Preparation and in vitro Evaluation of Enteric Coated Oral Vancomycin Hydrochloride Sustained Release Formulation with Mucoadhesive Properties

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ABSTRACT

Clostridium difficile is a species of gram-positive bacteria thought to infect patients with weakened immune response resulting in colitis. Oral vancomycin hydrochloride is given four times a day to treat Clostridium difficile colitis and is commercially available in the form of capsule and solution. Patient’s compliance is the main issue in this treatment due to the multiple dosing frequencies. Accordingly, replacement of such dose regimen with a once daily dosage will enhance patient compliance. In this study, mucoadhesive vancomycin hydrochloride tablets were prepared with the use of chitosan to exert a local effect in the colon. Sustained release property was also imparted by chitosan. Enteric coating with Eudragit® S 100 was applied to prevent the sticking of chitosan tablets in the stomach and small intestine and deliver the tablets intact to the colon. The prepared tablets were evaluated for In vitro drug release for 24 hours and compared with the marketed formulation. The formulation was found to release in a sustained manner in pH 7.4 buffer allowing the colon delivered oral vancomycin hydrochloride to be a promising formulation in the development of a once daily treatment for Clostridium difficile colitis.

Keywords: Clostridium difficile, Colon targeting, Oral vancomycin hydrochloride, Chitosan, Mucoadhesion, Eudragit® S 100, Sustained release

INTRODUCTION

Clostridium difficile infection is one of the common health care acquired diseases. Although hospitalization and antibiotic exposure are the most contributing factors, colitis is spreading in the community. Clostridium difficile caused around half a million infections among American population in one year with 15,000 mortalities. From 2001 to 2012, the annual incidence of Clostridium difficile infection and multiply recurrent Clostridium difficile infection increased by 42.7% and 188.8%, respectively. In Europe, it’s estimated that 123,997 patients developed a health acquired Clostridium difficile infection each year within the European Union in 2011 and 2012. Findings revealed that Clostridium difficile prevalence throughout Asia in 2017 was 14.8% with a higher prevalence in East Asia (19.5%), compared with 10.5% in South Asia or 11.1% in the Middle East.

Colitis is the disease results from colonization of the colon with Clostridium difficile and production of its exotoxins. Clinical presentation of colitis varies from diarrhea to toxic megacolon, pseudomembranous colitis and death. Vancomycin hydrochloride is recommended for initial and recurrent episodes of Clostridium difficile infection. Treatment includes oral administration of 125 mg or 500 mg vancomycin hydrochloride four times a day for ten to fourteen days with or without metronidazole depending on the severity. Oral vancomycin Hydrochloride is commercially available in the form of capsules and solutions under different brand names such as Vancocin® and Vancoled®. Colon delivery has been strongly proved by researchers to be useful for the treatment of local diseases associated with the colon and to reduce the frequency of doses. The colon delivered formulation should be able to release the drug exclusively in the colon with appropriate inhibition of release during its path in...
the stomach and small intestine. This means that the colon specific formulation should resist the gastric and intestinal pH and dissolve at pH 7 in the colon. Colonic microflora is another factor that affects colon targeted drug delivery. Colon contains mainly anaerobic bacteria, example: Bacteroides, Clostridia, Eubacteria, and Enterobacteria, etc. Colonic bacteria produce enzymes that catalyze fermentation reactions of undigested polysaccharides. Reactions result in the formation of short chains fatty acids influencing by that the colonic pH. Based on that physiological nature, many colon delivered formulations have utilized pH dependent strategy by coating with pH sensitive polymers that dissolves at a particular pH. Among these polymers, Eudragit® S 100 that dissolves at pH 7 and above is commonly used for colon targeted delivery of drugs. Polymers like Levan polysaccharides and gelatin were utilized in pharmaceutical research to obtain a sustained release action of vancomycin hydrochloride. Chitosan was also utilized for the same release purpose. Besides being mucoadhesive, chitosan is degraded by the colonic microflora. More complicated techniques were also used to develop Vancomycin hydrochloride carriers including nanoparticles and microspheres.

