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Formulation and evaluation of controlled porosity osmotic pump tablets of verapamil hydrochloride

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Abstract:

Verapamil hydrochloride, a calcium channel blocker with pH-dependent solubility, was selected as the model drug for the development of osmotic pump tablets. The objective of this study was to prepare controlled porosity osmotic pump tablets containing 120 mg of verapamil hydrochloride that conform to the U.S. Pharmacopeia 2023 dissolution test requirements. The core tablets were formulated through wet granulation, utilising sodium chloride as an osmotic agent and succinic acid and citric acid as microenvironmental pH modifiers. The tablets were coated with a semi-permeable membrane containing Opadry CA and pore-forming agents such as PEG 400 (1.5:1), sorbitol, or PVP K30 in various ratios and weight gains. Dissolution tests revealed that drug release increased with the addition of pH modifiers. Sodium chloride served dual functions: enhancing core osmotic pressure to promote dissolution while also potentially reducing drug solubility, thereby diminishing dissolution. As for the membrane, increasing the amount of pore-forming agents and reducing the weight gain led to an increased drug release rate. The M7 tablets, containing 60 mg of NaCl, 60 mg of succinic acid, and 10 mg of citric acid in the core, and with membranes formulated with PEG 400 (1.5:1) at a 57.5% polymer ratio and 5% weight gain, successfully met the dissolution requirements of the U.S. Pharmacopeia 2023.

Keywords: **controlled porosity osmotic pump, drug release kinetics, extended release, osmotic pump, verapamil hydrochloride.**

Classification number: **3.3**

1. Introduction

Oral osmotically driven systems have garnered considerable attention from researchers since the 1970s. Unlike other extended-release drug systems, osmotic pumps exhibit zero-order drug release kinetics, meaning the release rate is independent of external dissolution conditions such as pH, resulting in a high *in vitro-in vivo* correlation (IVIVC) [1, 2]. Controlled porosity osmotic pump (CPOP) is a subset of osmotic pumps in which the core is encapsulated by a semipermeable membrane containing water-soluble pore-forming excipients [3]. CPOP devices do not require a release orifice, as drug release occurs via *in situ* pore formation within the membrane, thereby reducing gastric irritation [1].

Moreover, the film coating process eliminates the need for complex laser drilling equipment, potentially lowering production costs and time, while also facilitating the scale-up of formulation development.

Verapamil hydrochloride (VRH), a calcium channel blocker commonly used in cardiovascular therapy, has a short half-life (approximately 2-8 hours). Consequently, patients using an immediate-release dosage form must take the medication 2-3 times per day to maintain its therapeutic effect [4]. In aqueous solutions, VRH's solubility is pH-dependent, with higher solubility at low pH levels and reduced solubility at high pH [5]. Selecting VRH as the model drug for controlled porosity osmotic pumps can address VRH's short half-life and mitigate the effects of pH fluctuations on drug solubility.

For these reasons, the primary aim of this study is to formulate controlled porosity osmotic pump tablets containing 120 mg of verapamil hydrochloride that meet the dissolution test requirements set by U.S. Pharmacopeia 2023.

2. Materials and methods

2.1. Materials

Verapamil hydrochloride (VRH) (India), conforming to the U.S. Pharmacopeia 2023 standard, lactose monohydrate, Opadry® CA (cellulose acetate 398-10:PEG 3350 = 9:1) (US), acetone, avicel PH-101, sodium chloride (NaCl), succinic acid (SA), citric acid (CiA), sorbitol, polyethylene

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glycol 400 (PEG 400), polyvinyl pyrrolidone K30 (PVP K30), magnesium stearate (MgSt), 96% ethanol, isopropyl alcohol (China), and other excipients that meet the standards for pharmaceutical purity.

2.2. Methods

2.2.1. Preparation methods

Construction of ternary phase diagram of solvent-dissolved solution: To prepare a semi-permeable coating solution, ensuring homogeneity between different coatings, the solvent mixture's composition (comprising water, 96% ethanol, and acetone) was investigated with the ratios shown in Table 1. The procedure was as follows: Sorbitol was dissolved in water to form the sorbitol solution. Subsequently, 96% ethanol and acetone were added to the sorbitol solution to create mixture A. The formation of a solution or suspension was observed. To assess polymer solubility, solutions from mixture A were combined with Opadry® CA, stirred magnetically at 25°C for 15 minutes to form mixture B, and observed for solution or suspension formation. The ternary phase diagram was constructed using Chemix School 10.0 software. The total solvent volume in each experiment was 10 ml; the fixed Opadry® CA concentration was 0.4 g (4% w/v of the solvent mixture); sorbitol content was 0.27 g (75% of polymer (cellulose acetate)).

Table 1. Solvent mixture ratios for film coating fluids.

	No.	1	2	3	4	5	6	7	8	9	10
Components (%)	Water	5	5	5	5	5	5	5	5	5	5
	96% ethanol	0	5	10	15	20	25	30	35	40	45
	Acetone	95	90	85	80	75	70	65	60	55	50
	No.	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Components (%)	Water	10	10	10	10	10	10	10	10	10	10
	96% ethanol	0	10	20	30	40	50	60	70	80	90
	Acetone	90	80	70	60	50	40	30	20	10	0

Preparation of controlled porosity osmotic pump tablets: The preparation of the tablets involved two key stages: (1) core tablet formulation and (2) coating with a semi-permeable membrane.

