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UNIVERSITY OF RUHUNA – FACULTY OF ALLIED HEALTH SCIENCES

DEPARTMENT OF PHARMACY

FOURTH BPHARM PART II EXAMINATION – OCTOBER 2021

PH 4223 QUALITY CONTROL – SEQ

TIME: TWO HOURS

INSTRUCTIONS

- There are **four** questions in the SEQ paper.
- Answer all questions.
- No paper should be removed from the examination hall.
- Do not use any correction fluid.
- Use illustrations where necessary.

PART A

01.

1.1. Define the term "quality management". (***15 marks***)

1.2. Answer following questions based on essential aspects of GMP related to pharmaceuticals.

1.2.1. List down the key steps recommended for a good complaint handling procedure. (***15 marks***)

1.2.2. Define the term "contract" in relation to pharmaceutical contract manufacturing. (***15 marks***)

1.2.3. State three purposes of good documentation practices. (***15 marks***)

1.3. In vivo - in vitro correlation of the assay of active pharmaceutical ingredient is critically important for sustained release products. Briefly explain the reasons for it. (***20 marks***)

1.4. Briefly explain the factors to be considered when selecting materials for the construction of pharmaceutical machinery and equipment. (***20 marks***)

02.

2.1. Comment on the following statement *"conducting only finish product quality control tests are sufficient to ensure the quality of medicines"* (***30 marks***)

2.2. Answer below questions using the monograph of valacyclovir tablets provided.

2.2.1. State the name of the active pharmaceutical ingredient with upper and lower limits of the content. (***15 marks***)

2.2.2. List down the main tests that will appear in the finished product certificate of analysis (CoA) of valacyclovir tablets. (***15 marks***)

2.2.3. Comment on the labeling, packaging, and storage requirements of the valacyclovir tablets. (***15 marks***)

2.3. Briefly explain one test method that can be used to perform pyrogen test for parenteral products. (***25 marks***)

PART B

03.

3.1. Differentiate the in-process quality control (IPQC) and finished product quality control (FPQC) tests. (***10 marks***)

3.2. Briefly discuss the test methods used to assess the quality of viscosity in syrups. (***15 marks***)

3.3. Hardness, thickness, and diameter are three parameters used to assess the quality of tablets.

3.3.1. State two factors affecting the hardness, thickness, and diameter of tablets. (***06 marks***)

3.3.2. Briefly describe the methods used to assess each of the above parameter with acceptance criteria/ reference limits. (***35 marks***)

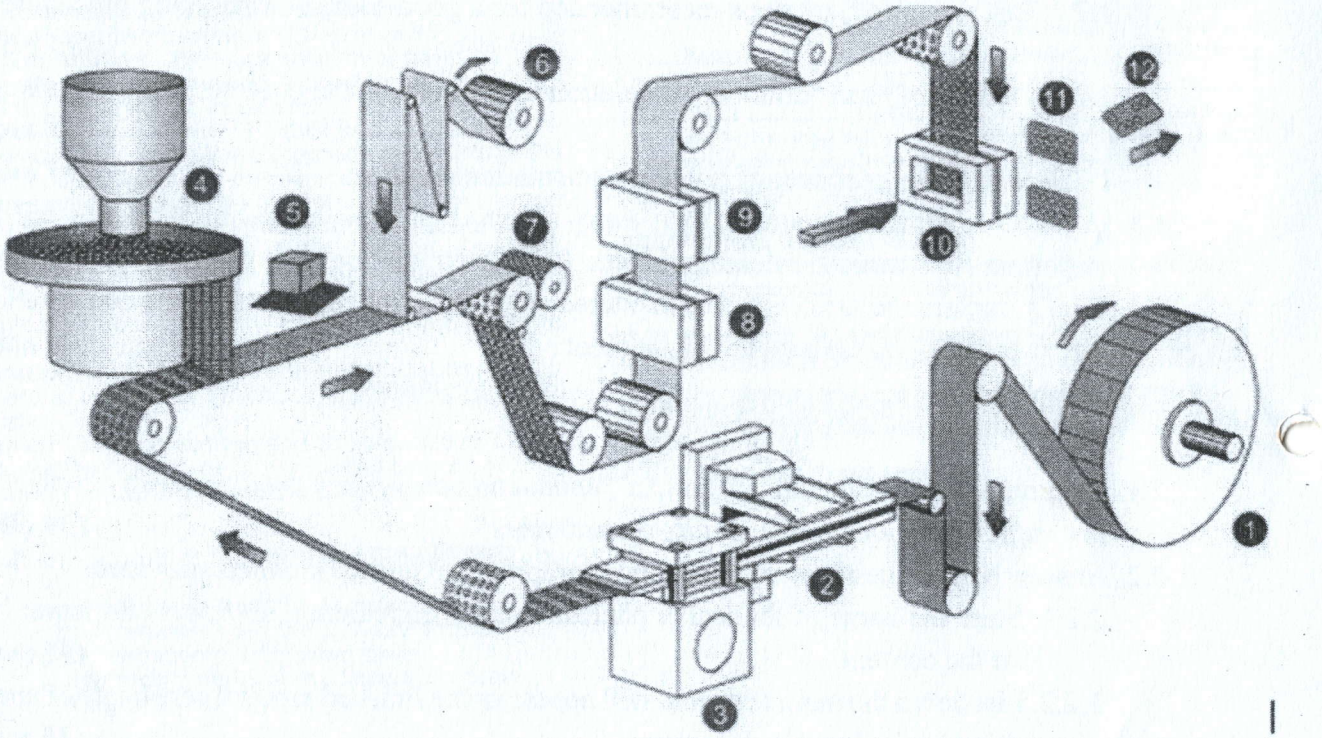
3.4. Write a short note on 'evaluation of *in-vitro* dissolution of solid dosage forms'. (***34 marks***)

