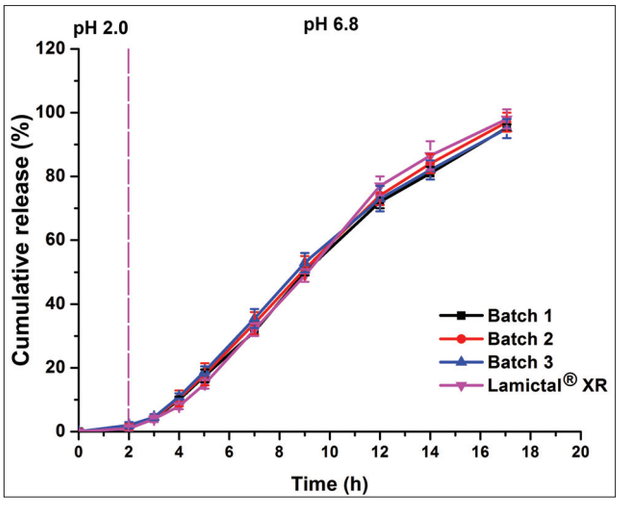

Fig. 5: Reproducibility of dissolution behavior of three batches of optimized CPOP tablets (n = 3).

2.5. *Stability studies*

The stability study results are presented in Table 3. LTG content and tablets weight gained was lower than 5% after accelerated stability study. CPOP tablet release profiles after accelerated stability study were similar to 0 day formulation.

Table 3: Result of accelerated stability experiment (n=3)

Condition	Time (day)	Weight gained (%)	Content (%)	f_2^*
	0	0	99.65 ± 1.5	-
High temperature (60°C)	5	-0.35 ± 0.00	99.13 ± 0.8	85
	10	-0.73 ± 0.00	98.85 ± 2.3	76
High humidity (92.5% RH)	5	1.56 ± 1.30	98.53 ± 1.5	80
	10	2.73 ± 2.10	96.15 ± 2.2	76
High illumination (4500 lx)	5	0.16 ± 1.30	99.32 ± 1.8	76
	10	0.25 ± 2.20	99.12 ± 2.5	66

*f_2 was the similarity factor of the dissolution curves on day 5 and day 10, respectively. The drug dissolution curve in initial (day 0) was used as reference.

As shown in Table 4, the CPOP tablets were stable in a three month stability test. No apparent change was noticed on the appearance of the tablets and the tablets possessed similar LTG content and f_2 values after three months when compared to Lamictal XR®.

Table 4: Result of 3-month stability experiment (n=3)

Batch	Time (month)	Appearance	Content (%)	f_2^*
1	0	Pink and smooth surface	99.7 ± 1.5	82
	3	Pink and smooth surface	99.4 ± 2.3	78
2	0	Pink and smooth surface	99.4 ± 1.8	85
	3	Pink and smooth surface	99.2 ± 2.3	81
3	0	Pink and smooth surface	99.5 ± 2.2	83
	3	Pink and smooth surface	99.1 ± 2.5	80

*f_2 was the similarity factor comparing CPOP tablets and Lamictal XR® in 0 month and 3 month.

3. Discussion

3.1. *Influence of formulation*

In this study, the factors influencing the CPOP release profile were investigated. As revealed in Fig. 2, LTG possessed the highest and lowest solubility in pH 2.0 and pH 6.8, respectively, which meant that LTG can be released in the gastric tract (pH 2.0) more easily than in the small intestine (pH 6.8). This is supported by a previous study revealing that LTG was absorbed principally in the small intestine (Mustafa and Al-Humayyd 1997). An extend release tablets could limit the release of LTG in gastric tract and promote it in small intestine.

