American Journal of Advanced Drug Delivery

http://www.imedpub.com/advanced-drug-delivery/

ISSN: 2321-547X

Original Article

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

Lana Alsharkas[1], Palanirajan Vijayaraj Kumar[1*] and Yeong Siew Wei[2]

[1]Faculty of Pharmaceutical Sciences, Department of Pharmaceutical Technology, UCSI University, Kuala Lumpur, Malaysia
[2]Faculty of Pharmaceutical Sciences, Department of Clinical Pharmacy, UCSI University, Kuala Lumpur, Malaysia

Date of Receipt- 23-11-2018
Date of Revision- 25-11-2018
Date of Acceptance-05-12-2018

Address for Correspondence
Faculty of Pharmaceutical Sciences, Department of Pharmaceutical Technology, UCSI University, Kuala Lumpur, Malaysia.

E-mail:
vijayarajkumar_p@yahoo.com

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[1]. *Clostridium difficile* caused around half a million infections among American population in one year with 15,000 mortalities[2]. 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[3]. 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[4]. 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[4-6].

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[1]. Oral vancomycin Hydrochloride is commercially available in the form of capsules and solutions under different brand names such as Vancocin® and Vancoled®[6]. 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[7]. 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[8]. 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[9]. 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[10]. Polymers like Levan polysaccharides[11] and gelatin[12] 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[13]. More complicated techniques were also used to develop Vancomycin hydrochloride carriers including nanoparticles[14] and microspheres[15].

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 modification16. 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 industries17. 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 (Copen Scientific). 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:

$$\mathbf{SD} = \{\Sigma(\mathbf{xi} - \mathbf{x}_{\mathbf{ave}})^2 / \mathbf{n} - \mathbf{1}\}^{1/2}$$

$$\mathbf{RSD} = \mathbf{100\ SD} / \mathbf{x}_{\mathbf{ave}}$$

Where, x: individual tablet weight; x_{ave}: average tablet weight; n: number of tested tablets; RSD: relative standard deviation[18,19].

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[20].

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:

$$SD = \{\sum(xi - x_{ave})^2 / n - 1\}^{1/2}$$

$$RSD = 100\ SD / x_{ave}$$

Where, x: individual tablet weight; x_{ave}: average tablet weight; n: number of tested tablets; RSD: relative standard deviation[21].

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:

$$SD = \{\sum(xi - x_{ave})^2 / n - 1\}^{1/2}$$

$$RSD = 100\ SD / x_{ave}$$

Where, x: individual tablet weight; x_{ave}: average tablet weight; n: number of tested tablets; RSD: relative standard deviation[22].

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:

$$Friability\% = A - B / A \times 100$$

Where, A=Initial weight of tablets; B=Weight after friability test[23].

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:

$$CPE = [Wg_a\% / Wg_t\%] \times 100\%$$

Where, Wgt refers to the theoretical percentage of weight gain and Wg_a refers to the actual percentage of weight gain, and it is calculated from the following formula:

$$Wg_a\% = [(Wt_a - Wt_b) / Wt_b] \times 100$$

Where, Wtb and Wt_a are the total mass of the tablets before and after coating respectively[24,25].

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:

$$SD = \{\sum(xi - x_{ave})^2 / n - 1\}^{1/2}$$

$$RSD = 100\ SD / x_{ave}$$

Where, x: individual tablet weight; x_{ave}: average tablet weight; n: number of tested tablets; RSD: relative standard deviation[26].

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:

$$S.I = (M_t - M_o) / M_o x\ 100$$

Where, S.I=swelling index; Mt=weight of tablet at specific time; M_0=weight of tablet at zero time[27].

