RESEARCH ON FILM COATING FORMULATION OF SUSTAINED RELEASE PELLETS OF VERAPAMIL HYDROCHLORIDE

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SUMMARY

Objectives: *To determine the optimized parameters of the technical process and the adequate excipient ingredients of the pellet film coat which control release to develop the basic formula of the sustained release (SR) pellet of Verapamil hydrochloride (VER.HCl).* ***Materials and method:*** *Prepare SR VER.HCl pellet with film coating using Mini-Glatt fluidized bed; quantify VER.HCl with UV spectroscopy method; examine the effect of excipients (EC, HPMC, DBP, TEC and Talc) on the dissolution of SR VER.HCl pellet.* ***Results:*** *With excipients EC N20, HPMC E15, HPMC E5, TEC and Talc, the release rate of VER.HCl was 9.02%, 26.55%, 48.90% and 83.73% at the time of 1, 2, 4 and 8 hours, respectively.* ***Conclusion****: EC N10, HPMC E15 and HPMC E5 controlled release excipients suitable for formula of SR VER.HCl pellet film 120 mg.*

** Keywords: Verapamil hydrochloride; Pellet; Sustained release; Preparation.*

INTRODUCTION

Verapamil hydrochloride (VER.HCl) is a calcium channel blocker used to treat angina pectoris, hypertension and arrhythmia. VER.HCl is completely absorbed in the gastrointestinal tract (about 90%), but the bioavailability is only 20 - 35% due to its rapid metabolism through liver. This pharmaceutical substances have a short half - life (2.8 - 7.4 hours) causing patients to administer many times a day [1, 2, 3]. Therefore, in order to improve bioavailability and reduce the dosing frequency for patients, the study of SR VER.HCl pellet preparation is essential [4, 5]. In the formulation of SR VER.HCl pellet, controlled release film coating ingredients play a critical role, greatly influencing the rate and degree of pharmaceutical substance release from the drug form and drug bioavailability. Through this study, we aimed: *To produce the results of investigating the effects of certain parameters of the technical process and controlled release film coating excipient as the basis for developing the basic formulation of SR VER.HCl pellet film 120 mg*.

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MATERIALS AND METHODS

1. Materials and equipment

**Materials and chemicals*: VER.HCl Standard: Provided by Ho Chi Minh City Drug Quality Control Institute (QT242010914, concentration 100.52%), Pharmaceutical VER.HCl: USP 38 (China), HPMC E6, E15: USP 38 (China), Talc: USP 38 (China), EC N10, N20: USP 38 (China), DBP: USP 38 (India), TEC: USP 38 (China), Ethanol 96%: Vietnamese Pharmacopoeia IV.

**Equipment and tools:* Mini-Glatt film coating fluidized bed (Germany), Copley DIS 8000 dissolution tester (UK), Labomed UV-VIS spectrophotometer UVD-2960 (USA), analytical balance Mettler Toledo with readability down to 0.1 mg (Switzerland), PHARMATEST PTF E abrasion tester (Germany), ERWEKA SVM powder and granule tapped volume tester (Germany), ERWEKA GWF granular tester (Germany), sieve analysis (China) and other tools meeting laboratory and analytical testing standards.

2. Methods

**Preparation of VER.HCl controlled release pellets by pan coating technique:*

SR VER.HCl pellet was prepared by coating a release control film onto the core pellet which is a composition including: EC (release control polymer), HPMC (creating diffusion channel), DBP, TEC (plasticizer), Talc (anti-sticking agent), 96% ethanol (solvent). The process of coating release control film was carried out in steps as follows:

- Prepare coating solution: Soak and dissolve completely EC in approximately 2/3 of 96% ethanol, add HPMC to dissolve. Add plasticizer to the solution above, stir to homogenize. Crush talcum powder, sift through a 125 µm sieve. Add 96% ethanol and grind thoroughly, and pull gradually into the beaker containing coating solution. Stir the solution on a magnetic stirrer for about 30 minutes. Filter through a 125 µm sieve to obtain a homogeneous coating solution. Make up to the needed volume with 96% ethanol. The solution was stirred continuously on a magnetic stirrer throughout the coating process.