In this study, a pH dependent system was developed. Colon specific, enteric coated sustained release oral vancomycin hydrochloride formulation was prepared by the use of chitosan, coated with the pH sensitive polymer Eudragit® S 100 to allow it to release locally in the colon, and evaluated.

METHODS OF DEVELOPMENT AND EVALUATION OF THE FORMULATION

Materials
Vancomycin hydrochloride USP grade (Gold Biotechnology, USA), low molecular weight chitosan (Sigma Aldrich, Iceland), corn starch (Gene Chem, Canada), Eudragit® S 100 (Evonik, Germany), triethyl citrate (Sigma Aldrich, Germany), talc (Sigma Aldrich, USA), pepsin from porcine gastric mucosa (Gold Biotechnology, USA), pancreatin from porcine pancreas (Sigma Aldrich, USA), acetone (Merk, Germany), isopropanol (Merk, Germany), and a goat intestinal segment.

Formulation Development
Preparation of vancomycin hydrochloride mucoadhesive tablets: Vancomycin hydrochloride mucoadhesive tablets were prepared by wet granulation technique using previously published method with modification. Super disintegrant and lubricant were not added So that rapidly disintegrated tablets with reduced hardness wouldn’t be obtained. The amount of ingredients used in the preparation of vancomycin hydrochloride tablets is specified in Table 1. The amount of 22 g of vancomycin hydrochloride and similarly of chitosan were weighed accurately, grinded into fine powder and mixed thoroughly. And amount of 122 ml of the granulating agent, starch mucilage 7.5% was added gradually to the powder mixture with proper mixing until the formation of a dummy mass. The produced mass was granulated by mesh (Fischer Scientific, N.16) with a pore size of 0.0469 inches. Then the granules were dried at room temperature until complete drying. The dried granules were screened using mesh (Fischer Scientific, N.16), and compressed using 10 mm punch in a rotary tablet compression machine. Before compression, the surfaces of the dies and punches were lubricated with magnesium stearate. The prepared 150 tablets were stored in an airtight container at room temperature for further evaluation.

Preparation of the coating suspension: A coating suspension of Eudragit® S 100 was prepared according to the formula specified by the manufacturer, Evonik industries. The formula is given in Table 2.

Coating with Eudragit® S 100: The prepared tablets were coated by dip coating method. Each tablet was held by forceps and dipped in a 100 ml beaker containing 50 g coating suspension in and out for fifteen times. The coat was dried with a stream of air by using a hair dryer after each dip.

EVALUATION OF THE PREPARED TABLETS

Evaluation of the Physical Properties of Tablets
Thickness and diameter: Ten tablets were randomly selected from both uncoated and coated ones. Their thickness and diameter were measured by Vernier caliper. Standard deviation of ± 5% for thickness of the tablets is considered tolerable. Standard deviation from the average diameter should not exceed ± 5%.

Standard deviation was calculated from the following formula:

\[
SD = \sqrt{\frac{\sum(x_i - x_{ave})^2}{n-1}}
\]

\[
RSD = \frac{100 \cdot SD}{x_{ave}}
\]

Where, \(x_i\): individual tablet weight; \(x_{ave}\): average tablet weight; \(n\): number of tested tablets; RSD: relative standard deviation.

Coating thickness was calculated from diameter measurements. The average diameter of uncoated tablet was subtracted from that of coated tablets and the result was divided by 2.
**Weight variation test:** Twenty coated and twenty uncoated tablets were collected randomly and weighted individually using electronic balance (OHUAS, PA214C). The average weight of the twenty tablets was calculated. Percentage of deviation in weight of each tablet from the average weight was noted.

Standard deviation was calculated from the following formula:

\[
SD = \frac{\sqrt{\sum (x_i - x_{ave})^2}}{n-1}
\]

\[
RSD = 100 \frac{SD}{x_{ave}}
\]

Where, \(x\): individual tablet weight; \(x_{ave}\): average tablet weight; \(n\): number of tested tablets; RSD: relative standard deviation.

