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RESEACH ON THE PREPARATION OF QUICK-RELEASE ACYCLOVIR 200MG TABLETS WITH SODIUM CROSCAMELOSE EXCIPIENT

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Abstract

Acyclovir is a potent and low-toxic antiviral drug used in the treatment of infections mainly caused by Herpes simplex and Varicella Zoster viruses. Although using the drug orally is convenient and easy to use, the drug has the disadvantage of low bioavailability because acyclovir is mainly absorbed at the end of the stomach and the beginning of the small intestine. Therefore, research was conducted to develop a formulation for rapid gastric release of Acyclovir 200 mg tablets. Tablets are prepared by wet granulation method, using excipients Amidon, Avicel PH101, lactose, polyvinyl pirolidone K30 (PVP K30), talc, magnesium stearate and soluble excipient sodium croscarmellose. Semi-finished granules are evaluated for moisture content, apparent density and flowability. Acyclovir 200 mg rapid release tablets are prepared from semi-finished granules using an 8-punch rotary tablet press and are evaluated for a number of quality criteria such as hardness, abrasion, mass uniformity, and dosage. active ingredients, disintegration and ability to control release of active ingredients. Research has developed a formula for preparing quick-release

Key words: preparation, tablets, acyclovir, rapid release.

acyclovir 200 mg tablets that can disintegrate in a 0.1 N HCl environment in under 300 seconds with the amount of active ingredient released reaching 92.68% at 5 minutes.

1. INTRODUCTION

Acyclovir belongs to the group of antiviral drugs, a synthetic nucleoside purine analog with in vitro and in vivo inhibitory activity against Herpes simplex virus type 1 (HSV-1) and (HSV-2) and Varicella zoster virus (VZV). acyclovir is a poorly absorbed substance with oral bioavailability of about 10 - 20% [1]. One of the reasons for poor oral absorption is that it is poorly soluble and has reduced bioavailability due to absorption at the end of the stomach and beginning of the small intestine. In order to absorb in the optimal area, research has been conducted to Develop a formula to prepare quick-release acyclovir tablets, which can release the active ingredient in the stomach to help optimize absorption and increase the bioavailability of the active ingredient. Therefore, research has been conducted to prepare acyclovir rapid-release tablets using the superdisintegrating excipient sodium croscarmellose by wet granulation method. Acyclovir quick-release tablets have been researched and developed for a long time, but now continue to research and develop new formulas to bring the best products to patients. The purpose of this study is to establish the formula and manufacture acyclovir 200 mg rapid-release tablets, which can completely release the active ingredient within 5 minutes after the drug enters the digestive tract.

EXPERIMENTAL

2.1. MATERIALS

Materials: Acyclovir (China); Amidon (France); Avicel (China); lactose (China); sodium croscarmellose (China); polyvinyl pirrolidon K30 (China); Talc (China); magnesi stearat (China), ethanol (China).

Instruments: OHAUS MB45 moisture tester (USA), ERWEKA GTL flow tester (Germany), PHARMATEST PTB311E hardness tester (Germany), friabilator GOUMING CS3 (China), ERWEKA ZT122 2-hour automatic disintegration tester (Germany), PHARMA PTWS 820D dissolution testing system (Germany), UV spectrometer-Vis HITACHI, PHARMA 8 punches rotary roller, METLER TOLERDO analytical weighing, KERN technical weighing (Germany), MEMMERT IN30 dryer (Germany).

2.2. METHODS

2.2.1. Preperation of tablets

Acyclovir 200 mg rapid release tablets are prepared by wet granulation method employing a disintergrant as the formulation given in table 1. Weigh the amount of active ingredients and excipients according to the formulation (except for glidant). Finely grind active pharmaceutical ingredients and excipients according to single powder grinding principle. Homogeneously mix the prepared ingredients according to the principle of uniformity to form a double dough. Granulation with 70 % ethanol. Grind the granules through a 1 mm sieve. The wet granules were dried for 10 minutes, at 45-50 oC. Fix the granules through a 1 mm sieve, continue to dry the granules at 50 ^{0}C for 20 minutes until the moisture content is less than 3%. The tablet granulations were blended with the glidant thoroughly in a closed polyethene bag and compressed into 400 mg tablets using PHARMA 8 punches rotary roller with a diameter of 10 mm, the hardness is 50 - 80 N.