As shown in Fig. 1 B, the CPOP tablets consisted of two coating layers and a core containing LTG. Opadry®200 was dissolved in media immediately and the coating of Acryl-EZE® and HPMC E5 could adjust the LTG release profile. The core of CPOP tablets formulation also had an effect on the release profile. Moreover, there were some excipients in the CPOP tablets core to adjust the osmotic pressure to promote the media penetration because of the low solubility of LTG in small intestine (Mustafa and Al-Humayyd 1997). The influences of these factors will be discussed in later sections.

3.1.1. *Influence of tablet coating*

A coating with Acryl-EZE® and HPMC E5 was used to adjust the CPOP tablets release profile after the outermost coating of

Opadry®200 was dissolved. The Acryl-EZE® was responsible to adjust the LTG release profile. The pore-forming agent, HPMC E5, acted as water absorbent which leads to the formation of micro pores after the dissolution of Opadry®200 outermost coating. CPOP tablets were designed to release LTG through these micro pores on the coating driven by high osmotic pressure in the core.
As shown in Fig 3 C, a relatively higher release rate and longer time of zero order release could be seen with higher ratios of HPMC E5 in coating which possibly suggested the impact of the pore forming agent of LTG release. HPMC E5 is a hydrophilic polymer and played an important role in adjusting the drug release profile. During the process, the outermost coating of Opadry®200 was dissolved firstly, and the internal coating layers were exposed when the tablets reached the intestinal tract. As shown in Fig. 6, there might be many micro pores formed across the Acryl-EZE® coating after the dissolution of HPMC E5.

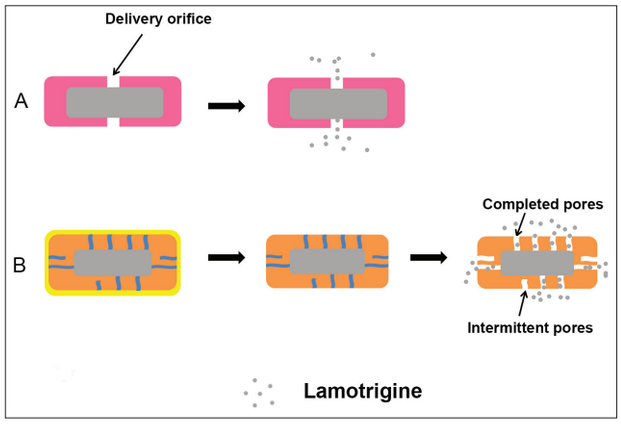

Fig. 6: Mechanism of LTG releasing in Lamictal XR® (A) and CPOP tablet (B).

Pores were formed in the coating layer as drug release paths connecting with the core of tablets. HPMC E5 could swell easily in water and helps in enlarging the pores before it was completely dissolved. The quantity and diameter of micro pores might increase with the increase in amount of pore-forming agent. Higher ratio of HPMC E5 in the coating could increase the number of pores and water channels and promote their completion and broadening as revealed in Fig. 7. The large micro pores could be helpful in media penetration to the tablet core and accelerate the LTG release rate.

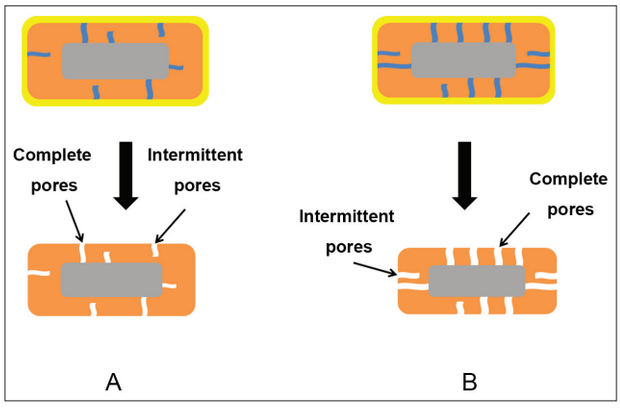

Fig. 7: Pore forming process of different ratio of HPMC E5 in coating.

Meanwhile, a certain period of time was required for the dissolution of HPMC and channels formation, which might be the reason for slow release rate in initial time. Formation of micro pores was slow and incomplete at lower ration of HPMC E5, which limited the LTG release.