PART C

04.

4.1. Define the term 'packaging line'. (***12 marks***)

4.2. Following figure shows a blister packaging machine. List the stages of production process from step 1 to 12. (***30 marks***)



4.3. List three types of information stated in appendices of British Pharmacopoeia. (***12 marks***)

4.4. Define the term 'liquefaction time' for suppositories. (***12 marks***)

4.5. Suppose you are given randomly selected 20 suppositories of Montelukast sodium from a batch and asked to conduct weight variation test. Following table shows weight of

(13)

individual suppository. Determine whether this batch is satisfied with the quality standard or not. (***34 marks***)

Limit: Not more than 2 suppositories differ from the average weight by more than ±5%, and no suppository differs from the average weight by more than ±10%.

Sample number	Weight of suppository (g)
1	1.012
2	1.048
3	1.026
4	1.034
5	1.087
6	1.102
7	1.043
8	1.038
9	1.032
10	1.049
11	1.007
12	1.036
13	1.024
14	1.063
15	1.023
16	1.034
17	1.039
18	1.024
19	1.073
20	1.021

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Valacyclovir Tablets

DEFINITION

Valacyclovir Tablets contain an amount of Valacyclovir Hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of valacyclovir ($C_{13}H_{20}N_6O_4$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B. IDENTIFICATION TESTS—GENERAL,** *Chloride* ⟨**191**⟩**:** Meet the requirements

ASSAY

- **PROCEDURE**

Diluent: 0.1% (v/v) phosphoric acid in water
Mobile phase: Methanol and *Diluent* (5:95)
Standard solution: 0.1 mg/mL of USP Valacyclovir Hydrochloride RS in *Diluent*. [NOTE—USP Valacyclovir Hydrochloride RS contains a detectable quantity of D-valacyclovir.]
Sample solution: Transfer NLT 5 Tablets into a suitable volumetric flask, and add 0.1 M hydrochloric acid (approximately 80% of the volume of the flask). Mechanically shake the sample until the Tablets disintegrate into a fine suspension (60 min), and sonicate for 10 min. Cool to ambient temperature, dilute with 0.1 M hydrochloric acid to volume, and mix to obtain a solution having a concentration of 2.5 mg/mL. Dilute a portion of the sample with *Diluent* to obtain a nominal concentration of 0.1 mg/mL of valacyclovir, and mix. Pass a portion of this solution through a membrane filter of 0.45-µm or finer pore size, and use the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4-mm × 15-cm; 5-µm packing L66
Column temperature: 10°
Flow rate: 0.75 mL/min
Injection volume: 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 1.3 between the D-valacyclovir and valacyclovir peaks
Tailing factor: NMT 2.0 for the valacyclovir peak
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of valacyclovir ($C_{13}H_{20}N_6O_4$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Valacyclovir Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of valacyclovir in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of valacyclovir, 324.34
M_{r2} = molecular weight of valacyclovir hydrochloride, 360.80

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨**711**⟩

•**Test 1**• (RB 1-May-2012)
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 45 min
Diluent: Prepare as directed in the *Assay*.
Mobile phase: Acetonitrile and *Diluent* (5:95)
Standard solution: Prepare a solution in *Diluent* containing USP Valacyclovir Hydrochloride RS equivalent to 0.044 mg/mL of valacyclovir free base.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute with *Diluent* to obtain a final concentration of about 0.044 mg/mL of valacyclovir free base considering complete dissolution of the Tablet label claim.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 5-cm, 5-µm packing L1
Flow rate: 2.0 mL/min
Injection volume: 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of valacyclovir ($C_{13}H_{20}N_6O_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times D \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of •USP Valacyclovir Hydrochloride RS• (RB 1-May-2012) in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
M_{r1} = molecular weight of valacyclovir, 324.34
M_{r2} = molecular weight of valacyclovir hydrochloride, 360.80
L = label claim (mg/Tablet)
D = dilution factor of the *Sample solution*

Tolerances: NLT 75% (*Q*) of the labeled amount of valacyclovir ($C_{13}H_{20}N_6O_4$) is dissolved.