The core tablets consisted of the following components: The active pharmaceutical ingredient (VRH), an osmotic agent (NaCl), microenvironmental pH modifiers (SA, CiA), a binder (PVP K30), fillers (lactose monohydrate, Avicel PH 101), and a lubricant (MgSt). Core tablets were prepared via wet granulation, with the formulations shown in Table 2. VRH was initially milled and sieved through a 125-micron sieve. Avicel PH 101 was sieved through a 250-micron sieve, while the remaining excipients were milled and screened through a 180-micron sieve. The VRH, fillers, pH modifiers, and osmotic agents were mixed and

Table 2. Formulations of core tablets.

Components (mg)	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11
NaCl	**30**	**60**	**120**	60	60	60	60	60	60	**30**	**80**
CiA	-	-	-	-	-	-	**5**	**10**	**20**	10	10
SA	-	-	-	**20**	**40**	**60**	60	60	60	60	60

The above formulations have fixed components as follows: 120 mg VRH, 10 mg PVP K30 dissolved in isopropyl alcohol, 20 mg lactose monohydrate, 7 mg MgSt, avicel PH-101 sufficient for 400 mg.

screened through a 250-micron sieve. The binder was dissolved in an appropriate quantity of isopropyl alcohol to form a binder solution. The homogeneous powder mixture was then blended with the binder solution, and the moist mass was passed through a 750-micron sieve to produce wet granules. These granules were dried at 60°C until the moisture content, as determined by an Ohaus MB25 moisture analyser (US), reached 1-3%. The dried granules were sieved through a 750-micron sieve and coated with the lubricant. Finally, the lubricated granules were compressed into convex cylindrical tablets using a DP 30A single-punch tablet press (China) with an 11-mm-diameter die and a tablet breaking force of 7-9 kP.

The semi-permeable membrane consisted of cellulose acetate as the polymer and PEG 3350 (Opadry® CA) as a plasticiser, along with pore-forming agents (PEG 400 = 1.5:1, PVP K30, and sorbitol), with the ratios detailed in Table 3. The coating solution was prepared by dissolving the pore-forming excipients in water, followed by the sequential addition of 96% ethanol and acetone, with continuous stirring. Opadry CA powder was gradually added to the mixture and stirred with a magnetic stirrer for 1 hour until homogenous. Film coating was conducted using a mini Caleva coating machine (UK) with the following parameters: agitator speed 10%, fan speed 90%, temperature 30-32°C, pump flow rate 1.5 ml/min, and pressure 1-1.1 bar. Post-coating, the tablets were dried at 40°C for 24 hours.

Table 3. Formulations of semi-permeable membranes.

Components (%)*	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11
PEG 400 : sorbitol = 1.5:1	50	55	57.5	70	50	55	57.5	70	-	-	70
PVP K30	-	-	-	-	-	-	-	-	57.5	-	-
Sorbitol	-	-	-	-	-	-	-	-		57.5	-
Weight gain	3±0.5				5±0.5						7 ±0.5

The above formulations have a fixed composition: Opadry ® CA 4% (w/v), a solvent mixture of water, 96% ethanol, and acetone at a ratio of 5:25:70. *: The ratio of excipients is calculated based on cellulose acetate.

2.2.2. Evaluation method

Weight gain: Weight gain was calculated using the formula:

$$w = \frac{m_2 - m_1}{m_1}$$

where m_1 and m_2 are the mass of the tablet before and after coating, respectively (mg).

Development and validation of assay method: Method development: The assay method was developed with reference to [6]. The coated tablet was stripped of its membrane, and the VRH content was quantified using an absorption method in HCl solution (pH 1.2) at a wavelength of 278 nm, measured using a UV-Vis spectrophotometer (Hitachi U1900, Japan). The method was validated, demonstrating specificity, linearity, accuracy, and precision. The VRH content must fall within the range of 90.0-110.0% of the labelled content [7].

Dissolution test: The dissolution test was conducted as per the U.S. Pharmacopeia 2023 monograph for "Verapamil hydrochloride extended-release tablets", using an ERWEKA DT 600 dissolution tester (Germany). The parameters were: paddle dissolution apparatus, 50 rpm rotation speed, dissolution medium of 900 ml phosphate buffer (pH 7.5), and a temperature of 37±0.5°C. Sampling time points were: 1, 2, 3, 4, 5, 6, 7, and 8 hours. Samples were filtered and diluted with the medium as required. The percentage of VRH released, relative to the labelled content (120 mg), was determined by measuring absorption at 278 nm using a UV-VIS spectrophotometer. The drug release requirements were: 1 hour: 2-12%, 2 hours: 10-25%, 4 hours: 25-50%, and 8 hours: not less than 80% [7].

The cumulative VRH release over 1 to 8 hours for CPOP tablets was statistically compared using paired samples T-Test in Excel 2016.

Evaluation of kinetics model for in-vitro dissolution profiles: Dissolution data were analysed using Splus 8.0 software to fit zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas kinetic models. The Akaike information criterion (AIC) value was used to determine the best-fit model. The AIC value was calculated using the formula:

$$AIC = n \times \log(\delta^2) + 2p$$

where n is the sample size, δ is the residual standard error, and p is the number of parameters [8]. The AIC values are compared for the different kinetic models, and the model with the lowest AIC value corresponds to the most suitable model.

Scanning electron microscopy: Scanning electron microscopy (SEM) images of the coating membrane of M7 tablets were taken before and after the dissolution study to examine the effect of PEG 400 and sorbitol as pore-forming agents. Membranes were dried at 45°C for 12 hours prior to examination.

