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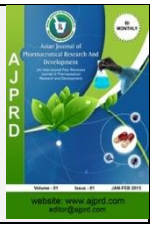

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Review Article

Review on Process Validation of Amoxicillin Potassium Clavulanate Dry Syrup

Anjana Devi*, Sanjay Kumar, Kamal Jeet, Vikash Sharma, Aman Chaudhary

School of Pharmacy, Career Point University, Hamirpur, Himachal Pradesh, INDIA – 176041

A B S T R A C T

Modern medicines for human use are required to comply with specific standards and regulation set forth by the concerned authorities. A simple and sensitive UV spectrophotometric method was developed and validated for the simultaneous determination of Potassium Clavulanate (PC) and Amoxicillin. As complementary of this work, an assay method for amoxicillin and potassium clavulanate mixtures was developed and validated; stress-testing and stability studies of amox/clav mixtures was carried out under specified conditions according to ICH and analyzed by using validated stability-indicating assay and related substances methods. Aim of this study was to test the validation of derivative spectrophotometric method in simultaneous determination the content amoxicillin and clavulanate potassium in dry syrup by derivative spectrophotometric method with zero crossing technique, in buffer phosphate pH 4,4-methanol (91:9) mixture.

Keywords: Amoxicillin, Clavulanate, Spectrophotometer, Dry syrup, Validation.

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*Address for Correspondence:
Anjana Devi, School of Pharmacy, Career Point University, Hamirpur, Himachal Pradesh, India – 176041

INTRODUCTION

Amoxicillin is a penicillin derivative antibiotics used to treat infections of the respiratory tract, gastrointestinal tract and urinary tract. Clavulanate potassium is a form of a salt of clavulanic acid. Clavulanic acid has antimicrobial working very weak, but can inhibit penicillinase of streptococci and β-lactamase as gram-negative microbes to bind to the active center of the enzyme.[1] Therefore, these compounds are used in combination along with β-lactam antibiotics are not stable against β-lactamase1. According to the World Health Organisation (WHO) latest list of Critically Important Antimicrobials for Human Medicine, β-lactam antibiotics with β-lactamase inhibitors are the high priority drugs since they have shown a lower resistance potential and have a high frequency of use for various indications. [2-5] Thereby, it is recommended as a first-choice medicine for treating upper and lower respiratory tract diseases, hospital and community-acquired pneumonia, exacerbations of chronic obstructive pulmonary disease (COPD), etc. [6] The stability of a drug or any product is the time from manufacture and packaging of the product to the time when its chemical activity is not lower than a predetermined level of labelled potency. Its physical characteristics should also be intact.Generally, 90% of labelled potency is generally regarded as the minimum acceptable potency level. [7]A stable drug should also be able to guard against microbial contamination.[8] The parameters that are peculiar to stability include; environmental conditions of storage such as temperature, light, air, humidity and the type of packaging . Pharmacopoeial articles must have the requisite storage conditions on their labelling. [9-10] There is a generalized fact that a combination of drugs have a wider range to treat ailments as compared to the single drug component, therefore industries launches its multicomponent formulations to meet the demand of the market.[11] Pharmaceutical analysis, a branch of pharmacy plays the key role in quality control of pharmaceuticals, through rigid check of raw materials, in process quality of product and finished product.[12] Quality of drugs can only be maintained by developing analytical methods with high degree of

accuracy and precision and should satisfy all other validation parameters. Validation of analytical methods is an important and mandatory aspect of their development or utilization and is widely required on support of industrial product development and regulation so methods developed and utilized for analytical monitoring of products must be validated.[14] Regardless of the various pharmacopeias and reported methods available, development of procedures that is simple, rapid, precise, and economical and gives a clear separation of drugs is barely needed to maintain the quality of pharmaceuticals.[15] It may be a difficult task, but can be achieved by giving a sincere effort. Amoxicillin is a penicillin derivative antibiotics used to treat infections of the respiratory tract, gastrointestinal tract and urinary tract. Clavulanate potassium is a form of a salt of clavulanic acid.[16] Clavulanic acid has antimicrobial working very weak, but can inhibit penicillinase of streptococci and β-lactamase as gram-negative microbes to bind to the active center of the enzyme. It was first introduced into clinical medicine in Europe in 1981 and in United States in 1984.[17] Since its release, combination of amoxicillin and clavulanate has been extensively used in patients of all ages including infants, children and adults.[18] The highly desirable antibacterial spectrum of the drug combined with its favorable pharmacokinetic and safety profiles underscore its rapid acceptance as one of the most commonly prescribed antibiotics. In many countries, the standard regimen for pediatric patients aged over 3 months for the treatment of mild to moderate infections is now amoxicillin/clavulanic acid 25 mg/3.6 mg per kg/day, divided in either two or three doses. For more severe infections such as acute otitis media, the standard regimen is amoxicillin/clavulanic acid 45 mg/6.4 mg per kg/day divided in two doses.[19] Reported data support a nonlinear absorption process for amoxicillin. Saturable transport mechanisms, limited solubility and the existence of an absorption window are possibly involved in the gastrointestinal absorption of amoxicillin leading to a decrease in the pharmacokinetic parameters of this drug. [20] Furthermore, a possible interaction between amoxicillin and clavulanic acid that might decrease the absolute bioavailability of clavulanic acid is reported. [21]