The release rate and total release amount of LTG were decreased with the increase of coating level (Fig. 3 D) might be due to the increase in length of channels. A long period of time might be required for the dissolution of the pore-forming agent and channel formation which ultimately resulted in slow release rates.

3.1.2. *Influence of tablet core*

The formulation of the CPOP core was also influenced the release profile. Lactose and HPMC were used in the core to adjust the release profile. The LTG release from CPOP tablets was driven by the osmotic pressure difference. The lactose in the core could be dissolved rapidly and create a high osmotic pressure to help LTG release. Sustained release excipients should be added into the core to adjust and obtain a reasonable zero-order release profile. HPMC could swell and form high viscosity gel after absorbing water, which results into slow release rate. The similar release profile as reference could be obtained by adjusting the HPMC and lactose amounts.
As shown in Fig. 3 A, both dissolution rate and total release amount increased with the increase in lactose amount. The rough surface and hydrophilic nature of compressed Lactose (Flow Lac®100) was responsible to increase the osmotic pressure difference and promote the LTG release. The higher concentration of lactose leads to the generation of high osmotic pressure in the tablets core. Meanwhile, few reports suggested that increasing lactose amount could competitively inhibit the HPMC swelling and therefore, promote drug release (Siepmann et al. 2013).
The contents in the core would be dissolved in water to form a high osmotic pressure solution after water penetration through micro channels. According to Fick's diffusion law:

$$\frac{\partial c}{\partial x} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right) \quad (1)$$

where c is the concentration of the diffusing species; t denotes time, D is the diffusion coefficient and x, y and z are the three spatial (Cartesian) coordinates (Siepmann and Siepmann 2012).
In the core of the CPOP tablets, the concentration of lactose had an important influence on drug release. On the one hand, it was higher than the saturated concentration of lamotrigine (about 0.05%, *w/w*). The driving force resulting from the concentration of lamotrigine could be neglected. On the other hand, the initial lactose concentration is below its saturated solubility in water (17.5%, *w/w*) (Talley and Hunter 1952), and the concentration of lactose decreased with time. The mathematical model should be a reservoir system with non-constant activity source. The tablet could be considered as a piece of slabs, so the following equation was derived:

$$\frac{M_t}{M_\infty} = 1 - \exp\left(-\frac{ADKt}{VL}\right) \quad (2)$$

where M_t and M_∞ denote the cumulative amounts of drug released at time t and infinity, respectively; A is the total surface area of the device; D is the diffusion coefficient of the drug within the membrane; V is the volume of the reservoir; K is the partition coefficient of the drug between the membrane and the reservoir, and L is the thickness of the membrane (Siepmann and Siepmann 2012). According to the Eq. (2), a high content of lactose in core will induce a high M_∞. The M_t will increase with the M_∞ when the right part of the equality sign keeps constant, which means the release rate will rise with the content of lactose increasing, too. The lactose dissolution process could generate a high osmotic pressure in the core, which could promote the LTG diffusion to outside the coating. The osmotic pressure generated by lactose was the main driving force for the LTG release, which has a low solubility in the GI tract.
In addition, HPMC acted as hindrance in the core to adjust the LTG release profile. The LTG release rate and total release amount were

the highest in the CPOP tablets containing HPMC K100 LV CR, followed by HPMC K4M CR and HPMC K15M CR, respectively. The HPMC K4M CR and HPMC K15M CR contained tablet possessed lower total release amount and release rate compared to HPMC K100LV CR due to their high viscosity. HPMC with high viscosity possessed a low diffusion rate and total release amount compared to that with low viscosity. Studies revealed that the drug release rate decreased with the increase in the viscosity grade of HPMC (Campos-Aldrete and Villafuerte-Robles 1997; Viriden et al. 2009; 2011). Due to the core volume restriction, HPMC could not be dissolved completely and form a hydrogel. The HPMC with high viscosity might form a more compact and complex net structure with longer and narrow channels and decrease the LTG release rate. These net structures could lengthen the LTG release path and prolonged the LTG release process subsequently. The formation of HPMC hydrogel might form non-covalent bonds with LTG, which could lengthen the LTG diffusion period in hydrogel and decrease the total release rate.