2.2.2. Quality standard assesment methods

a. Evaluation the quality criteria of semi-finished granules

Moisture [2] The moisture content of semi-finished granules is determined by weighing the moisture content of granules and powder OHAUS MB45 (USA) according to Appendix 9.6 Vietnamese Pharmacopoeia 5 [2].

Flowability The time taken for 80 g of the acyclovir granules to pass through the orifice of an Erweka flow tester (Model: ERWEKA GTL (Germany) with a funnel hole diameter of 10 mm) was recorded. This was conducted in triplicates and the mean value recorded

Apparent density

Acyclovir granules (30 g) were weighed and poured gently into a 100 ml measuring cylinder. It was tapped mechanically on a flat surface until a constant volume which was recorded as a tapped volume. The apparent density is calculated according to the formula.

$$d = \frac{m}{V}$$

Where

m: Mass of the grain of granules (g);

V: The volume of granules after tapping (ml)

d: The apparent density (g/ml)

b. Evaluation of rapid release tablets prepepared

The following post compression tests were carried out on the compressed tablets using standard procedures: tablet properties, hardness, friability, uniformity of tablet weight, quantiation, disintegration time and dissolution test.

Tablet properties

Physical characteristics The tablets were off-white, with no odour. The tablet surfaces were elegant and smooth to touch.

Hardness test Ten tablets were randomly selected from each batch and hardness of tablets was determined by using a motorized tablet hardness tester (PHARMATEST, Model PTB311E, Germany) and measured in terms of Newton (N). The mean hardness values and standard deviation for each bathch were recorded.

Friability test [2] Pre-weighed twenty tablets (m1) were placed in the drum of the friabilator GOUMIN CS3 (China) and is expressed in percentage (%). The friabilator was operated at 25 rpm. After 4 minutes, the tablets were brought out, de-dusted and reweighed (m_2). Their percentage loss in weight value was calculated by using the following formula.

$$X(\%) = \frac{m_1 - m_2}{m_1} \times 100$$

where: X: The friability (%) m_1: Mass of the tablet before test (g); m_2: Mass of the tablet after test and de-dusted (g).

Triplicate determination was carried out and the mean and standard deviation were reported.

Uniformity of tablet weight [2] Twenty tablets from each batch were used for the test. The weight of each tablet was determined, and the mean or average weight and standard deviation was computed.

Drug Content Uniformly [2] Test sample: weigh the exact weight of 20 tablets, calculate the average weight of the tablets and grind them into fine powder. Accurately weigh a quantity of pellets equivalent to about 100 mg of acyclovir into a 100 ml volumetric flask. Fill in enough 0.1 N HCl solution to the volumetric flash and shake well. The solution was filtered through dry filter paper, discarding the first 20.0 ml of the filtrate. Draw exactly 1 ml of solution into a 100 ml volumetric flask, add 0.1 N HCl solution to the mark, and shake well.

Standard sample: Accurately weigh about 100 mg of acyclovir and place in a 100 ml volumetric flask. Fill in enough 0.1 N HCl solution to the volumetric flash and shake well. The solution was filtered through dry filter paper, discarding the first 20.0 ml of the filtrate. Diluting 1 ml of the filtrate to 100 ml with 0.1 N HCl solution and shaking well.

Blank sample: 0.1 N hydrochloric acid solution.

Measure the absorbance of the resulting solution at the maximum wavelength, using a 1 cm thick beaker. Calculate the concentration of acyclovir in the test sample by comparison with a standard sample of known concentration. The results are the average value calculated over 3 experiments.

Disintegration time [2] Disintegration time was measured with Erweka apparatus Type ZT122 (Germany). Tests were carried out in 500 ml of 0.1 N hydrochloric acid at 37 0.5C. All tests were run using six tablets of each formulation.