**Hardness test:** Hardness of twenty randomly selected tablets of both coated and uncoated ones was determined by using Monsanto hardness tester (Tab Machines, T-MNT-20). Standard deviation from the mean was calculated from the following formula:

\[
SD = \frac{\sqrt{\sum (x_i - x_{ave})^2}}{n-1}
\]

\[
RSD = 100 \frac{SD}{x_{ave}}
\]

Where, \(x\): individual tablet weight; \(x_{ave}\): average tablet weight; \(n\): number of tested tablets; RSD: relative standard deviation.

**Friability test:** Twenty uncoated tablets were selected randomly and weighed. These pre-weighed tablets were subjected to friability testing using Friabilator (Gouming, CS2) for 100 revolutions at 25 rpm. Tablets then were taken, dedusted and weighed again. The friability of the tablets was calculated from the initial and final weight and expressed in percentage by applying the following formula:

\[
\text{Friability}\% = \frac{A - B}{A} \times 100
\]

Where, A=Initial weight of tablets; B=Weight after friability test.

**Evaluation of the coating process efficiency (cpe) of the prepared eudragit® s 100 coated tablets:** Bulk weight of all fifty eight prepared tablets before and after coating was measured. Then, CPE was calculated by applying the following formula:

\[
\text{CPE} = \left[ \frac{W_{tg} \%}{W_{a} \%} \right] \times 100\%
\]

Where, \(W_{tg}\) refers to the theoretical percentage of weight gain and \(W_{a}\) refers to the actual percentage of weight gain, and it is calculated from the following formula:

\[
W_{a} \% = \left[ \frac{(W_{t} - W_{b})}{W_{b}} \right] \times 100
\]

Where, \(W_{tb}\) and \(W_{t}\) are the total mass of the tablets before and after coating respectively.

**Drug content analysis:** Ten uncoated tablets were selected randomly, weighted accurately and tested individually for its drug content. Amount of drug present in each tablet and relative standard deviation were calculated.

Standard deviation was calculated from the following formula:

\[
SD = \frac{\sqrt{\sum (x_i - x_{ave})^2}}{n-1}
\]

\[
RSD = 100 \frac{SD}{x_{ave}}
\]

Where, \(x\): individual tablet weight; \(x_{ave}\): average tablet weight; \(n\): number of tested tablets; RSD: relative standard deviation.

**Determination of swelling index:** The swelling behavior of tablets was studied by keeping it in a petri dish containing pH 7.4 phosphate buffer. Each tablet was withdrawn and soaked with tissue paper, then weighed and returned into the petri dish. The weight was checked at time intervals of hours and continued till twelve hours. Percentage weight gain of each tablet was calculated by the formula:

\[
\text{S.I} = \left( \frac{M_t - M_0}{M_0} \right) \times 100
\]

Where, S.I=swelling index; \(M_t\)=weight of tablet at specific time; \(M_0\)=weight of tablet at zero time.

**Determination of the mucoadhesive property:** The mucoadhesive property of the prepared vancomycin hydrochloride tablets was determined by using the rotating cylinder method. The method was carried out using USP dissolution apparatus type I (Jora-AKI Technology, S031107). An intestinal segment was removed from a goat and fixed on a stainless steel cylinder, the baso-lateral side facing the cylinder. Then the mucoadhesive tablet was pressed on the apical side of the cylinder. The assembly was allowed to run with a rotation speed of 50 rpm. A medium containing 500 ml phosphate buffer having pH 7.4 was used. The time that the tablet takes to detach from the mucosa was observed. The test was performed on six uncoated tablets, since the coating layer will dissolve upon reaching the colon allowing the mucoadhesive tablet to adhere on the mucosal surface. The same procedure was performed on six coated and six uncoated tablets using pH 1.2 buffer.