3. Results

3.1. Screening solvent mixture ratios by constructing a ternary phase diagram

According to the manufacturer, the solvent used to dissolve Opadry® CA is a mixture of acetone and water in a ratio of approximately 90:10 to 94:6 [9]. In this study, the amount of water is expected to range from 5-10% of the total solvent volume. During the preliminary investigation of excipients, sorbitol and PEG 400 were combined to function as pore-forming agents for the film coating. Unlike PEG 400, which is soluble in both solvents, sorbitol only dissolves in water and precipitates when acetone is added. The process of applying the coating solution not only presents formulation difficulties, requiring continuous stirring, but also poses challenges in maintaining the particle size and uniform distribution of sorbitol particles between different coating runs.

It was observed that sorbitol dissolves well in ethanol, and acetone is infinitely soluble in ethanol [10]. Therefore, 96% ethanol was selected as an "intermediate" solvent to assist in forming the coating solution. The phase diagram for the solvent mixture was constructed using the method described in Section 2.2.1, and the results are presented in Fig. 1. The experimental investigation was conducted within the region ABCD, while the solvent ratio for mixture A to form a solution (indicating the ability to dissolve the pore-forming excipient) lies within region CDEF. The solvent ratio for both mixtures A and B to form a solution (indicating the ability to dissolve the pore-forming excipients and polymer) falls within region EFGH.

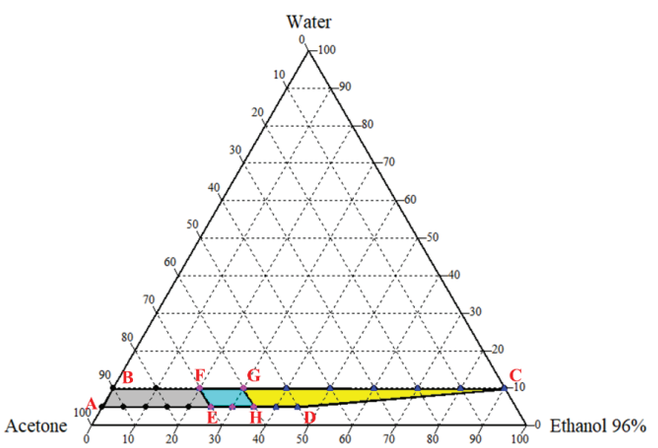

Fig. 1. Ternary phase diagram of coating solvent.

In this study, due to the small scale of the formulation and the low coating temperature (around 30°C), a solvent mixture with low water content helps minimise weight gain differences in the film coating before and after drying, resulting from water solvent evaporation. Consequently, the solvent mixture ratio of water:96% ethanol at 5:25:70 (point E in Fig. 1) was selected for use in this study.

3.2. Effects of certain variations in the formulation of the core tablet on the drug dissolution profile

To evaluate the impact of specific variations in the core tablet formulation, including the quantity of microenvironmental pH excipients, the amount of osmotic agent either alone or combined with microenvironmental pH modifiers, C1-C11 tablets were prepared according to the formulation outlined in Table 2. The tablets were coated with the M2 coating formulation. Dissolution testing of the resulting tablets produced the data shown in Table 4.

Table 4. Results of the dissolution test for C1-C11 (%, mean±SD, n=3).

	Time (h)	1	2	3	4	5	6	7	8
	Required amount dissolved (%)	*2-12*	*12-25*	*-*	*25-50*	*-*	*-*	*-*	*≥80*
Drug release	C1	1.58±0.28	2.57±0.03	3.52±0.12	6.24±0.13	11.05±0.43	19.89±0.15	29.37±1.14	34.6±2.59
	C2	1.63±0.43	2.32±0.39	3.3±0.36	6.11±1.75	17.05±1.37	27±0.63	36.65±0.95	42.87±2.24
	C3	1.52±0.22	1.97±0.22	2.68±1.19	3.99±1.08	8.05±2.45	12.44±0.94	18.85±2.11	25.34±0.44
	C4[a]	1.58±0.92	2.32±1.13	4.28±0.33	12.02±0.66	21.18±1.34	32.13±1.21	39.15±1.04	43.43±1.63
	C5[a]	1.6±0.12	3.3±0.18	17.9±1.24	33.6±1.09	45.17±1.62	55.8±2.48	61.27±0.64	65.5±0.66
	C6	4.1±0.05	14±0.98	23.2±4.35	35.8±4.36	48.32±3.3	59.8±1.88	66.24±0.29	71.4±2.23
	C7[b]	6.27±1.68	17.68±2.52	29.97±0.84	44.74±0.7	55.31±1.31	65.33±2.28	71.46±0.86	74.12±1.08
	C8	8.87±0.51	20.44±2.25	32.57±1.56	45.63±1.39	57.51±2.53	66.87±2.75	74.88±0.12	81.19±2.71
	C9[b]	16.58±0.39	31.77±2.06	46.26±0.06	59.57±0.3	70.95±2.17	78.15±0.45	83.67±1.09	88.16±0.05
	C10[b]	7.61±0	10.49±0.52	15.32±0.59	21.75±0.53	31.63±0.48	39.8±0.5	49.11±0.68	53.88±0.53
	C11[b]	2.3±1.32	5.7±1.14	13.2±2.86	21.9±1.08	31.45±2.58	40.2±2.6	48.23±0.55	55.2±2.53

[a]: The cumulative drug release of the CPOP tablets and C6 show statistically significant differences ($p<0.05$); [b]: The cumulative drug release of the CPOP tablets and C8 show statistically significant differences ($p<0.05$).