Dissolution test Based on Vietnamese Pharmacopoeia 5 [2]

The dissolution analyses of the various bathches of the acyclovir tablets were carried out using the paddle method described in Vietnamese Pharmacopoeia 5. A dissolution apparatus PHARMA PTWS 820D (Germany) containing 900 ml of 0.1 N HCl solution maintained at 37 ± 0.5^0C with a paddle speed of 50 rpm was used. Each experiment was carried out using six tablets. Samples of dissolution fluid (10 ml) were withdrawn through a filter at specific time intervals 5, 10 minutes and replaced with an equivalent volume maintained at same temperature (37 ± 0.5^0C . The withdrawn samples were filtered and diluted appropriately with 0,1 M HCl solution.

Test sample: Each sample (10 ml) was filtered through dry filter paper, discarded the first 2 ml of the filtrate. Diluting 5 ml of the filtrate to 10 ml with 0.1 N HCl solution and mix. Then dilute 5 ml of the filtrate to 100 ml with 0.1 N HCl solution and mix. Each dissolution experiment is run in triplicate (n = 3).

Standard sample: Accurately weigh about 100 mg of acyclovir and place in a 100 ml volumetric flask. Fill in enough 0.1 N HCl solution to the volumetric flash and shake well. The solution was filtered through dry filter paper, discarding the first 20.0 ml of the filtrate. Diluting 1 ml of the filtrate to 100 ml with 0.1 N HCl solution and shaking well.

Blank sample: 0.1 N hydrochloric acid solution

The resulting solutions were subjected to spectrophotomnetric analysis (UV-Visible Spectrophotometer HITACHI) at maximum wavelength.

Their dissolution percentage was calculated by using the following formula.

$$\%Dissolution = \frac{At \times Cs \times Ks \times 900 \times 100 \times mlt}{As \times 325 \times mtt}$$

A_t: Absorption of test sample; A_s: Absorption of standard sample; C_s: Concentration of standard sample (mg/ml); K_s: Dilution of standard sample; 900: Volume of dissolution test medium (ml); mlt: Theoretical mass of pellets (mg); mtt: Actual mass of pellets (mg); 200: Drug content stated on the labeled (mg).

3. RESULT AND DISSCUSSION

Formulate formulation of rapid release acyclovir 200 mg tablets. 3.1. Formulation of semi-finished granules 3.1.1. Investigate the effect of disintergrant and adjuvant fillers According to some references [3], [4]. [5], rapid release acyclovir 200 mg tablets were formulated employing one disintegrant namely sodium croscarmellose (Sodium Cross) and three fillers namely Avicel PH 101, Amidon, and lactose. The tablets were prepared by wet granulation method as per the formulation given in table 1.

The role of excipients in the formulation Sodium croscarmellose is a white solid with a fine powder-like crystalline structure. It is used as an excipient in

Table 1. Composition of formulation to investigate the effect of filler and disintergrant excipients

Formulation (F)	Acyclovir (mg)	Sodium Cross (mg)	Amidon (mg)	Avicel PH 101 (mg)	Lactose (mg)	PVP K30 (mg)	Mg stearat – Talc (1:1) (%)	Total weight (mg)
F1	200	12	176	-	-	12	1.5	400
F2	200	16	172	-	-	12	1.5	400
F3	200	20	168	-	-	12	1.5	400
F4	200	12	-	176	-	12	1.5	400
F5	200	16	-	172	-	12	1.5	400
F6	200	20	-	168	-	12	1.5	400
F7	200	12	-	-	176	12	1.5	400
F8	200	16	-	-	172	12	1.5	400
F9	200	20	-	-	168	12	1.5	400

the form of a superdisintegrating agent for solid drugs. Avicel PH 101 is a microcrystalline cellulose widely used as an excipient in solid drug preparations. Avicel PH 101 is often employed for its filler and adhesive effects in preparations using the wet granulation method. Additionally, Avicel exhibits a non-stick effect and aids in tablet disintegration to release the active ingredient. Amidon is a carbohydrate that contains a mixture of amylose and amylopectin. Amidone is used as an excipient in the form of a filler, binder, and disintegrating agent for solid drugs.