Clavulanic acid is a β-lactamase inhibitor, which prevents the enzymatic destruction of the β-lactam ring of amoxicillin by β-lactamase, and has also shown minimal antibacterial activity1). [22] According to the World Health Organisation's (WHO) latest list of Critically Important Antimicrobials for Human Medicine, β-lactam antibiotics with β-lactamase inhibitors are the high priority drugs since they have shown a lower resistance potential and have a high frequency of use for various indications. Thereby, it is recommended as a fi rst-choice medicine for treating upper and lower respiratory tract diseases, hospital and community-acquired pneumonia, exacerbations of chronic obstructive pulmonary disease (COPD), etc. There is also a possibility of its usage in the treatment of complications of novel virus infections of the respiratory tract and to prevent secondary infection2–4). Amoxicillin still plays a signifi cant role in the treatment of Helicobacter pylori associated gastritis according to the last Maastricht V consensus since its moderate resistance5). It is also used in the treatment of complicated intraabdominal infections, lower urinary tract infections, skin and soft tissue infections, etc [24-26]Clavulanic acid is a β-lactamase inhibitor, which prevents the enzymatic destruction of the β-lactam ring of amoxicillin by β-lactamase, and has also shown minimal antibacterial activity1). According to the World Health Organisation's (WHO) latest list of Critically Important Antimicrobials for Human Medicine, β-lactam antibiotics with β-lactamase inhibitors are the high priority drugs since they have shown a lower resistance potential and have a high frequency of use for various indications. [27] Thereby, it is recommended as a fi rst-choice medicine for treating upper and lower respiratory tract diseases, hospital and community-acquired pneumonia, exacerbations of chronic obstructive pulmonary disease (COPD), etc. There is also a possibility of its usage in the treatment of complications of novel virus infections of the respiratory tract and to prevent secondary infection2–4). Amoxicillin still plays a signifi cant role in the treatment of Helicobacter pylori associated gastritis according to the last Maastricht V consensus since its moderate resistance5). [28] It is also used in the treatment of complicated intraabdominal infections, lower urinary tract infections, skin and soft tissue infections, etc Clavulanic acid is a β-lactamase inhibitor, which prevents the enzymatic destruction of the β-lactam ring of amoxicillin by β-lactamase, and has also shown minimal antibacterial activity1). According to the World Health Organisation (WHO) latest list of Critically Important Antimicrobials for Human Medicine, β-lactam antibiotics with β-lactamase inhibitors are the high priority drugs since they have shown a lower resistance potential and have a high frequency of use for various indications. [29] Thereby, it is recommended as a first-choice medicine for treating upper and lower respiratory tract diseases, hospital and community-acquired pneumonia, exacerbations of chronic obstructive pulmonary disease (COPD), etc. There is also a possibility of its usage in the treatment of complications of novel virus infections of the respiratory tract and to prevent secondary infection2–4). [30] Amoxicillin still plays a signify role in the treatment of Helicobacter pylori associated gastritis according to the last Maastricht V consensus since its moderate resistance5). It is also used in the treatment of complicated intra-abdominal infections, lower urinary tract infections, skin and soft tissue infections.[31-32]

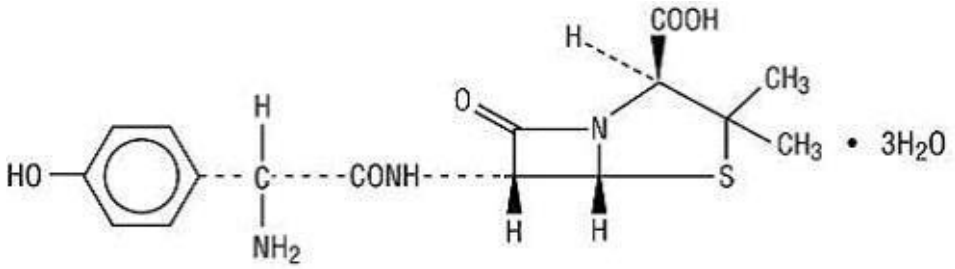
Apparatus

Tools used in this study is UV-Visible spectrophotometer equipped with software Probe 2.42 UV , analytical balance, cuvette, filter paper, rubber ball, spatula, tools-glassware and equipment-other tools required in sample preparation.