Determination of the mucoadhesive property: The mucoadhesive property of the prepared vancomycin hydrochloride tablets was determined by using the rotating cylinder method[28]. 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[29]. 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[30]. 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[31]. 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 DISSCUSSION

Standard deviations in thickness and diameter of the prepared uncoated and coated vancomycin hydrochloride tablets were found to be less than ± 5% and considered acceptable[32], as shown in Table 3. Calculations showed that the prepared tablets have 1.24 mm coating thickness. Compared with the results in previous literature, the obtained result indicates the ability of Eudragit® S 100 coating layer to deliver the tablets intact to the colon[33]. Standard deviation percentage from the average weight of vancomycin hydrochloride uncoated and coated tablets were of ± 3.96% and ± 3.37% respectively, as shown in Table 4. Considering ± 7.5% deviation limit for tablets ranging from 130 mg to 324 mg in weight, it is concluded that the tablets passed the test[26]. The hardness of uncoated and coated tablets was found to be in the acceptable range (between 4 to 8 kg/cm^2)[19], as shown in Table 5. The friability 0.61% of uncoated tablets in formulation was in acceptable range of less than 1%[23], as shown in Table 6. CPE for the prepared tablets was 90.3%. This result is within the accepted range 79 to 97%[25], as shown in Table 7. The relative drug content for each tablet was ranged from 94.96% to 106.8% ± 3.41%, as shown in Table 8. The obtained result meets USP requirements for dosage uniformity, since the amount of the active ingredient in each of the ten dosage units lies within the range of 85% to 115% of the label claim and relative standard deviation is less than 6%[26].

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[34]. 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[35] 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[36]. 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[37].

Comparison with the Commercially Available Vancomycin Hydrochloride Capsules

The commercially available vancomycin hydrochloride Vancocin® (Shire PLC, USA) is hard gelatin capsules. Hard gelatin capsules completely disintegrate within 10 minutes[38]. So, Vancocin® capsules disintegrate faster than the prepared tablets. In the published dissolution study on Vancocin® capsules, the dissolution medium 900 mL of 0.1 N HCl (pH 1.0) simulated gastric fluid was used[39]. 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

ACKNOWLEDGMENT

The author is grateful to UCSI University, Faculty of Pharmaceutical Sciences, Kuala Lumpur, Malaysia for logistic and financial support.

REFERENCES

1. Burke KE, Lamont JT. *Clostridium difficile* infection: A worldwide disease. Gut and Liver. 2014;8(1):1-6.
2. Centers for Disease Control and Prevention: Nearly half a million of Americans suffered from *Clostridium difficile* infections in a single year. US Department of Health and Human Services. 2015.
3. Ma GK, Brensinger CM, Wu Q, *et al.* Increasing incidence of multiple recurrent *Clostridium difficile*

infection in the United States: A cohort study. Annals of Internal Medicine. 2017;167(3):152-158.