- Put pellets in the coating equipment: Dry pellets for about 15 minutes to heat up before spraying on the coating. Spray the coating solution. Keep spraying until coating solution runs out, leave the equipment on for another 15 minutes.

Table 1: Parameters of the coating process.

Spray pressure	to be determined
Spray rate	to be determined
Fluidizing air volume	to be determined
Inlet air temperature	55 ± 5°C
Outlet air temperature	42 ± 1°C
Spray gun diameter	1.2 mm

- The obtained pellets were dried at 60°C for 6 hours and left overnight for the coating film to stabilize, then sifted to retain diameter of 0.8 - 1.5 mm.

- Film coating performance: calculated by the formula:

$$\text{Film-coating efficiency (\%)} = \frac{m1 - m2}{m3} \times 100\%$$

Of which: m1: Total weight of pellet after coating (g);

m2: Weight of core pellet before coating (g);

m3: Weight of solids in the formula of film coat (g).

** Drug content:*

- Test sample: Weigh approximately 2g of pellet, grind into fine powder. Precisely weigh the corresponding amount of fine powder to roughly 50 mg of VER.HCl. Transfer to a 50 mL beaker. Add approximately 30 mL of pH 7.5 phosphate buffer solution. Shake in ultrasonic shaker for 60 mins. Transfer to a 50 mL volumetric flask, add phosphate buffer of pH 7.5 to the mark and mix well. Filter through a filter paper, discard roughly 10 mL of the primary filtrate, the remaining filtrate was solution A. Pipette 0.5 mL of solution A into a 10 mL volumetric flask, make up to the mark with pH 7.5 phosphate buffer solution and mix. Read the solution in spectrophotometer at a wavelength λ = 278 nm. Simultaneously carry out the same procedure with the standard solution under the same conditions. The content of pharmaceutical substances in pellet was calculated by the following formula:

$$\% \text{ VER.HCl/pellet} = \frac{At.mc}{Ac.mt} \times 100\ (\%)$$

Of which: At: Optical density of sample solution;

Ac: Optical density of standard solution;

mc: Weight of VER.HCl standard weight to quantify;

mt: Weight of pellet to quantify.

** In vitro dissolution studies:*

Testing conditions: complied to USP 41 [5] under the following specific conditions:

+ Equipment: Stirrer.

+ Stirring speed: 50 ± 2 rpm.

+ Temperature: 37.0 ± 0.5°C.

+ Medium: 900 mL of phosphate buffer solution of pH 7.5.

+ Sampling time: At interval of 1, 2, 4 and 8 hours.

+ Test sample: Pellet quantity equivalent to 120 mg VER.HCl

+ Quantify pharmaceutical substances released at sampling times by measuring the absorbance at a wavelength of 278 nm. Calculate the amount of pharmaceutical substances release based on the reference point of VER.HCl in pH 7.5 phosphate buffer medium using UV-VIS spectroscopy method.

RESULTS AND DISSCUSION

1. Results of investigation of the effects of certain parameters in the technical procedure

In order to determine the adequate film coating parameters, fundamental pellet film formula includes: Core pellets of VER.HCl: 20.00g; EC N10: 3.00g; DEP: 0.24 g; Talc powder: 1.50g; Ethanol 96%: 50 mL.

- Effects of coating solution spray rate:

The coating solution spray rate varied at 0.45 mL/min; 0.85 mL/min and 1.25 mL/min. Core pellet of VER.HCl was overcoated with coating parameters and the results were shown as below:

Table 1: Results of effects of coating solution spray rate on the coating process.

No.	Parameters	Value		
1	Fluidizing air volume (m^3/hour)	18		
2	Spray pressure (bar)	1.2		
3	Inlet air temp (°C)	55 ± 5		
4	Outlet air temp (°C)	42 ± 1		
5	Spray gun diameter (mm)	1.2		
6	Spray rate (mL/min)	0.45	0.85	1.25
Results	Coating efficiency (%)	60.76	73.21	-
	Physical properties	Uniform coat, stabilized pellet fluidizing		Pellet agglutination

Spray rate increasing from 0.85 to 1.25 mL/min resulted in pellet agglutination. Whereas spray rate at 0.45 and 0.85 mL/min led to stabilized coating fluidizing results. However, the coating efficiency at 0.45 mL/min was lower due to slower spray rate and fast evaporation rate of the coating solution solvent. Therefore, spray rate of 0.85 mL/min was selected in the next studies to increase optimization.