Lactose is a disaccharide derived from animal milk, acting as a water-soluble excipient, thereby supporting the decomposition of tablets to release the active ingredient.

PVP is a solid that acts as a sticky excipient, aiding in granule formation during wet granulation to enhance the fluidity and compressibility of acyclovir. 70% ethanol is utilized for granulation. Semi-finished granules are prepared using the wet granulation method. The physical parameters of the rapidly releasing acyclovir granules are provided in table 2.

- Moisture: moisture percentage of all 9 formulas ranges from 1.09 - 2.67%, meeting the moisture content standard of medicinal granules less than 5% - the standard of Vietnamese Pharmacopoeia 5 [2].

- The apparent density of granules was in the range of 0.42 0.57 g/ml that shows good flowability with the highest value is 0.57 g/ml in F1 and the lowest value is 0.42 g/ml in F9.

- The flowability was between 4.56 6.89 g/sec with the highest values observed in F7 (6.89 g/s) and the lowest values observed in F1 (4.56 g/s).

Table 2. Physical Parameters of Acyclovir Granules Prepared

Formulation (F)	Moisture (%)	Apparent density (g/ml)	Flowability (g/s)
F1	2.34	0.57	4.56
F2	2.56	0.54	4.78
F3	2.45	0.52	4.89
F4	2.34	0.55	5.34
F5	2.67	0.53	5.56
F6	2.25	0.48	5.87
F7	1.22	0.46	6.89
F8	1.24	0.44	6.56
F9	1.09	0.42	6.34

The formulation meets the quality standards for semi-finished granules, so we added a 1:1 ratio of talc - magnesium stearate excipient and prepared rapid release acyclovir 200 mg tablets with weight of 400 mg by using PHARMA 8 punches rotary roller with a diameter of 10 mm. After tablets are formed, check the quality criteria of them. The results are shown in Table 3.

Table 3. Physical Parameters of Acyclovir Tablets Prepared

Formulation (F)	*Hardness (N)*	*Uniformly of tablet weight (± 5 %)*	Friability (% Wt loss)	*Disintegration time (sec)*	*Drug content uniformly (%)*
F1	55-79	PASS	0.30	220	98.76
F2	53-70	PASS	0.26	180	99.34
F3	58-80	PASS	0.34	150	98.35
F4	55-80	PASS	0.27	75	99.72
F5	50-77	PASS	0.24	60	99.37
F6	58-78	PASS	0.20	41	99.95
F7	59-80	PASS	0.27	480	99.73
F8	60-75	PASS	0.23	450	99.04
F9	65-80	PASS	0.35	400	99.95

- The hardness of the tablet samples is all in the range of 50-80N and the

abrasion level is all within less than 3% as prescribed in Vietnamese Pharmacopoeia 5 [2]

- Quantification: The drug content uniformly was in the range of 98.35 % - 99.95 %, conforming to the requirement that acyclovir tablets must contain not less than 95.0 % and not more than 105.0 % of labeled amount of acyclovir.

- Tablets prepared according to 9 formulas all meet the basic quality criteria of tablets according to Pharmacopoeia standards: Hardness ranges from 50 - 80 N, abrasion less than 3%, mass uniformity within 5 % according to Vietnamese Pharmacopoeia 5 [2].

- Disintegration rate: the formula with the shortest disintegration time is F6 (41 seconds) and the formula with the longest disintegration time is F7 (480 seconds). According to the references, a disintergration time of less than 5 minutes $\equiv$ 300 sec is expected for rapid release acyclovir tablets. Tablets in F7, F8 and F9 had an average disintegration time of 480, 450 and 400 sec respectively, hence did not meet the standards. Meanwhile for tablets in F1-F6, the disintegration time was within the standard limits. Therefore, the F7 F9 formulations were excluded from further studies. Conduct solubility test of the F1 F6 formulation, the results of solubility and release of active ingredients are presented in table 4 and figure 1.