4. Suetens C, Hopkins S, Kolman J, *et al.* Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. ECDC, Stockholm. 2014.
5. Borren NZ, Ghadermarzi S, Hutfless S, *et al.* The emergence of *Clostridium difficile* infection in Asia: A systematic review and meta-analysis of incidence and impact. 2017;12(5):e0176797.
6. PharmaCompass.com: LePro PharmaCompass OPC Private Limited. List of All Manufacturers & Suppliers of Vancomycin Hydrochloride. 2018.
7. Ghugarkar P, Kulat P, Swain K, *et al.* Colon targeted drug delivery system: A review on primary and novel approaches. International Journal of Pharmaceutical Sciences and Research. 2015;6(7):2681-2688.
8. Trivedi HD, Puranik PK. Colon targeted delivery system (CODESTM): Propitous approach in targeting colon. World Journal of Pharmacy and Pharmaceutical Sciences. 2017;6(4):768-789.
9. Amidon S, Brown JE, Dave VS. Colon targeted oral drug delivery systems: Design trends and approaches. AAPS PharmSciTech. 2015;16(4):731-741.
10. Jena GK, Sahoo SK, Patra CN, *et al.* Design, optimization, and evaluation of capecitabine-loaded chitosan microspheres for colon targeting. Asian Journal of Pharmaceutics. 2017;11(3):592-603.
11. Sezer AD, Sarilmiser HK, Rayaman E, *et al.* Development and characterization of Vancomycin-loaded levan-based microparticular system for drug delivery. Pharmaceutical Development and Technology. 2015;22(5):627-634.
12. Zhou J, Fang T, Wang Y, *et al.* The controlled release of vancomycin in gelatin/beta-TCP composite scaffolds. Journal of Biomedical Materials Research. 2012;100A:2295-2301.
13. Godge G, Hiremath S. Development and evaluation of colon targeted drug delivery system by using natural polysaccharides/polymers. Dhaka University Journal of Pharmaceutical Sciences. 2014;13(1):105-114.
14. Esmaeillou M, Zarrini G, Ahangarzadeh RM, *et al.* Vancomycin capped with silver nanoparticles as an antibacterial agent against multi-drug resistance bacteria. Advanced Pharmaceutical Bulletin. 2017;7(3):479-483.
15. Du L, Yang S, Li W, *et al.* Scaffold composed of porous vancomycin-loaded poly(lactide-co-glycolide) microspheres: a controlled-release drug delivery system with shape-memory effect. Mater Sci Eng C Mater Biol Appl. 2017;78:1172-1178.
16. Devi U, Thiruganesh S. Preparation and characterization of chitosan tablets of aceclofenac for colon targeted drug delivery. Asian Journal of Pharmaceutical Research and Health Care. 2010;2(1):46-65.
17. Evonik Industries. Organic coating for gastro-intestinal targeting. Darmstadt, Germany. 2011.
18. Purushothaman M, Kalvimoorthi V. Formulation and evaluation of colon targeted drug delivery system of flurbiprofen using HPMC and K4M sodium alginate as polymeric carrier. International Journal of ChemTech Research. 2017;10(10):156-168.
19. Gad SC. Tablet production: Pharmaceutical Manufacturing Handbook Production and Processes. Joan Wiley and Sons, USA. 2008.
20. Zhong S, Shen Y-C, Ho L, *et al.* Non-destructive quantification of pharmaceutical tablet coatings using terahertz pulsed imaging and optical coherence tomography. Optics and Lasers in Engineering. 2011;49:361-365.
21. Lachman L, Lieberman HA. Weight variation: The Theory and Practice of Industrial Pharmacy. CBS Publishers & Distributers Pvt. Ltd, India. 2009
22. Gad SC. Tablet production: Pharmaceutical Manufacturing Handbook Production and Processes. Joan Wiley and Sons, USA. 2008.
23. The Board of Trusties. USP 24-NF 19: Tablet friability, Philadelphia, PA. 2000
24. Thakkar V, Mahida H, Baldaniya L, *et al.* Risk based approach for design and optimization of novel tablet for type-II diabetes. Pharmaceutical and Biological Evaluations. 2015;2(6):243-263.
25. Porter SC. Scale-up of film coating: Good Manufacturing Practices for Pharmaceuticals. (5th ed), Marcel Dekker, New York. 2001.
26. The Board of Trusties. Uniformity of dosage units: USP 24-NF 19, Philadelphia, PA. 2000.

27. Kaleemullah M, Jiyauddin K, Thiban E, *et al.* Development and evaluation of ketoprofen sustained release matrix tablet using hibiscus rosa-sinensis leaves mucilage. Saudi Pharmaceutical Journal. 2017;25:770-779.

28. Odeniyi MA, Atolagbe F, Aina OO, *et al.* Evaluation of mucoadhesive properties of native and modified starches of the root tubers of cocoyam (Xanthosoma sagittifolium). African Journal of Biomedical Research. 2013;14(3):169-174.

29. Goto T, Tanida N, Yoshinaga T, *et al.* Pharmaceutical design of a novel colon-targeted delivery system using two-layer-coated tablets of three different pharmaceutical formulations, supported by clinical evidence in humans. Journal of Controlled Release. 2004;97:31-42.

30. Stamatopoulos K, Batchelor HK, Simmons MJH. Dissolution profile of theophylline modified release tablets, using a biorelevant dynamic colon model (DCM). European Journal of Pharmaceutics and Biopharmaceutics. 2016;108:9-17.

31. Mehta R, Chawla A, Sharma P, *et al.* Formulation and in vitro evaluation of Eudragit S-100 coated naproxen matrix tablets for colon-targeted drug delivery system. Journal of Advanced Pharmaceutical Technology & Research. 2013;4(4):31-41.

32. Giri TK, Parveen N, Thakur D, *et al.* In vitro evaluation of commercially available enteric coated tablet containing diclofenac sodium. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2012;3:875-81.