3.2.1. Effect of the amount of osmotic agent NaCl when used alone

Tablets were formulated according to three preliminary experimental formulas (C1-C3), using only NaCl as the osmotic agent in varying amounts from 30 to 120 mg. The dissolution test results are presented in Table 4 and Fig. 2.

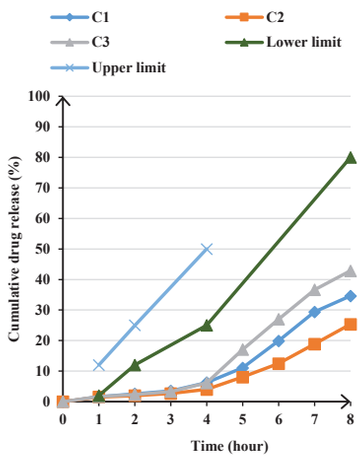

Fig. 2. The dissolution profiles of controlled porosity osmotic pump tablets with different amount of NaCl: C1 (30 mg), C2 (60 mg), C3 (120 mg).

It can be observed that, within the first four hours, almost no drug was released into the medium. This can be explained as follows: The drug release process from osmotic pump tablets involves several steps. First, the pore-forming excipients in the membrane dissolve, allowing water to pass through the semi-permeable membrane and porous channels into the core tablet. This water then dissolves the drug, the osmotic agent, and other components, creating osmotic pressure. The drug is subsequently released from the osmotic pump tablet due to this osmotic pressure and its diffusion through the porous channels.

However, NaCl significantly reduces the solubility of verapamil hydrochloride (VRH) [11], inhibiting the dissolution of the drug into its molecular form. This results in the inability of the VRH to be pushed out into the medium. After eight hours, the tablet had released only approximately 40% of the drug substance. The tablet exhibited poor water permeability, and after the dissolution test, the core tablet remained dry, indicating that water may not have fully penetrated the core.

3.2.2. Effect of microenvironmental pH modifiers

Verapamil hydrochloride (VRH) is a weak base, and its solubility increases in a low-pH environment. This led to the idea of incorporating excipients to create a microenvironmental pH, thereby enhancing the solubility of VRH. Tablets with formulations C4-C6 included additional succinic acid (SA) in varying amounts from 20-60 mg. The dissolution test results (Table 4, Fig. 3) demonstrated that the inclusion of SA significantly improved tablet solubility. After 8 hours, the drug release was 43.4, 65.5, and 71.4% for tablets C4, C5, and C6, respectively. Increasing the SA content resulted in greater drug release at each time point. This is because SA not only enhances VRH solubility but also increases osmotic pressure within the core tablets,

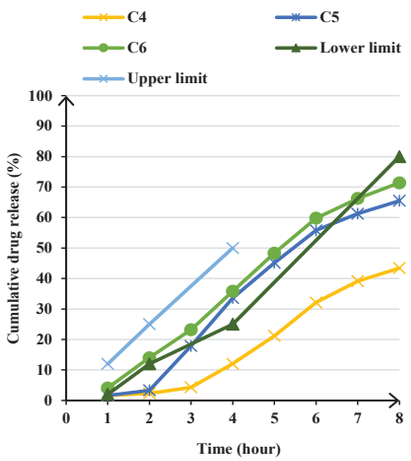

Fig. 3. The dissolution profiles of controlled porosity osmotic pump tablets with different amount of SA: C4 (20 mg), C5 (40 mg), C6 (60 mg).

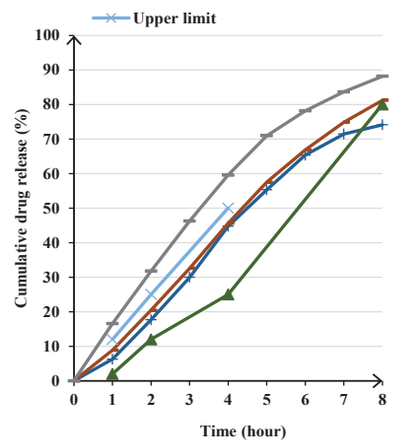

Fig. 4. The dissolution profiles of controlled porosity osmotic pump tablets with different amount of CiA: C7 (5 mg), C8 (10 mg), C9 (20 mg).

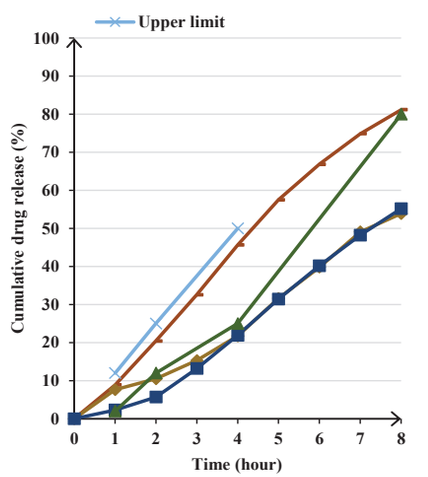

Fig. 5. The dissolution profiles of controlled porosity osmotic pump tablets with different amount of NaCl when combined with pH modifies: C8 (60 mg), C10 (30 mg), C11 (80 mg).

thereby boosting drug solubility and its subsequent release. After the dissolution test, the core tablet was fully wetted. However, the initial dissolution rate remained low, and increasing the SA amount from 20 to 60 mg only slightly improved the drug release rate at the early stage, from 1.58 to 4.10%. This might be due to SA's moderate solubility, which requires time to dissolve and create the acidic microenvironment needed to improve VRH solubility and increase the osmotic pressure within the tablet.