Table 4. Dissolution Parameters of Acyclovir 200 mg Tablets Prepared

Formulation (F)	Dissolution (%)	
	5 minutes	10 minutes
F1	59.95	76.76
F2	65.67	83.76
F3	60.40	88.76
F4	71.68	91.45
F5	80.94	98.76
F6	92.87	101.02

Dissolution rate From the data of Table 4 and Fig 1, it was concluded that F6 was best among all the tablets which had shown the percentage of drug dissolving more than 90 % of the drug within 5 minutes. In addition, that is better than conventional tablet forms that are usually released 30 45 minutes. 3.1.2. Investigate the effect of glidant excipient ratio. The glidant excipients in the formulation of acyclovir tablets are talc and magnesium stearate, both of which are water-based excipients, which make the tablets impermeable and therefore tend to extend the decomposition time of the tablets. Therefore, the research team investigated the effect of the proportion of four glidant excipients on drug release and dissolution ability. To conduct this study, four tablet

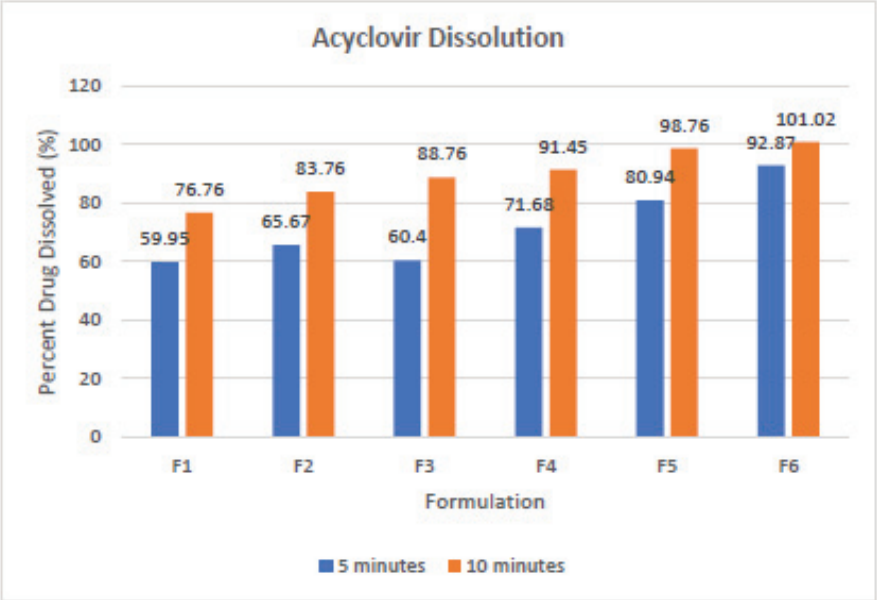

Fig 1. Percent Drug Dissolved (%)

samples were prepared using glidant excipients of talc and magnesium stearate (1:1), namely 1.5% (F6), 1.0 % (F6a), 2.0 % (F6b), and 3.0 % (F6c). The data is shown in table 5.

Table 5. Composition of formulation to investigate the effect of glidant excipients

Formulation (F)	Acyclovir (mg)	Sodium Cross (mg)	Avicel PH 101 (mg)	PVP K30 (mg)	Mg stearat – Talc (1:1) (%)	Total weight (mg)
F6	200	20	168	12	1.5	400
F6a	200	20	168	12	1.0	400
F6b	200	20	168	12	2.0	400
F6c	200	20	168	12	3.0	400

The dissolution test results in 5 and 10 minutes are shown in table 6 and

figure 2.

Table 6. Dissolution Parameters of Acyclovir 200 mg Tablets Prepared

Formulation (F)	Dissolution (%)	
	5 minutes	10 minutes
F6	92.68	101.02
F6a	93.78	102.83
F6b	53.28	76.00
F6c	35.54	52.59