- Effects of spray pressure:

In order to determine the optimized spray pressure, various spray pressures were used while other parameters were kept constant: Fluidizing air volume: 18 m^3/hour, spray rate: 0.85 mL/min, inlet air temp: 55 ± 5°C, outlet air temp: 42 ± 1°C, spray gun diameter: 1.2 mm. The testing parameters used to determine spray pressure and their results are demonstrated in table 2.

Table 2: Results of effects of spray pressure on the coating process.

Parameters	Value		
Spray pressure (bar)	1.0	1.2	1.4
Results			
Coating efficiency (%)	-	73.21	67.30
Physical properties	Pellet agglutination	Uniform coat, stabilized pellet fluidizing	Pellet pulverization

Low spray pressure (1.0 bar) increased spray droplet sizes, reduced evaporation rate and enhanced pellet agglutination. In contrast, higher spray pressure (1.4 bar) caused pellet pulverizations, reduced spray droplet sizes, enhanced evaporation rate, altogether resulting in efficiency loss. The technical specifications of equipment greatly affected coating performance as well as the quality of the pellet film. Therefore, spray pressure of 1.2 bar was selected to be used in the next studies.

- Effects of fluidizing air volume:

In order to determine the optimized fluidizing air volume, various fluidizing air volumes were used while other parameters were kept constant: spray pressure: 1.2 bar, spray rate: 0.85 ml/min, inlet air temp: 55 ± 5°C, outlet air temp: 42 ± 1°C, spray gun diameter: 1.2 mm. The testing parameters and results are shown in table 3.

Table 3: Results of effects of fluidizing air volume.

Parameters	Value		
Fluidizing air volume (m^3/hour)	12	18	24
Results			
Coating efficiency (%)	36.50	73.21	43.88
Physical properties	Ununiformed coat, poor pellet fluidizing	Stabilized pellet fluidizing	Ununiformed coat, strong attrition, strong fluidizing

Fluidizing air volume of 12 m^3/hour reduced coating efficiency (36.50%) and ununiformed coating surface due to poor fluidizing which caused pellet core to take on the next layer of coating solution before the previous one fully evaporated. On the other hand, poor fluidizing also caused pellets fail to take on the full coating solution volume. Fluidizing air volume of 24 m^3/hour also gave a low efficiency (43.88%). Due to strong fluidizing, pellets collided with the film sides in which ununiformed pellet surface resulting from pellets unable to fully take on the coating solution volume. Also, the solvent evaporated quickly left the pellet surface dry. Fluidizing air volume of 18 m^3/hour produced the highest efficiency (73.21%), the surface was smooth, uniform and stable. Subsequently, fluidizing air volume of 18 m^3/hour was selected.

From the testing results, the following coating parameters are selected:

Spray pressure: 1.2 bar; spray rate: 0.85 mL/min; inlet air temperature: 55 ± 5°C; outlet air temperature: 42 ± 1°C; spray gun diameter: 1.2 mm; fluidizing air volume: 18 m^3/hour.

2. Results of determining the effects of the release control film formulation

- Effects of proportion and type of release control polymer:

Screening studies have found that different proportions of pellet film ingredients changed the rate of pharmaceutical substance release from pellets. The formulations designed to determine the effects of the EC proportion were presented in table 4.

Table 4: The formulations designed to determine the optimized EC proportion.

Ingredients	Formulations					
	F1	F2	F3	F4	F5	F6
EC N10 (g)	3	4	5	-	-	-
EC N20 (g)	-	-	-	3	4	5
DBP (% w/w EC)	6	6	6	6	6	6
Talc (% w/w EC)	50	50	50	50	50	50
EtOH 96% (mL)	50	50	50	50	50	50

Prepare coating solution and carry out coating each batch of 20g core pellets of VER.HCl. Testing results of the film forming polymer concentration were shown in table 5 and figure 1.