The core tablets were also combined with another organic acid, citric acid (CiA). Tablets were prepared according to formulations C7-C9 with increasing amounts of CiA, ranging 5-20 mg. During the dissolution test, it was observed that the tablets exhibited effervescence immediately upon introduction into the medium. The results (Table 4, Fig. 4) showed that even a small amount of CiA greatly improved tablet solubility after 1 hour. This may be because CiA is highly soluble in water, whereas SA has moderate solubility. While SA takes time to dissolve and create a microenvironmental pH within the core of the coated tablet, this time is noticeably shorter with CiA. Similar to SA, increasing the CiA amount resulted in higher drug release rates. However, when the CiA content reached 20 mg (C9), the tablets experienced capping during compression. The C8 formulation, which contained a lower amount of CiA (10 mg), did not encounter any issues during compression and met the dissolution requirements of the U.S. Pharmacopeia 2023. Therefore, it was selected for further studies.

Thus, the inclusion of organic acids to create a microenvironmental pH successfully addressed two challenges that arise when using NaCl as an osmotic excipient: enhancing drug solubility and improving the water uptake capacity of the tablets.

3.2.3. Effect of NaCl when combined with microenvironmental pH modifiers

To evaluate the impact of NaCl as an osmotic agent in combination with microenvironmental pH excipients on drug release, tablets C10, C8, and C11 were formulated with increasing amounts of NaCl, ranging from 30-80 mg. The dissolution test results (Table 4, Fig. 5) revealed that when the NaCl amount was increased from 30 mg (C10) to 60 mg (C8), the dissolution rate significantly improved. At the 1-hour time point, both tablets released approximately the same amount of drug (around 8%). From the 2-hour time point onward, while the drug release rate of tablet C10 increased by approximately 5% per hour, tablet C8's rate increased by about 12% per hour, nearly twice that of C10. This demonstrates the role of NaCl as an osmotic agent: increasing NaCl content raises the osmotic pressure within the core, leading to a greater pressure gradient between the core and the surrounding medium, which accelerates drug release.

Further increasing the NaCl content to 80 mg (C11) caused a significant reduction in drug release from the 1-hour time point, though the release rate remained at around 10% per hour from the 2-hour mark onward. This can be explained as follows: despite the addition of two organic acids to improve drug solubility, the NaCl amount in formulation C11 (80 mg) exceeded the combined total of SA and CiA (70 mg). As a result, the influence of NaCl on drug solubility may have outweighed the beneficial effects of the microenvironmental pH modifiers.

Thus, NaCl demonstrates two opposing effects during drug release: on the one hand, NaCl reduces drug solubility, hindering dissolution into its molecular form; on the other hand, it increases osmotic pressure within the tablet, facilitating drug release into the surrounding medium. Optimising the amounts of both NaCl and organic acids in the formulation is essential to ensure good drug solubility while maintaining sufficient osmotic pressure to enhance drug release. The NaCl content of 60 mg (C8) appears suitable for further studies.

3.3. Effects of certain variations in the formulation of the membranes on the drug dissolution profile

To evaluate the influence of various factors related to the membrane, including the type and total amount of pore-forming agents, weight gain, and the selection of core tablet formulation C8, membrane coating of the tablets was conducted using formulations M1-M11, as detailed in Table 3. The results obtained are presented in Table 5.

Table 5. Results of the dissolution test for M1-M11 (%, mean±SD, n=3).

	Time (h)	1	2	3	4	5	6	7	8
	Required amount dissolved (%)	*2-12*	*12-25*	-	*25-50*	-	-	-	*≥ 80*
Drug release	M1[c]	7.80±0.48	13.64±2.47	20.44±2.69	29.61±2.1	38.22±1.44	45.5±1.47	51.31±2.81	57.34±1.59
	M2[c]	8.87±0.51	20.44±2.25	32.57±1.56	45.63±1.39	57.51±2.53	66.87±2.75	74.88±0.12	81.19±2.71
	M3[c]	17.48±1.19	30.40±1.54	42.50±1.25	53.68±1.6	65.42±0.67	74.05±1.41	81.33±1.76	84.78±1.82
	M4	22.38±1.4	38.01±1.2	51.62±1.44	64.09±0.96	73.23±1.03	80.56±0.65	85.79±2.82	89.44±0.65
	M5[d]	4.42±1.27	12.19±1.17	15.42±1.51	22.36±2.77	32.03±2.7	38.03±1.65	46.15±2.91	55.63±1.32
	M6[d]	5.18±0.8	15.53±2.3	28.17±0.48	42.32±0.1	55.61±2.77	65.09±1.62	73.20±2.49	79.12±0.9
	M7[d,e]	7.90±2.38	19.54±2.98	33.76±2.5	46.80±1.73	60.24±0.02	70.21±1.63	79.58±1.21	84.61±2.25
	M8[c]	17.5±0.51	32.2±1.09	45.8±1.57	57.5±0.78	68.6±2.38	75±0.47	79.9±0.18	85.7±0.43
	M9	23.76±0.26	38.8±2.53	53.05±1.06	68.32±1.35	78.33±2.42	86.71±1.64	91.1±1.61	95.81±0.91
	M10[e]	11.01±1.96	23.69±1.89	35.67±1.11	46.74±2.03	56.94±2.46	67.73±0.02	73.55±1.1	82.13±1.9
	M11[c]	12.82±1.72	26.64±1.69	39.72±0.05	52.11±1.57	65.02±0.34	70.54±0.94	78.75±1.32	84.39±0.39

[c]: The cumulative drug release of the CPOP tablets and M4 show statistically significant differences ($p<0.05$); [d]: The cumulative drug release of the CPOP tablets and M8 show statistically significant differences ($p<0.05$); [e]: The cumulative drug release of the CPOP tablets and M9 show statistically significant differences ($p<0.05$).