Preparation of the Stock Solution Amoxicillin [34]

About 50 mg of amoxicillin were accurately weighed, then diluted with a solvent mixture of Amoxicillin and clavulanate potassium for oral suspension, USP is an oral antibacterial combination consisting of amoxicillin and the beta-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin, USP is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. Chemically, amoxicillin is (2S, 5R, 6R)-6-[(R)-(-)-2-amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-

azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate and may be represented structurally as:



C 16H 19N 3O 5S•3H 2O M.W. 419.45

Product Specification

- Composition – Amoxicillin 400mg / Clavulanate Potassium 57mg/5ml
- Common Name – Amoxicillin Clavulanate Potassium
- Brand Name – CLEDOMOX
- Trade Name – Co-Amoxiclav, Amoxiclav
- Available Strength – 457mg/5ml
- Therapeutic use – Antibiotic
- Packing – 1 Dry Syrup & 1 Sterile Water for Reconstitution

Product Description

Cledomox 457 DS comes in a dosage combination of Amoxicillin 400mg and Potassium Clavulanate 57mg per 5ml of reconstituted syrup. Medopharm is a leading Amoxicillin and Clavunate Potassium tablets manufacturer and supplier in India.

Cledomox 457 DS acts as an antibiotic and helps to fight against bacteria, particularly in the treatment of Respiratory Tract Infections, Urinary Tract Infections, Skin Infections, and Dental Infections.

Cledomox 457 DS – The truly International Co-Amoxiclav

Co-amoxiclav is the scientific approved name for the combination of antibiotic containing amoxicillin trihydrate, which is a β-lactam antibiotic and potassium clavulanate which is a β-lactamase inhibitor. Cledomox 457 DS is a truly international Co-Amoxiclav that is used to treat bacterial infections in children.

- Recurrent Lower Respiratory Infection
- Upper Respiratory Tract Infection
- Acute Otitis Media
- Pyrexia of Unknown Origin

Cledomox 457 DS – The Best Co-Amoxiclav[36]

- Drug of Choice in Recurrent LRTI
- Manufactured in UK MHRA Accredited Plant
- Dedicated Beta-Lactam Facility
- Extra Dry Grade Amoxicillin for Greater Stability
- Sterile Water to Reconstitute
- Retains Potency till Consumption

Preparation of the Stock Solution Clavulanate Potassium

About 50 mg of clavulanate potassium were accurately weighed, then diluted with a solvent mixture of phosphate buffer pH 4.4-methanol (91:9) in a 50 mL flask and paid back with the same solvent to obtain a solution with a concentration of 1000 µg/mL (Standard Solution I). From this solution pipette 10 mL, was put into a 100 mL flask, diluted with a mixture of phosphate buffer pH 4.4-methanol (91:9) to mark the line, shaken until homogeneous in order to obtain a solution with a concentration of 100 µg/mL (Standard Solution II).

Preparation Maximum Absorption Spectrum Amoxicillin

Taken as much as 2.0 mL of amoxicillin concentration 100 µg/mL was then inserted into a 10 mL flask and then diluted with buffer phosphate pH 4,4-methanol (91:9) mixture solvent until the line mark, then shaken until to obtain a homogeneous amoxicillin solution with a concentration of 20 µg/mL. Absorbance was measured at a wavelength of 200-400 nm.

Preparation Maximum Absorption Spectrum Clavulanate Potassium

Taken as much as 1.65 mL of clavulanate potassium concentration 100 µg/mL was then inserted into the 10 mL flask to be diluted with buffer phosphate pH 4,4-methanol (91:9) mixture solvent until the line mark, then shaken until homogeneous to obtain a solution with a concentration of 16.5 µg/mL . Absorbance was measured at a wavelength of 200-400 nm.

Preparation Derivative Absorption Spectrum Amoxicillin

Taken by 1.0 mL; 1.5 mL; 2.0 mL; 2.5 mL; 3.0 mL and 3.5 mL of stock solution amoxicillin concentration 100 µg/mL (SS II), then each put in a 10 mL flask to be diluted with the solvent buffer phosphate pH 4,4-methanol (91:9) mixture. Then shaken until homogeneous to obtain a solution with a concentration of 10 µg/mL; 15 µg/mL; 20 µg/mL; 25 µg/mL; 30 µg/mL and 35 µg/mL Then made the absorption spectrum, then the absorption spectrum is transformed into a first derivative absorption spectrum and the second derivative at a wavelength of 200-400 nm with $\Delta\lambda$=2nm.