Table 5: Release rate of VER.HCl during EC proportion testing (n = 6; $\bar{X}$ ± SD)

Formulations	Release rate of VER.HCl over time (hour)			
	1	2	4	8
CT1	42.08 ± 1.04	72.74 ± 1.66	86.84 ± 1.03	101.19 ± 1.53
CT2	21.65 ± 1.13	47.43 ± 1.12	67.92 ± 1.98	95.21 ± 1.97
CT3	17.42 ± 0.76	31.70 ± 0.90	61.20 ± 1.40	83.29 ± 3.35
CT4	6.91 ± 0.12	8.95 ± 0.43	18.83 ± 0.82	29.76 ± 1.05
CT5	6.11 ± 0.05	7.18 ± 0.10	11.07 ± 0.37	13.32 ± 0.75
CT6	5.67 ± 0.02	5.68 ± 0.02	5.82 ± 0.05	6.15 ± 0.07
USP 41 (%)	2 - 12	10 - 25	25 - 50	> 80

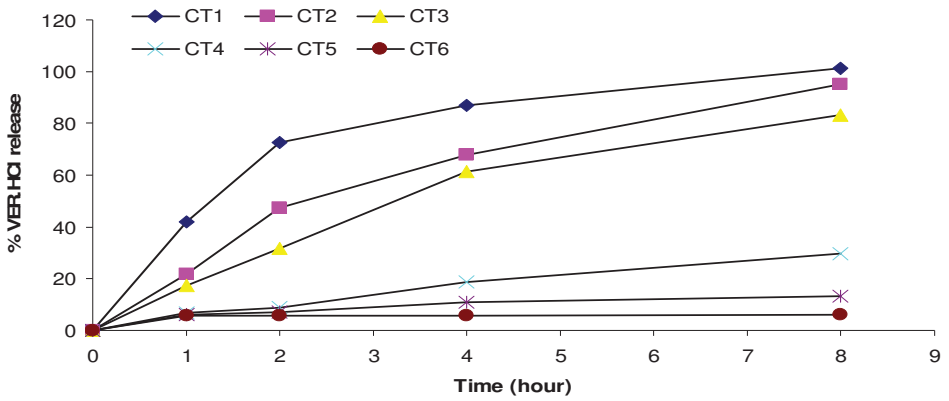

Figure 1: The release rate of VER.HCl over time during EC proportion testing.

Increased proportion of both types of EC in the film ingredients reduced the release rate of VER.HCl as when the EC proportion increases, the pellet film thickness also increases, thereby increasing the diffusion distance leading to a decrease in the release rate of pharmaceutical substance to the dissolved medium. With EC N10 film forming polymer, all three formulations yielded higher rate of pharmaceutical substance release than criteria in USP41. Particularly, at 1 hour, all three formulations CT1, CT2 and CT3 showed the release rate of pharmaceutical substance higher than 12%. 4 hours later, it exceeded 50% and these formulations were almost completely released 8 hours later. The formulation using 5g of EC (CT3 and CT6), the coating had some difficulties due to the increased viscosity of the film-forming suspension resulting in pellet agglutination. Thus, EC N10 is not adequate to be used as an ingredient of release control VER.HCl pellet film. Replace EC N10 with EC N20, all three formulations adequately controlled rate of pharmaceutical substance release. CT5 and CT6 gave the lowest rate of drug release due to great film thickness which prevented VER.HCl from diffusing into the dissolved medium. After 8 hours, both CT5 and CT6 yielded rate lower than 15%. CT4 using 3g of EC N20 was capable of controlling pharmaceutical substance release. As a result, CT4 was selected for the next studies.

- Effects of the proportion and type of polymer combination:

As CT4 gave a relatively small rate of pharmaceutical substance release compared to what was required by USP 41, it was necessary to increase the rate of pharmaceutical substance release by combining some hydrophilic polymers to create diffusion channels on the pellet film to enhance the rate. Based on the formulations designed as in table 6, the dissolution is evaluated and presented as results in table 7 and figure 2.

Table 6: Formulations designed to determine the optimized proportion of polymer combination.