33. Sharma P, Chawla A, Pawar P. Design, development, and optimization of polymeric based-colonic drug delivery system of naproxen. The Scientific World Journal. 2013;2013:1-13.

34. Obeidat WM, Abuznait AH, Sallam A-SA. Sustained release tablets containing soluble polymethacrylates: comparison with tableted polymethacrylate IPEC polymers. AAPS PharmSciTech. 2010;11(1):54-63.

35. Chang SH, Lin HTV, Wu GJ, *et al.* pH effects on solubility, zeta potential, and correlation between antibacterial activity and molecular weight of chitosan. Carbohydrate Polymers. 2015;134:74-81.

36. The Board of Trusties. Disintegration: USP 24-NF 19. Philadelphia, PA. 2000.

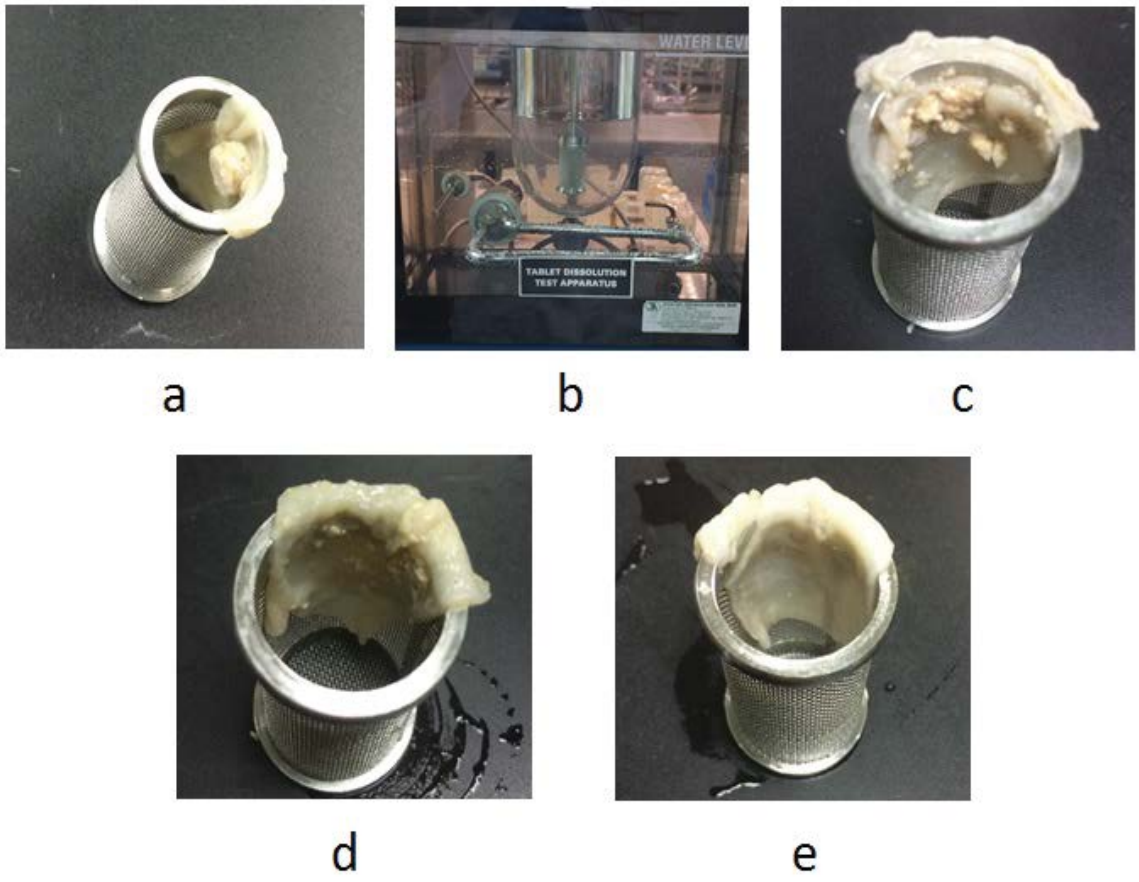
37. Neeraj B, Tangum, Tanvi B, *et al.* Colon targeted drug delivery system: A review. World Journal of Pharmacy and Pharmaceutical Sciences. 2017;6(4):364-377.