**In vitro Sustained Release Evaluation Studies**

**In vitro disintegration time:** Random six coated tablets were selected and placed the basket rack assembly USP disintegration apparatus (Gouming,
BJ-2). The test was performed at 37 ± 0.5°C based on a previously published method by Goto T et al. with slight modifications. The media used in Goto T et al. have pH values of 5.5, 6.4, 6.8, 7.4, and 7.5. In this study two types of media were used as follows:

Initial media (pH 1.2 and 6.8 media): The basket rack assembly was set up according to the In vitro disintegration test. This rack was inserted in the simulated gastric fluid that has pH 1.2. After two hours, the basket rack assembly was removed and slightly rinsed with water. Then, the test was repeated by using pH 6.8 simulated intestinal fluids as the immersion fluid for two hours. Simulated gastric fluid and simulated intestinal fluid were prepared according to USP specifications.

Testing medium: After rinsing with water, the basket rack assembly was inserted in pH 7.4 buffer solutions where the disintegration time was noted.

In vitro dissolution study: Assessment of colon delivered formulation release behavior is complicated and not explained completely in USP. To characterize the In vitro release of vancomycin hydrochloride from the prepared tablets, a previously published method using USP dissolution test apparatus II (Electro Lab, TDT08L) with minor modifications was conducted in 900 ml dissolution medium at 37 ± 0.5°C with 100 rpm. The study was performed by placing six coated tablets in six vessels each containing pH 1.2 buffer solution for two hours. After two hours, the previous buffer was replaced by pH 6.8 buffer and the same procedure was repeated for three hours. Finally, pH 6.8 buffer was also replaced by pH 7.4 phosphate buffer in each vessel where the tablets had maintained for 24 hours instead of 19 hours in the reference method. All the buffer solutions were kept at 37 ± 0.5°C. Aliquot of 5 ml was withdrawn from the dissolution medium at specific time intervals and replenished directly with the same volume of fresh medium. Aliquots were filtered with Whatman filter paper before measuring their absorbance using UV spectrophotometer.

Statistical analysis: The results were expressed as mean ± standard deviation (SD) and statistical analysis was performed using SPSS. For thickness, diameter, weight variation and hardness tests, the significance of any difference was evaluated by Paired Samples T Test. Difference was considered to be significant when P<0.05.

RESULTS AND DISCUSSION

The swelling index of tablets was increased with time as a result of hydration rate of chitosan that was increased with time and caused the weight gain of the tablets. Swelling reached its maximum, 105.9% w/w, after ten hours and then decreased after 12 hours to 90.2%, as shown in Table 9. The reduction in the swelling index indicates that the tablets were partially eroded into the medium. This phenomenon is explained by the formation of gel structure on imbibition of more and more water by polymers allowing the buffer to enter through this structure, dissolve vancomycin hydrochloride, and consequently, causing its release by.

The mucoadhesive test on vancomycin hydrochloride tablets in pH 7.4 revealed that the formulation had degraded into small particles under the effect of rotation. But, it had not detached from the mucosa throughout the observation period of 24 hours. Consequently, vancomycin hydrochloride tablets are estimated to exhibit a residence period of not less than 24 hours. In pH 1.2 buffer, coated tablets did not adhere to the mucosal surface due to the presence of the coating layer that isolates mucoadhesive chitosan from the mucosal surface. Uncoated tablets had
adhered then degraded and finally became very fine at the end of 24 hours, due to the solubility of chitosan in acidic pH as shown in Figure 1 and Figure 2. All the twelve tablets had showed an efficient withstanding to disintegration in pH 1.2 and pH 6.8 media. In pH 7.4 buffer, a complete disintegration of the six tablets within one hour was observed. This result meets USP requirements for delayed release enteric coated tablets in the 0.1 N HCl simulated gastric fluid where the six tablets should not show any evidence of cracking, softening or disintegration for one hour. Therefore, it could be postulated that vancomycin hydrochloride tablets can act adequately as a colon delivered formulation.