Ingredients	Formulations						
	CT4	CT7	CT8	CT9	CT10	CT11	CT12
EC N20 (g)	3	3	3	3	3	3	3
HPMC E6 (% w/w EC)	0	15.0	17.5	20.0	0	0	0
HPMC E15 (% w/w EC)	0	0	0	0	15.0	17.5	20.0
DBP (% w/w EC)	6	6	6	6	6	6	6
Talc (% w/w EC)	50	50	50	50	50	50	50
EtOH 96% (mL)	50	50	50	50	50	50	50

Table 7: Released rate of VER.HCl during polymer combination proportion testing (n = 6; $\overline{X}$ ± SD).

Formulations	Rate of VER. HCl released over time (hour)			
	1	2	4	8
CT4	6.91 ±0.12	8.95±0.43	18.83±0.82	29.76±1.05
CT7	7.44±0.13	17.89±0.83	38.67±1.16	66.74±1.38
CT8	16.95±0.85	35.93±0.97	83.77±2.16	93.54±2.16
CT9	30.06±0.90	50.12±1.56	91.27±4.21	98.66±3.97
CT10	7.21±0.36	8.73±0.13	16.68±0.79	27.24±1.06
CT11	8.02±0.11	19.93±0.89	40.23±0.81	70.30±2.52
CT12	18.02±0.58	28.88±1.15	55.03±1.49	84.34±2.61
USP 41 (%)	2-12	10-25	25-50	> 80

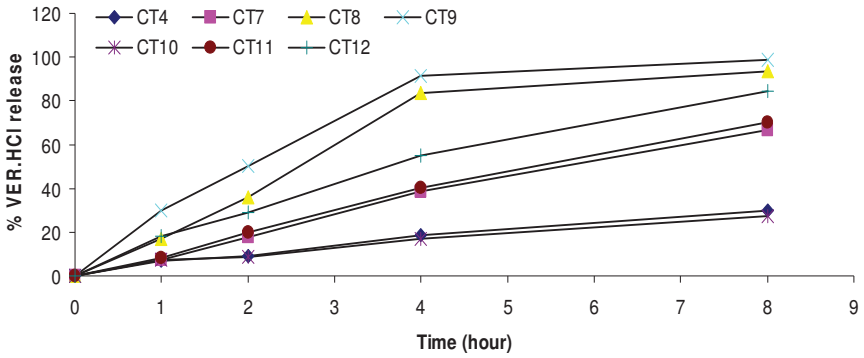

Figure 2: The release rate of VER.HCl over time during polymer combination proportion testing.

Increased amount of HPMC E6 and E15 enhanced the release rate of pharmaceutical substance of the formulation due to an increase in the number of pharmaceutical substance diffusion channels. The results showed that all six formulations increased the release rate of pharmaceutical substance compared to F4. With both types of HPMC used at low levels (CT7 and CT10), the rate after 8 hours of release was lower than 70% as compared to high levels (20%), the release rate of the formulation exceeded the requirement by USP 41. With two types of polymers, HPMC E15 controlled release better than E5 due to its higher viscosity. Based on the obtained results above, CT11 was selected (HPMC E15 = 17.5% compared to EC) to be used in the next studies.

- Effects of HPMC E6 and HPMC E15 proportion:

Based on HPMC type testing, it was found that HPMC E5 with lower viscosity would give higher rate of pharmaceutical substance release in the first hours while HPMC E15 with higher viscosity would corrode and swell more slowly enabling it to control pharmaceutical substance release in hours that follow. Therefore, it is necessary to select the combination of these two polymers to be used in pellet film ingredients. However, since HPMC has poorer solubility in ethanol than water, an additional 5 mL of distilled water should be used to dissolve HPMC. Based on the formulations designed as in table 8, the dissolution was evaluated and presented as results in table 9 and figure 3.

Table 8: Formulations designed to determine the optimized HPMC E6 and HPMC E15 combination proportion.