38. Stegemann S. Hard gelatin capsules today and tomorrow: Capsugel Library. 1999

39. Chiang C-C, Chen R. Sustained release delivery of antibiotics, USA2009. Orient Pharma, Dounan Town (TW), USA. 2009.

a b c

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



a b c

d e

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

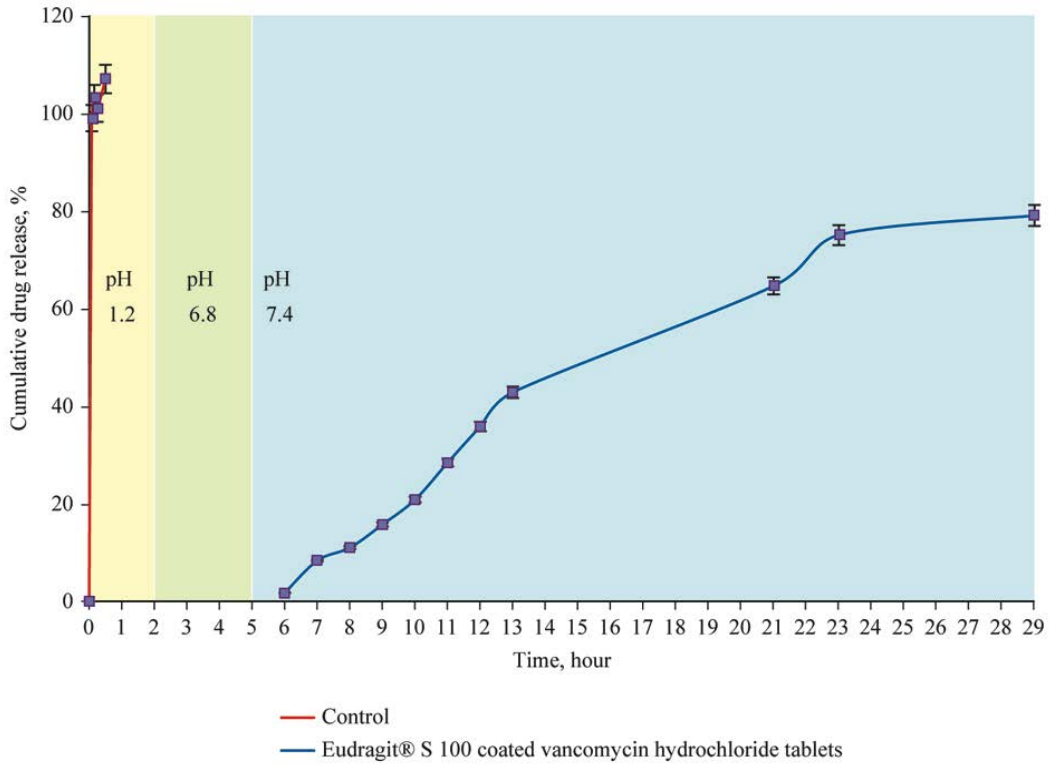


Figure 3. Release behavior of six coated vancomycin hydrochloride tablets in three buffer media of pH 1.2, 6.8 and 7.4 in comparison to the control

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 S® 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

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		

Table 6. Results of friability test on twenty uncoated vancomycin hydrochloride tablets

Bulk weight of 20 tablets before the test (g)	Bulk weight of 20 tablets after the test (g)	Percentage of weight loss (%)
6.047	6.01	0.61

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

Wt_b (g)	Wt_a (g)	W_a (g)	Wg_a (%)	Used amount of coating suspension (g)	Theoretical weight gain (g)	Wg_t (%)	CPE (%)
18.11	19.12	0.91	5.58	11.21	1.121	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; Wt_b: The Total Mass of the Tablets before Coating; Wt_a: The Total Mass of the Tablets after Coating; Wg_a: The Actual Amount of Weight Gain; Wg_a (%): The Actual Percentage of Weight Gain; Wg_t: 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
Relative standard deviation	± 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

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

Serial number	Time (hour)	Cumulative drug release from control* (%)	Average cumulative drug release form 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			