3.1.3. Complex influence on release profile

An orthogonal design was used to investigate the complex of these factors and optimize the formulation. According to Fig. 4 and Fig. 5, the optimized formulation obtained similar and reproducible release profile compared to Lamictal XR®.

The LTG release showed a zero order release profile after the media (pH 2.0) had been replaced by pH 6.8 PBS media, and the total release amount reached to 100% after 17 h. An optimized formulation with similarity factor, f_2 of 79 was obtained, which proved the successful development of LTG CPOP tablet with a release profile similar to Lamictal XR® formulation.

As presented in Table 1, the amount of HPMC (A and B) had a greater impact on the f_2 than the coating (C and D). This suggested that the driving force generated in the core played an important role in adjusting the release profile. According to Fick's law, the diffusion flux, J might be mainly influenced by the excipient concentration in the core after the pores formation. Higher amounts of HPMC could lead to the formation of a high viscosity gel which limited the LTG release. The HPMC E5 was responsible for the micro pores formation and the increase in its concentration could promote the formation and broadening of pores. The increase in the coating level could prolong the channels formation time and resulted into the formation of intermittent channels instead of completed ones which decides the LTG release ultimately.

3.2. Feasibility of CPOP system production

The CPOP tablet was developed to solve many problems faced in Lamictal XR® production. The CPOP tablet could circumvent the laser drill technology applied in Lamictal XR®, which increased the difficulty and cost to prepare a LTG pump osmotic tablet. The production process of CPOP tablets only requires a basic coating procedure instead of a complicated laser drill unit. The release of LTG from the micro pores on the whole surface could be helpful to reduce the intestinal irritation (Santus and Baker 1995).

In this study, the feasibility of LTG CPOP system was verified. The reproducibility of CPOP tablets was proved through three batches of optimized formulation and obtained similar release profile compared to Lamictal XR® with f_2 of 77. It was revealed that LTG CPOP tablets possessed good reproducibility and could be produced at a larger scale.

The release profiles of CPOP tablets in different release media were investigated. As shown in Fig. 4, the f_2 of release profiles of CPOP tablets compared to Lamictal XR® in pH 6.8, pH 7.4 and DI water with pH 6.9 were 81, 78, and 82, respectively. The obtained f_2 suggested that the CPOP tablets had similar release profile compared to the Lamictal XR® independent of pH variation.

Predesigned stability studies were performed to investigate the stability of CPOP tablets. As presented in Table 3, the obtained data indicated that the LTG CPOP tablets were stable at high temperature, high humidity and high illumination environment. The slight decrease in the weight of CPOP tablets at high temperature might be associated with the water evaporation from coating. These results showed that CPOP tablets could provide stable release profiles regardless of high temperature, high humidity and high illumination environment. The parameters such as hygroscopicity and chemical degradation were less sensitive to various environments as proved previously (Kim et al. 2017), hence, CPOP tablets could be stored in normal storage conditions without affecting the potential ability of the formulation. A 3-month stability experiments revealed the potential stability of CPOP tablets.

3.3. Conclusion

In this study, a CPOP system was successfully designed to prepare a LTG extend release tablet. The CPOP tablets had micro pores in membrane to adjust the LTG release profile. The LTG CPOP tablets showed a similar release profile as Lamictal XR® and the dissolution properties were in accordance with zero-order drug release characteristics. The LTG CPOP system with good reproducibility has the ability to exclude sophisticated and expensive laser drill technology required in Lamictal XR® formulation. The proposed system can reduce the osmotic pump preparing cost, increase the production efficiency and promote the osmotic pump generalizing. This CPOP system can be extensively used to produce extended release tablets in industry at large scale.