Preparation Derivative Absorption Spectrum Clavulanate Potassium

Taken by 0.85 mL; 1.25 mL; 1.65 mL; 2.05 mL; 2.45 and 2.65 mL of stock solution clavulanate potassium concentration 100 µg/mL (SS II), then each put in a 10 mL flask to be diluted with the solvent buffer phosphate pH 4,4-methanol (91:9) mixture. Then shaken until homogeneous to obtain a solution with a concentration of 0.85 µg/mL; 1.25 µg/mL; 1.65 µg/mL; 2.05 µg/mL; 2.45 µg/mL and 2.85 µg/mL.

Determination of Amoxicillin and Clavulanate Potassium levels in Dry Syrup

One bottle of dry syrup powder weighed. Then weighed carefully the amount of powder equivalent to 50 mg of amoxicillin and then the weight of which weighed analyte equivalent of 50 mg of amoxicillin clavulanate potassium is calculated equality contained therein (powder weighing as much as six times repetition), put in a 50 mL flask, added phosphate buffer pH 4.4-methanol (91:9) to line sign while shaken. The solution is then homogenized with an ultrasonic stirrer for 15 minutes. The solution is then filtered, approximately 10 mL of the first filtrate discarded. The filtrate subsequently accommodated. Then from this filtrate solution, 0.35 mL pipette and put into a flask and diluted with 10 mL of phosphate buffer pH 4.4- methanol (91:9) to mark the line (concentration of 35 µg/mL for amoxycillin and concentrations of 8,5 µg/mL for clavulanate potassium). The solution is measured at the second derivative absorbance at a wavelength analysis has been determined to amoxicillin and clavulanate potassium. Furthermore, the absorbance was measured at a wavelength of 200-400 nm, then the absorption spectrum is transformed into a second derivative Siti Morin Sinaga et al /Int.J. PharmTech Res. 2016,9(1),pp 79-89. 83 absorption spectrum Δλ 2 nm in wavelength analysis of amoxicillin and clavulanate potassium respectively 239.00 nm and 313.20 nm. Validation Test Accuracy Test Accuracy test was conducted by the addition of raw materials is to make three samples with the analyte concentration of a specific range of 80%, 100%, 120%. Where in each specific range is used 70% and 30% of raw samples to be added and then mix the sample and standard absorbance was measured at a wavelength of 200-400 nm, then the absorption spectrum is transformed into a second derivative absorption spectrum Δλ 2 nm in wavelength analysis of amoxicillin and clavulanate potassium respectively 239.00 nm and 313.20 nm. Percentage recovery can be calculated by the formula10 . % Recovery = 100 % Description: CF = concentration of the substance after the addition of raw materials CA = concentration of the substance before adding the raw materials C *A = number of raw added Precision Test Precision is measured as relative standard deviation or coefficient of variation.[37] Precision measured indicates the degree of fit between the individual test results when a method is repeated for a homogeneous sample. Relative standard deviation value which meets the requirements showed a precision method performed. Based on the results of recovery prescribed amoxicillin and clavulanate potassium standard deviation amoxicillin and clavulanate potassium of the formula: SD = Description: X = The number of substances in the sample X = Number of substances sample average n = Number of repetitions Standard Deviation (SD) obtained based on the value, calculated relative standard deviation of amoxicillin and clavulanate potassium by the formula: RSD = x 100% Description: X = Number of substances sample average SD = Standard deviation RSD = Relative Standard. Measurement of the concentration of amoxicillin in the 35 µg/mL, where as for clavulanate potassium at a concentration of 8.5 µg/mL and. Based on the research results, obtained the maximum wavelength amoxicillin and clavulanate potassium at 239.00 nm and 313.20 nm respectively. [32]

Validation Test

Accuracy Test

Accuracy test was conducted by the addition of raw materials is to make three samples with the analyte concentration of a specific range of 80%, 100%, 120%. [43] Where in each specific range is used 70% and 30% of raw samples to be added and then mix the sample and standard absorbance was measured at a wavelength of 200-400 nm, then the absorption spectrum is transformed into a second derivative absorption spectrum Δλ 2 nm in wavelength analysis of amoxicillin and clavulanate potassium respectively 239.00 nm and 313.20 nm. [34]