The drug release in Eudragit® S 100 coated vancomycin hydrochloride tablets during the first five hours of dissolution test in pH 1.2 and 6.8 buffers was retarded. On the contrary, the cumulative release had reached 79.01% ± 3.27 in pH 7.4 buffer, as shown in Table 10 and Figure 3. This release behavior is described by the protection provided by Eudragit® S 100 coating layer in pH 1.2 and 6.8. Upon reaching the colonic pH the coating layer was dissolved exposing the core tablet to the surrounding fluid that caused the tablet to disintegrate into particles due to the presence of starch. The resulted particles can adhere to the mucosal surface of the colon, because of the mucoadhesive property of chitosan. The basic surrounding fluids will cause swelling of particles allowing vancomycin hydrochloride to release in a sustained manner through diffusion effect. Digestion of chitosan by the micro flora should be considered when the tablet undergoes in vivo colonic environment. Thus, chitosan shall break down in the colon releasing the total amount of the drug from the formulation. Variation in pH along the small intestine should be also taken in account where the pH is more than 7 in some parts, which is the preferred dissolution medium for Eudragit® S 100. The formulation was found to release the drug only in a minimal concentration during the first hour in pH 7.4. Consequently, the formulation shall release the majority of the drug upon reaching the colon. The lag time of five hours is considered adequate to ensure the exclusive drug release in the colon.

Comparison with the Commercially Available Vancomycin Hydrochloride Capsules

The commercially available vancomycin hydrochloride Vancozin® (Shire PLC, USA) is hard gelatin capsules. Hard gelatin capsules completely disintegrate within 10 minutes. So, Vancozin® capsules disintegrate faster than the prepared tablets. In the published dissolution study on Vancozin® capsules, the dissolution medium 900 mL of 0.1 N HCl (pH 1.0) simulated gastric fluid was used. The results showed that the capsules released approximately 90% of vancomycin hydrochloride over less than one hour. In this study, vancomycin hydrochloride was not released from the prepared Eudragit® S 100 coated mucoadhesive tablets in the gastric pH buffer. By comparing the dissolution profile of the prepared vancomycin hydrochloride tablets and the marketed capsules, it could be postulated that the prepared tablets would have a sustained release action over 24 hours in the colon, whereas the commercially available capsules have an immediate release action in the stomach.

CONCLUSION

Eudragit® S 100 was able to protect the tablets in the gastric and intestinal pH while exclusively allowed vancomycin hydrochloride to release in 7.4 pH buffer. Chitosan was found to be effective in giving 24 hours of tablet adherence to the inner surface of goat intestinal segment even after degradation of the tablet. Vancomycin hydrochloride released in a sustained manner due to the swelling property of chitosan. Thus, this formulation is considered promising in reducing the dosing frequency from four times a day to once daily dosing. Future studies should include in vivo evaluation to observe the actual behavior in the gastrointestinal tract and confirming the mucoadhesive results using animal model.

CONFLICT OF INTEREST

None

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Figure 1. Coated vancomycin hydrochloride tablet undergoing mucoadhesive property test in pH 1.2 buffer (a) At the beginning of the test the tablet was pressed on the goat intestinal segment fixed into the cylinder, (b) Cylinder started to rotate upon running the dissolution apparatus (c) Immediate detachment of the tablet from the mucosal surface

Figure 2. Uncoated vancomycin hydrochloride tablet undergoing mucoadhesive property test in pH 1.2 buffer (a) At the beginning of the test the tablet was pressed on the goat intestinal segment fixed into the cylinder (b) Cylinder started to rotate upon running the dissolution apparatus (c) Degradation of the tablet after 2 hours (d) Degraded particles started to dissolve after 6 hours (e) Formation of fine particles after 24 hours
Figure 3. Release behavior of six coated vancomycin hydrochloride tablets in three buffer media of pH 1.2, 6.8 and 7.4 in comparison to the control.
Table 1. The Amount of ingredients used in the preparation of vancomycin hydrochloride tablets

| Ingredient                  | Amount per tablet (mg) | Amount for 150 tablets (g) | Function                        |
|-----------------------------|------------------------|-----------------------------|---------------------------------|
| Vancomycin hydrochloride    | 125                    | 22                          | Active ingredient               |
| Chitosan                    | 125                    | 22                          | Mucoadhesive polymer            |
| Starch                      | 52                     | 9.15                        | Granulating agent               |