4. Experimental

4.1. Materials

LTG was purchased from Hubei Kangbaotai Fine-chemicals Company (Hubei, China). Lactose (Flow Lac®100) was purchased from MEGGLE Pharma Company (Wasserburg, Germany). Acryl-EZE®, Opadry®200 and all kinds of HPMCs used in this study was purchased from Colorcon Coating Technology Company (Shanghai, China). Lamictal® XR was purchased from GlaxoSmithKline (Brentford, UK). All other solvents were purchased from XX and used without further purification.

4.2. Preparation of CPOP core

LTG, HPMC and lactose (FlowLac®100) were passed through 80 mesh sieves and blended in specific ratio as shown Table 5. Subsequently, colloidal silicon dioxide and magnesium stearate were added and mixed homogeneously. Compression was conducted by a 9 mm standard concave punch (Shanghai Far-east Pharmaceutical Machinery Company, Shanghai, China) using single punch machine with 70 N pressures, and the hardness of the core was 80-90 N. CPOP tablets with various HPMC types and using different amounts of lactose were prepared for further study.

Table 5: Different factors of CPOP tablets core formulation

Formulation	Lamotrigine (mg)	Lactose (mg)	Glidants (mg)	Type of HPMC	HPMC (mg)
F1	50	135	15	HPMC K4M CR	100
F2	50	150	15	HPMC K4M CR	85
F3	50	150	15	HPMC K100LV CR	85
F4	50	150	15	HPMC K15M CR	85
F5	50	165	15	HPMC K4M CR	70

* Glidants contained colloidal silicon dioxide and magnesium stearate.

4.3. Coating

The core of the CPOP tablets was coated with two layers of Acryl-EZE® and HPMC E5. The mixture of Acryl-EZE® and pore-forming agents HPMC E5 (Acryl-EZE®: HPMC E5 = 4: 1, 7: 1, 10: 1) were dissolved in water to obtain coating solution (20%, *w/v*) and blended by high shear mixing on a homogenizer (FA25, Fluko, Shanghai China) for 30 min. After Acryl-EZE® and HPMC E5 coating, Opadry®200 was coated as the outmost layer. A pan coater (HCT-30, FREUND, Germany) was used and the coating conditions were set as follow: bed temperature 35 °C, pan speed 13 r/min, spraying rate 1.4 mL/min and drying temperature 40 °C. The tablets were dried at 40 °C for 12 h in pan coater. The coating level reached 3%, 6% or 10% (*w/w*) of the tablet core, respectively. The effects of the HPMC E5 concentrations and the coating level were studied by LTG release profile. The coating level was calculated using following Eq. (3):

$$\text{Coating level}\left(\%\right) = \frac{W_2 - W_1}{W_1} \times 100\% \quad (3)$$

where W_1 and W_2 represent the weight of tablets before and after coating, respectively.

4.4. Saturated solubility

The saturated solubility of LTG in different media was measured. One gram LTG was added into 100 mL solution of pH 2.0 HCl, pH 4.5 PBS, pH 6.8 PBS, pH 7.4 PBS and deionized water (pH 6.9), respectively, and the suspension was shaken at 37 °C for 24 h. The solubility of supernatants filtered through 0.45 μm micro-porous was determined by HPLC-UV at 210 nm wavelength.

4.5. Orthogonal design

An orthogonal design of these four factors varied over three levels, namely, the amounts of HPMC K4M CR (50, 60 and 70 mg) and HPMC K100 LV CR (25, 30 and 35 mg) in the core of CPOP tablets, coating levels (12%, 18% and 24% of core weight) and pore-forming agents, HPMC E5 (2, 3 and 4 mg) in coating layers was conducted in order to investigate the influence of these factors on release profile and obtain a similar release profile as Lamictal XR® (Zeng et al. 2016; Cao et al. 2016). Similarity factor (f_2) was used as index to optimized formulation.