Percentage recovery can be calculated by the formula10 . % Recovery = 100 % Description: CF = concentration of the substance after the addition of raw materials CA = concentration of the substance before adding the raw materials C *A = number of raw added Precision Test Precision is measured as relative standard deviation or coefficient of variation. Precision measured indicates the degree of fit between the individual test results when a method is repeated for a homogeneous sample. [35] Relative standard deviation value which meets the requirements showed a precision method performed. Based on the results of recovery prescribed amoxicillin and clavulanate potassium standard deviation amoxicillin and clavulanate potassium of the formula: SD = Description: X = The number of substances in the sample X = Number of substances sample average n = Number of repetitions Standart Deviation (SD) obtained based on the value, calculated relative standard deviation of amoxicillin and clavulanate potassium by the formula: RSD = x 100% Description: X = Number of substances sample average SD = Standard deviation RSD = Relative Standard Deviation [36-37]

Sample preparation and estimation of amoxicillin and clavulanic acid

Eighteen samples of amoxicillin-clavulanate potassium (228.5mg/5ml) oral suspension were freshly reconstituted with table water. The reconstituted preparations were distributed into groups (n=6) and were subjected to three different simulated conditions that represent the different in-home storage conditions. [38] Samples stored under condition A were refrigerated with fluctuating temperatures between 5-25°C due to power outages during the period. Samples in condition B were stored inside a cupboard with room temperatures of 27-29°C and samples stored under condition C were submerged in a bowl filled water at room temperatures of 27-29°C for a period of 10 days. A room thermometer was used to assess room temperature and

temperature of fridge during power outages[39] 5ml of each sample was collected, diluted to a solution containing 100µg/ml of amoxicillin and 20µg/ml of clavulanic acid and filtered using 0.45µm syringe filter on each day of the analysis. The filtrate was injected into HPLC and the respective peak areas were plotted .into calibration equation .The concentrations of amoxicillin and clavulanic acid remaining after storage on day 1, 5, 7 and10 were extrapolated from the line of regression. The percentage assay purities were then evaluated.

Sample preparation for HPLC injection .

Amoxicillin Each serum sample was transferred to a filter tube for centrifugation at 5 °C and 5000×g for 40 min. A 20 l aliquot from the filtrated liquid was injected to the chromatograph by an autosampler. Wavelength of UV detection was set at 229 nm.[38] The mobile phase was pumped at a flow rate of 0.2 ml/min. and the run time was regulated at 12 min. 2.7.2. Clavulanic acid Each serum sample was transferred to a filter tube for centrifugation at 5 °C and 5000×g for 40 min. A 100 l aliquot of imidazole buffer was added to 400 l of the filtrated sample. The obtained solutions were vortxed and kept at 30 °C for 13 min. Then, 10 l was injected into the column by auto sampler. The wavelength of UV detection was set at 320 nm and flow rate of mobile phase was 0.1 ml/min. Run time was regulated at 10 min.[39-40]

CONCLUSION

Based on the research conducted, it can be concluded spectrophotometric method with zero crossing derivatives can be used to set the levels of amoxicillin and clavulanate potassium. Levels of amoxicillin and clavulanate potassium in dry syrup preparation Clavamox® and Claneksi® meet the requirements of an oral suspension levels according to the Farmakope Indonesia edisi V11. Validation test conducted on dry syrups Clavamox® showed that the spectrophotometric method of derivatives meet the requirements validation, which includes parameters of accuracy and precision. Pharmacokinetic parameters of amoxicillin and clavulanic acid in formulations used in this study were similar to previously published data [17, 18]. Furthermore, the new formulations of Co-Amoxiclav® (312 and 156 mg/5 ml) suspensions is bioequivalent to the reference formulation (Augmentin® 312 mg/5 ml) manufactured by Beecham, England.

The HPLC procedure was verified to further implementation into the SPhU monograph, and the UPLC procedure was fully validated. Both methods have met all requirements, and could be recommended for applying in the analysis of medicines containing amoxicillin and potassium clavulanate. The methods were compared in terms of environmental friendliness. In general, both methods have shown themselves to be ecofriendly, although the UPLC method showed a slightly better result. A Passing-Bablok regression method comparison showed the similarity of methods in obtained results. Both methods are reliable and could be used in laboratories during the quality control process.

Quality control is a concept that strives to produce an ideal product by assuring quality, safety, and effectiveness and designed to prevent and eliminate errors at different stages of production and after the production, therefore analysis of product is the key for maintaining the desired characteristics of product. Quality of pharmaceuticals has to be monitored from the very beginning i.e. from raw material to the end i.e. finished product, including marketing surveillance by analytical techniques.

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