Table 2. Eudragit® 100 coating suspension ingredients

| Ingredients          | Quantity for preparing 1000 g* | Weighed quantity for preparing 50 g** | Function          |
|----------------------|---------------------------------|--------------------------------------|-------------------|
| Eudragit® S 100      | 62.5                            | 3.125                                | Polymer           |
| Triethyl citrate     | 6.25                            | 0.312                                | Plasticizer       |
| Talc                 | 31.25                           | 1.56                                 | Anti-tacking      |
| Acetone              | 342.9                           | 17.145                               | Diluent           |
| Isopropanol          | 514.2                           | 25.71                                | Diluent           |
| Water                | 42.9                            | 2.145                                | Diluent           |

*Quantities given by Evonik industries to prepare 1000 g of coating suspension  
**Quantities were calculated to prepare 50 g of coating suspension

Table 3. Results of thickness and diameter measurements on ten vancomycin hydrochloride uncoated tablets and ten coated tablets

| Thickness (mm) | Diameter (mm) |
|----------------|---------------|
| Uncoated tablets | Coated tablets | Uncoated tablets | Coated tablets |
| 4.48* ± 2.9%    | 6.53* ± 2.75% | 10.11** ± 1.68% | 12.59** ± 4.6%  |

*p=0.000; **p=0.000

Table 4. Results of weight variation test on twenty vancomycin hydrochloride coated tablets and twenty uncoated tablets

| Average weight of coated tablets (mg) | Average weight of uncoated tablets (mg) |
|---------------------------------------|----------------------------------------|
| 317.45* ± 3.37%                       | 303.02* ± 3.96%                        |

*p=0.001

Table 5. Results of hardness test on twenty vancomycin hydrochloride uncoated tablets and twenty coated tablets

| Serial number | Hardness of uncoated tablets (kg/cm²) | Hardness of coated tablets (kg/cm²) |
|---------------|---------------------------------------|-------------------------------------|
| 1             | 7.2                                   | 6                                   |
| 2             | 6.1                                   | 7.7                                 |
| 3             | 7.3                                   | 7.5                                 |
| 4             | 6.5                                   | 7                                   |
| 5             | 6.8                                   | 6.4                                 |
| 6             | 7                                     | 7.5                                 |
| 7             | 6.4                                   | 7.6                                 |
| 8             | 7                                     | 6.8                                 |
| 9             | 5.7                                   | 7.3                                 |
| 10            | 6.5                                   | 6.7                                 |
| 11            | 7.4                                   | 7.5                                 |
| 12            | 7                                     | 7.4                                 |
| 13            | 5.9                                   | 6.3                                 |
| 14            | 7.3                                   | 7.5                                 |
| 15            | 6.8                                   | 6.9                                 |
### Table 6. Results of friability test on twenty uncoated vancomycin hydrochloride tablets

| Serial number | Bulk weight of 20 tablets before the test (g) | Bulk weight of 20 tablets after the test (g) | Percentage of weight loss (%) |
|---------------|----------------------------------------------|--------------------------------------------|--------------------------------|
| 16            | 6                                            | 6.4                                        |                                 |
| 17            | 6.3                                          | 7.6                                        |                                 |
| 18            | 7.2                                          | 6.3                                        |                                 |
| 19            | 5.6                                          | 6                                          |                                 |
| 20            | 6                                            | 7.2                                        |                                 |
| **Mean**      | **6.6 ± 0.58**                               | **6.98 ± 0.57**                            | **p=0.034**                     |

* p=0.034

### Table 7. Results of coating process efficiency test CPE on 58 vancomycin hydrochloride tablets

| Wt₀ (g) | Wt₁ (g) | Wₜ (g) | Wgₜ (%) | Used amount of coating suspension (g) | Theoretical weight gain (g) | Wg₁ (%) | CPE (%) |
|---------|---------|--------|---------|--------------------------------------|-----------------------------|---------|--------|
| 18.11   | 19.12   | 0.91   | 5.58    | 11.21                                | 6.12                        | 6.18    | 90.3   |