3.3.1. Effect of the total amount of pore-forming excipients

When the total amount of pore-forming excipients is increased from 50-70%, with a weight gain of 3% (M1-M4) (Fig. 6) or 5% (M5-M8) (Fig. 7), the drug release rate gradually increases. This can be explained as follows: In the dissolution medium, the pore-forming excipients create a microporous system on the surface of the membrane, allowing the drug substance and other components to pass through. As the total amount of pore-forming excipients increases, the number and size of the micropores may also increase, which enhances the release of VRH into the medium. Tablets M7, with a total pore-forming excipient content of 57.5% and a weight gain of 5±0.5%, meet the dissolution requirements of the U.S. Pharmacopeia 2023.

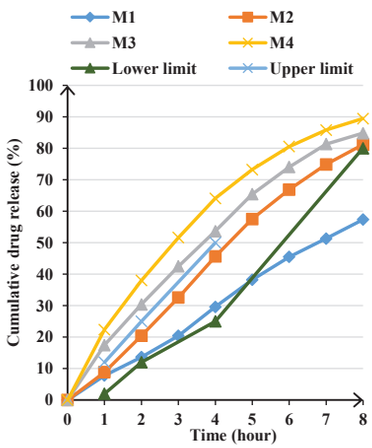

Fig. 6. The dissolution profiles of controlled porosity osmotic pump tablets with 3% weight gain and different amount of pore-forming agents: M1 (50%), M2 (55%), M3 (57.5%), M4 (70%).

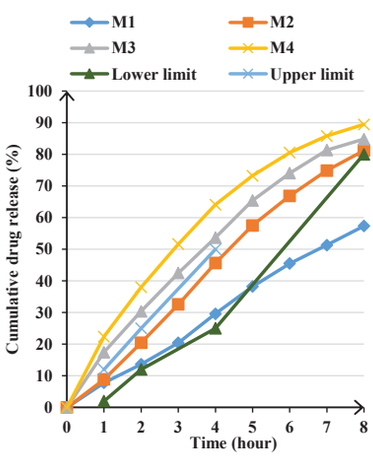

Fig. 7. The dissolution profiles of controlled porosity osmotic pump tablets with 5% weight gain different amount of pore-forming agents: M5 (50 %), M6 (55%), M7 (57.5%), M8 (70%).

3.3.2. Effect of weight gain

The tablet formulations were prepared with weight gains of 3% (M4), 5% (M8), and 7% (M11). The dissolution results are presented in Table 5 and Fig. 8. With the same total amount of porous excipients, the drug release rate was inversely proportional to the membrane weight gain, particularly evident at dissolution time points between 1 and 4 hours. As previously explained, as the membrane thickness increased, the permeation of the surrounding medium through the semi-permeable membrane into the core slowed down, resulting in a decrease in the drug release rate. Interestingly, the amount of drug released after 8 hours for tablet formulations with the same total amount of porous excipients showed negligible differences.

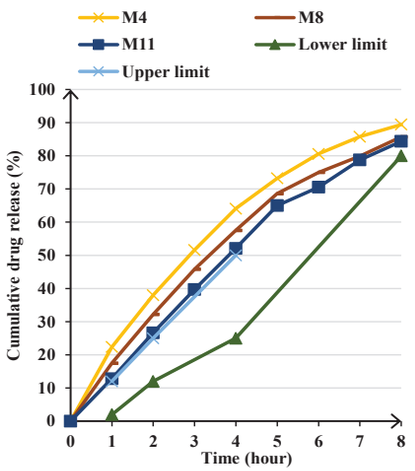

Fig. 8. The dissolution profiles of controlled porosity osmotic pump tablets with different weight gain: M4 (3%), M8 (5%), M11 (7%).

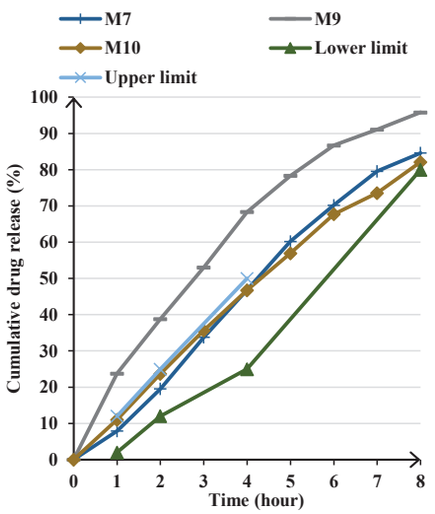

Fig. 9. The dissolution profiles of controlled porosity osmotic pump tablets with different types of pore-forming agents: M7 (PEG 400:sorbitol = 1.5:1), M9 (PVP K30), M10 (sorbitol).