Ingredients	Formulations			
	CT11	CT13	CT14	CT15
EC N20 (g)	3	3	3	3
HPMC E6 (% w/w EC)	0	2.5	5.0	7.5
HPMC E15 (% w/w EC)	17.5	15.0	12.5	10.0
DBP (% w/w EC)	6	6	6	6
Talc (% w/w EC)	50	50	50	50
Distilled water (mL)	5	5	5	5
EtOH 96% (mL)	50	50	50	50

Table 9: The release rate of VER.HCl during HPMC E6 and HPMC E15 combination proportion testing (n = 6; $\overline{X}$ ± SD).

Formulations	Release rate of VER. HCl over time (hour)			
	1	2	4	8
CT11	8.02 ± 0.11	19.93 ± 0.89	40.23 ± 0.81	70.30 ± 2.52
CT13	9.31 ± 0.45	26.62 ± 0.82	52.12 ± 1.19	83.21 ± 2.70
CT14	13.65 ± 0.54	30.06 ± 2.21	56.81 ± 0.59	89.30 ± 3.50
CT15	21.47 ± 0.98	42.33 ± 1.29	65.09 ± 1.44	96.84 ± 3.34
USP 41 (%)	2 - 12	10 - 25	25 - 50	> 80

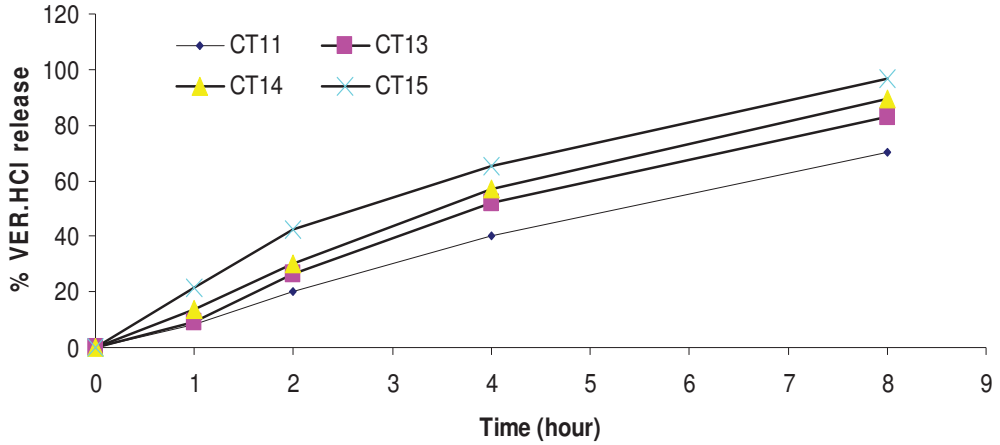

Figure 3: The release rate of VER. HCl over time during HPMC E6 and HPMC E15 combination proportion testing.

Reduced HPMC E15/HPMC E6 increased the release rate of pharmaceutical substance of all formulations due to an increase in the weight of HPMC E5 in the polymer mixture. The results showed that all three formulations increased the rate compared to CT11 (without HPMC E5). CT14 and CT15 (using HPMC E5 at 5% and 7.5%) which yielded higher release rate of pharmaceutical substance in the first hours due to low viscosity accounted for a large proportion in the combined polymer mixture. They absorbed water and dissolved quickly creating porous diffusion in pellet film, thus released more pharmaceutical substances than CT13 (HPMC E15 = 2.5% compared to EC). Based on the findings above, CT13 (HPMC E15 = 2.5% compared to EC) was selected to be used in the next study.

- Effects of plasticizer:

Testing with two plasticizers, DBP and TEC were conducted. Based on the formulations designed as in table 10, the dissolution was evaluated and presented as results in table 11 and figure 4.

Table 10: Formulations designed to determine the optimized plasticizer.

Ingredients	Formulations					
	CT13	CT16	CT17	CT18	CT19	CT20
EC N20 (g)	3	3	3	3	3	3
HPMC E6 (% w/w EC)	2.5	2.5	2.5	2.5	2.5	2.5
HPMC E15 (% w/w EC)	15.0	15.0	15.0	15.0	15.0	15.0
DBP (% w/w EC)	6	8	10	-	-	-
TEC (% w/w EC)	-	-	-	6	8	10
Talc (% w/w EC)	50	50	50	50	50	50
Distilled water (mL)	5	5	5	5	5	5
EtOH 96% (mL)	50	50	50	50	50	50

Table 11: Release rate of VER.HCl during plasticizer testing (n = 6; $\bar{X}$ ± SD).