Similarity factor, f_2, was used to assess the similarity of release profile between CPOP tablet and Lamictal XR®. It could be calculated as the following:

$$f_2 = 50\lg\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]\times 100\right\}^{-0.5} \quad (4)$$

where n is the number of samples, R_t and T_t are percentage of the dissolved drug for the reference and LTG CPOP tablets at each time interval, respectively.

In this orthogonal design, different levels factors were used to investigate the relationship between different factors and elected the optimized formulation. The optimized formulation was expected to have the most similar release profile compared with Lamictal XR®. In another words, the optimized formulation should have the highest f_2 value (Pan et al. 2013; Huang et al. 2015).

4.6. Reproducibility of LTG CPOP tablets

Reproducibility of LTG CPOP tablets optimized formulation was investigated at large scale. Three batches (500 tablets per batch) of optimized formulation were produced. The LTG release profiles of three batches were studied and compared with Lamictal® XR according to section 4.9.

4.7. Stability studies

The stability of drugs or products is influenced by high temperature, high humidity and strong illumination. The stressing testing is important to assess the stability of drugs and products (Singh et al. 2013), and there have been many studies about stress testing (Peng et al. 2015; Zhou et al. 2011; Sun et al. 2008). A stress testing was performed on the tablets according to Chinese Pharmacopoeia 2015 (Part 4, Guidelines 310). The optimized formulation was subjected to stress testing conditions of high temperature (60 °C), high humidity (92.5% RH) and high illumination (4500 lx). Under the corresponding conditions, the samples were withdrawn at time intervals of 0, 5 and 10 day. They were evaluated for weight gained, LTG content and *in vitro* LTG release profile. HPLC was used to determine LTG content and study *in vitro* release profile. A three month stability experiment was carried to investigate the stability of LTG CPOP tablets under actual storage conditions.

4.8. HPLC analysis

HPLC with Gemini C_{18} (4.6 mm × 250 mm, 5 μm) at 37 °C was used to determine the LTG content herein. 20 μL sample solution was injected each time and the mobile phase consisted of acetonitrile and ammonium acetate buffer salt (pH = 4.5) (30 : 70, *v/v*) at a flow rate of 1.0 mL/min. Analysis was performed at a wave length of 210 nm. The lower limit of quantification for LTG was 10 μg/mL and calibration curve ranges from 10 μg/mL to 600 μg/mL, where an $R^2 = 0.9996$ was obtained.

4.9. In vitro release study

The *in vitro* release of LTG tablets was investigated in accordance with FDA guidance. This method employed the United States Pharmacopeia (USP) rotating paddle method (RCZ-8M dissolution tester, TIANDA TIANFA, Tianjin, China), the temperature was maintained at 37.0±0.5 °C with agitation speed of 50 rpm. 700 mL of 0.01 mol/L hydrogen chloride for the initial 2 h, and then 900 mL of pH 6.8 PBS containing 0.5% sodium dodecyl sulfate was used as dissolution media. Aliquots (5 ml) were collected at predefined time periods of 1, 2, 3, 5, 7, 10, 12 and 15 h after initial 2 h. The media was replenished with 5 mL of fresh buffer preheated to 37°C after each sample collection. Samples were analyzed using HPLC after filtered through 0.45 μm micro porous membrane.

The release profile was investigated in different pH environments of pH 6.8 (PBS), pH 7.4 (PBS) and pH 6.9 (deionized water). The similarity of release profile between CPOP tablets and Lamictal XR® was explored to investigate their release resistance to the variety of dissolution media.

The total release amount and release rate of LTG were used as indices to evaluate the release profile. The total LTG release amount in the end was determined as release amount, and the release rate after pH shift was used to assess the release profile. The release profile was fitted with zero-order model, first-order model, Higuchi model and Ritger-Peppas model to prove the extend release ability of the CPOP tablets.

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