3.3.3. Effect of pore-forming agent type

To evaluate the influence of different pore-forming excipients on drug release, tablet formulations were prepared using the same ratio of pore-forming excipients and membrane weight gain but with different pore-forming agents: PEG 400:sorbitol = 1.5:1 (M7), PVP K30 (M9), and sorbitol (M10). The dissolution results (Fig. 9) showed that using a mixture of sorbitol and PEG 400 or using sorbitol alone did not significantly affect the dissolution profile. However, the tablet formulation with PVP K30 as the pore-forming excipient exhibited a noticeable increase in dissolution rate.

After investigating various factors related to the formulation of controlled porosity osmotic pump tablets, the M7 tablets, which consisted of 60 mg NaCl, 60 mg SA, and 10 mg CiA as core components, and a semi-permeable membrane with pore-forming excipients (PEG 400:sorbitol = 1.5:1) at a proportion of 57.5% and a weight gain of 5%, achieved the desired dissolution profile according to the U.S. Pharmacopeia 2023 requirements.

3.4. Evaluation of kinetics model for in vitro dissolution profiles

The evaluation of the kinetic model of the drug release process from M7 tablets is presented in Table 6. The zero-order kinetic model has the lowest AIC value, indicating that it is the most appropriate model for describing drug release. Additionally, the Korsmeyer-Peppas model has the second-lowest AIC value, with a release exponent (n) of 0.9798. The value of the release exponent (n) close to 1 suggests that the drug release mechanism follows zero-order kinetics.

Table 6. Kinetics model of M7 tablet.

Model	Zero order		First order	Higuchi		Hixson -Crowell	Korsmeyer-Peppas	
AIC	10,2941		16,2390	19,4498		14,0833	12,7713	
	k_0	R^2	k_1	k_H	R^2	k_s	k_K	n
	11,2346	0,9971	0,1789	26,2264	0,9588	0,0517	11,6523	0,9798

AIC: Akaike information criterion, R^2: Goodness of fit, k: Release rate constant for respective models (k_0 (%.h^{-1}), k_1 (h^{-1}), k_H (%.$h^{-1/2}$), k_s (%$^{1/3}$.h^{-1}), k_K (%.h^{-n})) for zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas rate equations, respectively, n: Release exponent.

3.5. Scanning electron microscopy microphotographs

The cross-sectional surface of the M7 tablet before the dissolution test reveals a densely packed multilayer structure with a thickness ranging from approximately 95-101 µm (Fig. 10A). Before exposure to the dissolution medium, the SEM micrograph shows a rough membrane surface (Fig. 10B). After dissolution, a porous and loose