Formulations	Release rate % of VER. HCl over time (hour)			
	1	2	4	8
CT13	9.31 ± 0.45	26.62 ± 0.82	52.12 ± 1.19	83.21 ± 2.70
CT16	8.99 ± 0.14	19.31 ± 0.59	42.16 ± 1.34	76.11 ± 1.84
CT17	8.58 ± 0.42	17.71 ± 0.88	39.56 ± 1.27	69.35 ± 2.97
CT18	10.45 ± 0.36	30.51 ± 1.28	50.04 ± 1.70	86.56 ± 3.88
CT19	12.71 ± 0.43	30.09 ± 1.23	55.04 ± 1.93	90.49 ± 3.60
CT20	18.31 ± 0.85	39.29 ± 1.53	58.75 ± 1.68	97.09 ± 4.32
USP 41 (%)	2 - 12	10 - 25	25 - 50	> 80

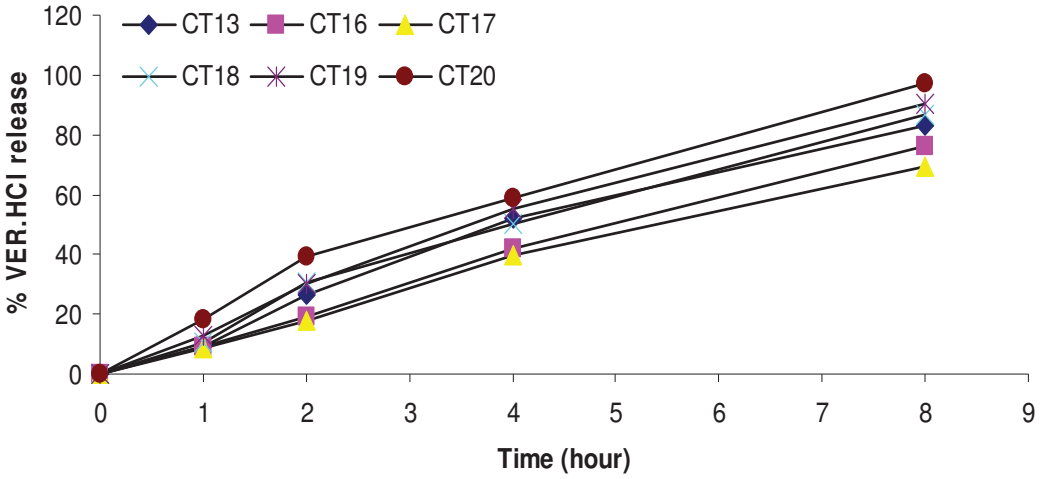

Figure 4: Release rate (%) of VER. HCl over time during plasticizer testing.

Increased proportion of DEP in pellet film formulations would reduce film permeability as DEP, a known hydrophobic plasticizer, lower pharmaceutical substance release rate. Specifically: CT16 and CT17 with large DEP proportions reduced pharmaceutical substance release rate more clearly than CT13. These two formulations released less than 80% pharmaceutical substance after 8 hours. In the case of TEC plasticizer, a hydrophilic plasticizer, higher proportion of TEC would result in higher rate of pharmaceutical substance release. During the preparation process, DBP was also found to be difficult to dissolve in 96% ethanol, the coating solution easily formed a sheen on the surface. It was difficult for DBP to disperse to uniformly plasticize the film surface. Based on the findings above and to be in line with the USP 41 standard on solubility, CT18 with TEC proportion of 6% of EC weight is selected to be used in the next study.

- Effect of anti-sticking agent:

Testing out formulations with different talc proportions as shown in table 12 and coating on 20g pellets with 50 mL of coating solution containing approximately 10% solids with similar coating performance. Dissolution evaluation results are shown in table 13 and figure 5.

Table 12: Formulations designed to determine the optimized anti-sticking agent.