Note: The theoretical weight gain is the weight of the dry substance present in the used amount of the coating suspension; Wt₀: The Total Mass of the Tablets before Coating; Wt₁: The Total Mass of the Tablets after Coating; Wgₜ: The Actual Amount of Weight Gain; Wg₁ (%): The Actual Percentage of Weight Gain; Wg: The Theoretical Percentage of Weight Gain

### Table 8. Results of drug content analysis test on ten uncoated vancomycin hydrochloride tablets

| Serial number | Amount of drug present in each tablet (mg) | Relative amount of drug present in each tablet (%) |
|---------------|---------------------------------------------|---------------------------------------------------|
| 1             | 121.8                                       | 97.44                                             |
| 2             | 118.7                                       | 94.96                                             |
| 3             | 133.5                                       | 106.8                                             |
| 4             | 122.8                                       | 98.24                                             |
| 5             | 127.6                                       | 102.08                                            |
| 6             | 125.3                                       | 100.24                                            |
| 7             | 123.6                                       | 98.88                                             |
| 8             | 129.4                                       | 103.52                                            |
| 9             | 128.9                                       | 103.12                                            |
| 10            | 127.1                                       | 101.68                                            |
| **Mean**      | 125.87 ± 4.29                               | 97.44 ± 3.41                                       | ± 3.41%                      |

### Table 9. Results of swelling index measurements on six uncoated vancomycin hydrochloride tablets

| Serial number | Time (hour) | Average weight of the six tablets at specified time (mg) | Swelling index (SI%) |
|---------------|-------------|----------------------------------------------------------|----------------------|
| 1             | 0           | 303.5 ± 2.56                                             | 0                    |
| 2             | 2           | 410.7 ± 8.4                                              | 35.3                 |
| 3             | 4           | 458.1 ± 6.9                                              | 50.9                 |
| 4             | 6           | 522.9 ± 6.4                                              | 72.3                 |
| 5             | 8           | 577.6 ± 7.6                                              | 90.3                 |
| 6             | 10          | 625.1 ± 9.1                                              | 105.9                |
| 7             | 12          | 577.3 ± 13.9                                             | 90.2                 |
| Serial number | Time (hour) | Cumulative drug release from control* (%) | Average cumulative drug release from six coated tablets (%) |
|---------------|------------|------------------------------------------|----------------------------------------------------------|
| 1             | 0          | 0                                        | 0                                                        |
| 2             | 0.083      | 99                                       | 0                                                        |
| 3             | 0.16       | 103                                      | 0                                                        |
| 4             | 0.25       | 101                                      | 0                                                        |
| 5             | 0.5        | 107                                      | 0                                                        |
| 6             | 1          | 107                                      | 0                                                        |
| 7             | 2          | 107                                      | 0                                                        |
| 8             | 3          | 107                                      | 0                                                        |
| 9             | 4          | 107                                      | 0                                                        |
| 10            | 5          | 107                                      | 0                                                        |
| 11            | 6          | 107                                      | 1.7 ± 0.89                                               |
| 12            | 7          | 107                                      | 8.34 ± 1.79                                              |
| 13            | 8          | 107                                      | 10.99 ± 2.01                                             |
| 14            | 9          | 107                                      | 15.76 ± 2.1                                              |
| 15            | 10         | 107                                      | 20.84 ± 1.72                                             |
| 16            | 11         | 107                                      | 28.48 ± 2.31                                             |
| 17            | 12         | 107                                      | 35.94 ± 2.73                                             |
| 18            | 13         | 107                                      | 42.88 ± 3.06                                             |
| 19            | 21         | 107                                      | 64.61 ± 5.73                                             |
| 20            | 23         | 107                                      | 74.93 ± 4.39                                             |
| 21            | 29         | 107                                      | 79.01 ± 3.27                                             |

*Vancomycin hydrochloride pure powder (125 mg) was used as a control

Table 10. Results of dissolution study on six coated vancomycin hydrochloride tablets