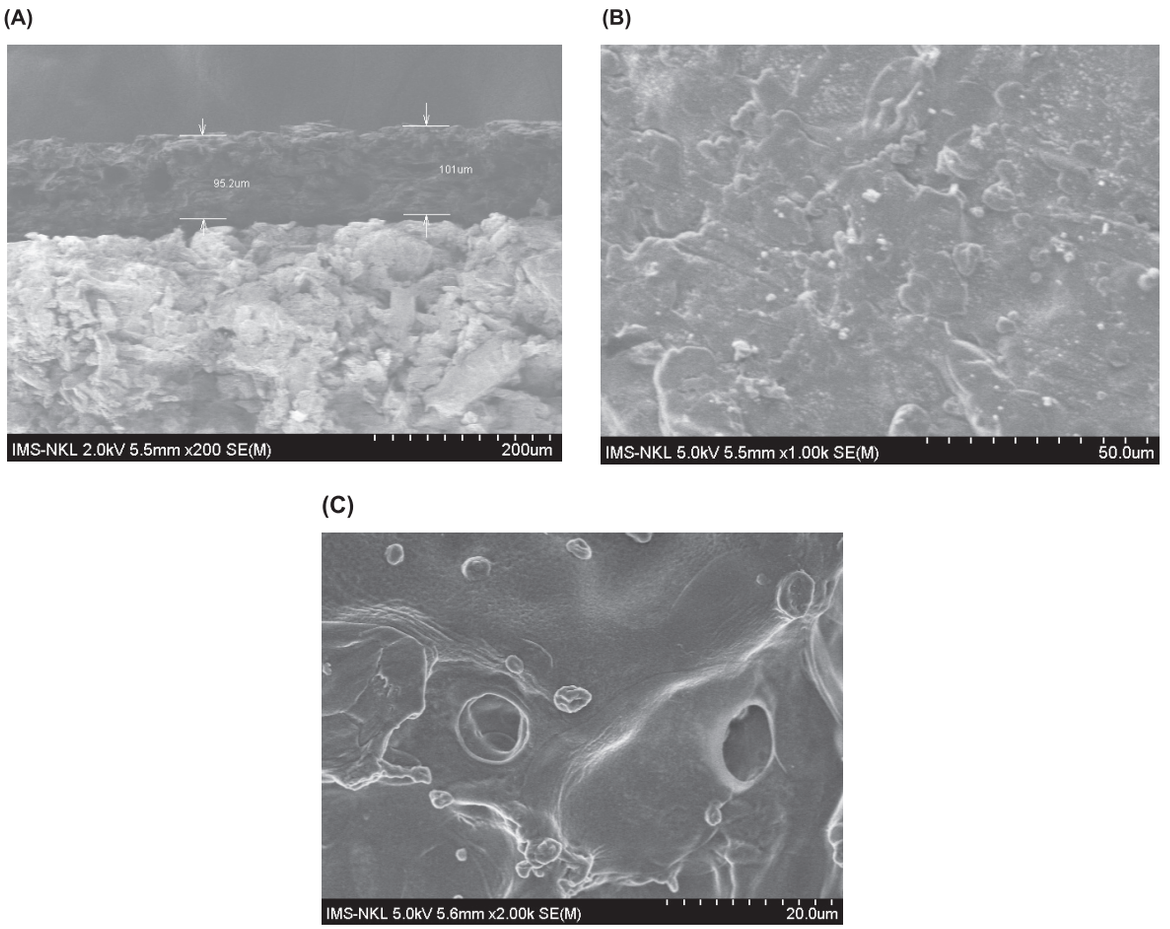

Fig. 10. Scanning electron microscopy micrographs of M7 membrane: (A, B) taken before dissolution study and (C) taken after dissolution study for 8 hours.

structure was observed in the SEM micrograph, indicating that PEG 400 and sorbitol dissolved upon contact with the dissolution medium (Fig. 10C). These observations suggest the following sequence in the drug release process from the CPOP tablets: dissolution of the pore-forming agents upon contact with the dissolution medium, permeation of the dissolution medium through the pore-forming excipients, dissolution of the drug substances and osmogents in the core to create an osmotic pressure gradient, followed by drug release through the pore channels.

4. Discussion

During the experiment, several factors related to the drug release capability of controlled porosity osmotic pump tablets were investigated. However, some aspects warrant further analysis, as discussed below:

Regarding the construction of the mixed solvent phase diagram: The semi-permeable coating solution of the CPOP can exist as either a solution or a suspension. However, coating with a suspension, as previously mentioned, carries the risk of unevenness between different coating cycles due to variations in particle size and distribution. Inadequate mixing may also disrupt the coating process by clogging the spray gun. Therefore, identifying the optimal composition and ratio of the solvent mixture to ensure a solution, as demonstrated in this study, simplified the coating process. No clogging issues were encountered during the experimental process. Constructing a solvent mixture ratio phase diagram facilitates adjusting the solvent ratio without affecting the coating solution's properties. Additionally, identifying 96% ethanol as an intermediate solvent to dissolve sorbitol and distribute it into acetone provides a potential solution for preparing a solution-based coating for excipients not soluble in acetone. Specifically, in this study, the solvent mixture ratio of water:96% ethanol:acetone at 5:25:70 was used for the coating solution of formula M9 (with PVP K30 as the excipient).

Regarding the selection of microenvironmental pH modifiers: Two key factors when selecting excipients to create an acidic pH microenvironment are water solubility and pKa. For sustained-release tablets, excipients with low pKa values can be prioritised to create a low pH environment

while exhibiting low water solubility to minimise excipient diffusion out of the tablets. Among various organic acids such as fumaric acid, succinic acid, citric acid, and tartaric acid, succinic acid balances both factors: a low pKa and moderate water solubility [12], making it the primary excipient for investigation. Using a large amount of succinic acid does not significantly improve the initial dissolution of the tablets, so combining succinic acid with another organic acid with better water solubility, such as citric acid, is necessary. The experimental results show that the excipient selection based on solubility is appropriate.

Regarding the osmotic agent: VRH is highly water-soluble but has low osmotic pressure (the osmotic pressure of a VRH-saturated solution at 37°C is 11 atm [11], so an osmogent is required to increase the core's osmotic pressure, thereby pushing the drug into the medium. When selecting an osmotic agent, two characteristics to consider are water solubility and osmotic activity [13]. NaCl dissolves well in water, and the osmotic pressure of a NaCl-saturated solution is relatively high. This excipient is also cost-effective and readily available, making it a preferred choice as the main osmogent. However, it is important to note that the solubility of VRH decreases significantly in the presence of osmotic excipients such as NaCl and mannitol [11]. As a result, if NaCl is used alone, water permeates through the membrane into the tablet core, but while the osmotic agent dissolves, creating a pressure difference with the environment, the drug does not dissolve into its molecular form to be pushed through the membrane pores. Therefore, when selecting an osmotic agent, in addition to considering the excipient's solubility and the osmotic pressure of its saturated solution, it is crucial to account for the excipient's impact on drug solubility.

5. Conclusions

The study successfully achieved the formulation of controlled porosity osmotic pump tablets of verapamil hydrochloride (M7 formulation) that meet the dissolution requirements according to the U.S. Pharmacopeia 2023. Additionally, the study explored several variations in the core tablets and membrane formulations that affect the *in vitro* dissolution profile. Increasing the amount of microenvironmental pH excipients enhanced the drug release by improving drug solubility and increasing osmotic pressure within the tablet. The osmogent NaCl played two contrasting roles: increasing osmotic pressure within the tablet, which enhanced dissolution, and reducing drug solubility, which diminished dissolution. Increasing the total amount of porous excipients improved dissolution, while increasing membrane thickness decreased the dissolution rate. The use of PVP K30 as a pore-forming excipient significantly increased the drug release rate compared to using sorbitol alone or a combination of PEG 400:sorbitol = 1.5:1.

CRediT author statement

Nhat Hoang Thi Anh: Methodology, Data analysis, Writing - Reviewing and Editing; Hung Pham Van: Methodology, Writing - Reviewing and Editing; Xuan Dam Thanh, Quang Le Dinh: Methodology; Duyen Nguyen Thi Thanh: Methodology, Writing - Reviewing and Editing.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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