Ingredients	Formulations			
	CT18	CT21	CT22	CT23
EC N20 (g)	3	3	3	3
HPMC E6 (% w/w EC)	2.5	2.5	2.5	2.5
HPMC E15 (% w/w EC)	15.0	15.0	15.0	15.0
Talc (% w/w EC)	50	60	40	30
TEC (% w/w EC)	6	6	6	6
Distilled water (mL)	5	5	5	5
96% EtOH (mL)	50	50	50	50

Table 13: Release rate of VER.HCl during anti-sticking agent testing (n = 6; $\overline{X}$ ± SD).

Formulations	Release rate % of VER. HCl over time (hour)			
	1	2	4	8
CT18	10.45 ± 0.36	30.51 ± 1.28	50.04 ± 1.70	86.56 ± 3.88
CT21	22.90 ± 1.02	46.90 ± 2.03	79.54 ± 3.09	97.33 ± 3.69
CT22	9.02 ± 0.14	26.55 ± 1.20	48.90 ± 1.42	83.73 ± 2.70
CT23	32.65 ± 1.24	60.11 ± 1.65	90.59 ± 3.37	98.18 ± 4.09
USP 41 (%)	2 - 12	10 - 25	25 - 50	> 80

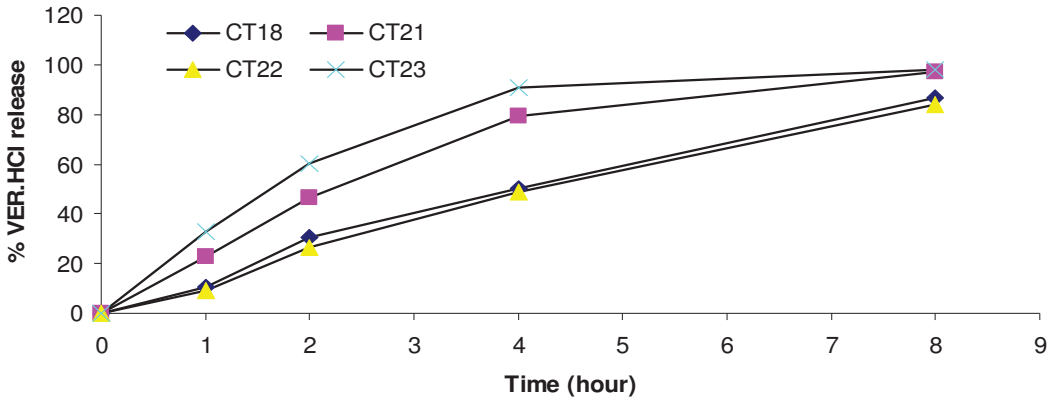

Figure 5: The rate of VER. HCl released over time during anti-sticking agent testing.

With a small talc proportion (30%), the release rate of pharmaceutical substance obtained was more than 30%. The cause may be due to the insufficient amount of talc which failed to prevent agglutination during the coating process, ultimately causing agglutination and puncture in pellet films. As for the large talc proportion (60%), high rate of pharmaceutical substance release was also obtained (22.9% after 1 hour) for which the reason was that an excessive amount of talc powder led to unstable and cracked films when measuring solubility. CT18 and CT22 have similar solubility curves, the less the amount of talc, the slower pharmaceutical substance is to release. It was observed that CT22 released more slowly and gave the release rate of pharmaceutical substance at all hours closer to what is stipulated by USP 41.

CONCLUSIONS

- Having determined the effects of certain parameters of the technical film coating process to control the release of core pellet of VER.HCl. With parameters such as: Spray pressure: 1.2 bar, spray rate: 0.85 mL/min, fluidizing air volume: 18 m^3/hour, inlet air temperature: 55 ± 5°C, outlet air temperature: 42 ± 1°C, spray gun diameter: 1.2 mm, the coating process gave a high efficiency (73.21%) in which pellet fluidizing was stable, uniform and smooth surface finish was achieved.

- Having selected release control excipients EC N20 as well as two hydrophilic polymers, HPMC E15/E6, to create diffusion channels, from which the pellet film formulation is formulated consisting of: EC N20, HPMC E6, HPMC E15, Talc, TEC, distilled water and EtOH 96%.

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