•**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 45 min
Instrumental conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Analytical wavelength: 252 nm
Cell: 0.02 cm
Blank: *Medium*
Standard solution
For Tablets labeled to contain 500 mg: 0.6 mg/mL of USP Valacyclovir Hydrochloride RS in *Medium*. A small volume of methanol, not exceeding 5% of the final volume, may be used to help solubilize valacyclovir.

For Tablets labeled to contain 1000 mg: 1.2 mg/mL of USP Valacyclovir Hydrochloride RS in *Medium*. A small volume of methanol, not exceeding 5% of the final volume, may be used to help solubilize valacyclovir.

Sample solution: Pass a portion of the solution under test through a filter of 0.45-µm pore size. Discard the first 3 mL of sample filtrate.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of valacyclovir ($C_{13}H_{20}N_6O_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times D \times 100$$

r_U = absorbance of the *Sample solution*
r_S = absorbance of the *Standard solution*
C_S = concentration of USP Valacyclovir Hydrochloride RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
M_{r1} = molecular weight of valacyclovir, 324.34
M_{r2} = molecular weight of valacyclovir hydrochloride, 360.80
L = label claim (mg/Tablet)
D = dilution factor of the *Sample solution*

Tolerances: NLT 80% (Q) of the labeled amount of valacyclovir ($C_{13}H_{20}N_6O_4$) is dissolved. • (RB 1-May-2012)

Change to read:

• **Uniformity of Dosage Units** ⟨905⟩

Procedure for content uniformity

[Note—All of the concentrations are expressed as valacyclovir free base.]

Diluent: Prepare as directed in the *Assay*.

Mobile phase: Acetonitrile and *Diluent* (5:95)

Standard solution: Prepare a solution of USP Valacyclovir Hydrochloride RS, equivalent to 0.04 mg/mL of valacyclovir, in *Diluent*.

Sample solution: Transfer 1 Tablet into a suitable volumetric flask. Add *Diluent* (approximately 60% of the volume of the flask), and mechanically shake the samples until the Tablet disintegrates into a fine suspension, and sonicate for 10 min. Cool, dilute with *Diluent* to volume, and mix. Dilute a portion of each sample with *Diluent* to obtain a nominal concentration of 0.04 mg/mL of valacyclovir. Pass a portion of each sample through a membrane filter of 0.45-µm pore size, and use the filtrate.

Chromatographic system and **System suitability:** Proceed as directed in *Dissolution*, •*Test 1*.• (RB 1-May-2012)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of valacyclovir ($C_{13}H_{20}N_6O_4$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times \bullet(M_{r1}/M_{r2}) \times \bullet \text{ (RB 1-May-2012)} \ 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Valacyclovir Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of valacyclovir in the *Sample solution* (mg/mL)
•M_{r1} = molecular weight of valacyclovir, 324.34
M_{r2} = molecular weight of valacyclovir hydrochloride, 360.80• (RB 1-May-2012)

Acceptance criteria: Meet the requirements

IMPURITIES

• **Organic Impurities**

Diluent, Mobile phase, Standard solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of D-valacyclovir and acyclovir in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of D-valacyclovir or acyclovir from the *Sample solution*
r_S = peak response of USP Valacyclovir Hydrochloride RS from the *Standard solution*
C_S = concentration of valacyclovir hydrochloride in the *Standard solution* (mg/mL)
C_U = nominal concentration of valacyclovir in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of valacyclovir, 324.34
M_{r2} = molecular weight of valacyclovir hydrochloride, 360.80
F = relative response factor (see *Table 1*)

Acceptance criteria

Individual impurities: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
D-Valacyclovir[a]	0.82	1.0	—
Acyclovir[b]	0.56	1.4	2.5

[a] D-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy] ethyl ester, monohydrochloride. [Note—This is a process impurity.]
[b] 2-Amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one (acyclovir).

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

Add the following:

•• **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.• (RB 1-May-2012)

• **USP Reference Standards** ⟨11⟩

USP Valacyclovir Hydrochloride RS