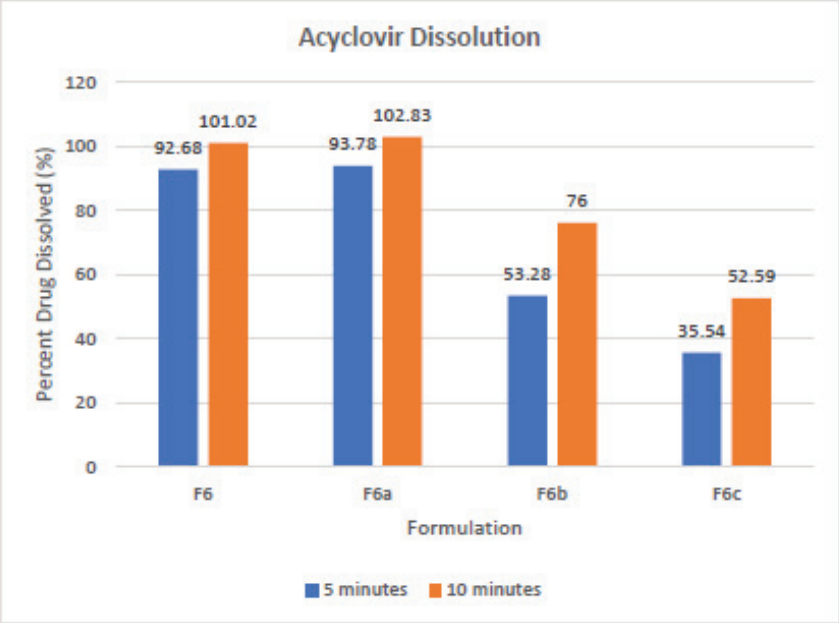

Fig 2. Percent Drug Dissolved (%)

From figure 2, When increasing the ratio of plain excipients from 1% to 1.5%, the ability to release active ingredients at 5 minutes is not much affected. Only when the ratio of plain excipients is 2% and 3% does the ability to release acyclovir decrease clearly, 53.28 % (F6b) and 35.5 % (F6c) respectively compared to 92.68 % (F6) which is 1.5%. The ratio of plain excipients is 1.5%, the tablet presses very well, has a beautiful shiny surface, uniform mass and meets the requirements for quality criteria of tablets, on the other hand, the ratio of plain excipients is 1%. The crushed tablet has a rough surface and

does not satisfy sensory requirements. Therefore, the study chose a glidant excipient ratio of 1.5% to prepare quick-release acyclovir 200 mg tablets.

3.2. Formulation of acyclovir tablets From the survey's result, the most effective formulation for 200 mg rapid-release acyclovir tablets consists of acyclovir 200 mg, sodium croscarmellose 20 mg, Avicel PH 101 168 mg, PVP K30 12 mg, and a talc:magnesium stearate ratio of 1:1 (1.5

3.3. Recommend some quality criteria

Based on these results of the evaluation granules and tablets, we would like to recommend the quality criteria for rapid release 200 mg acyclovir tablets presented in table 7.

Table 7. Recommended quality criteria for rapid release acyclovir 200 mg tablets

Criteria	Requirement
Tablet properties	off-white, with no odour, smooth, and elegant
Hardness test	50 – 80N
Friability test	≤ 3 %
Uniformly of tablet weights	± 5 %
Disintergration time	Totally disintergrattion < 300 seconds
Dissolution rate	After 5 minutes: > 90 % of the drug was released

4. CONCLUSION

The study has successfully created a formulation for producing rapid-release acyclovir tablets containing 200 mg. This formulation incorporates sodium croscarmellose as a disintegrating agent, PVP K30 as binder excipient, Avicel PH101 as filler, a 70% ethanol concentration, and a mixture of talc and magnesium stearate (1.5%) in a 1:1 ratio as glidant excipients. Tablets are prepared by wet granulation method and compressed by PHARMA 8 punches rotary roller with a diameter of 10 mm. After preparing acyclovir 200 mg rapid-release tablets, some basic criteria have been achieved as follows: the hardness of the tablets is in the range of 50-80N, the friability is less than 1 %, and the required uniformity of tablets weigh is met Vietnamese Pharmacopoeia, good disintergration time and dissolution rate (disintergration totally within 5 minutes and over 90 % of drug release after 5 minutes).

With this result, it is possible to put the formulation and process of preparing rapid release acyclovir 200 mg tablets to study, upgrade the batch size and aging under normal conditions.

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