CLEANING VALIDATION PROCEDURE OF MANUFACTURING EQUIPMENT AFTER PRODUCTION OF SULFAMETHOXAZOLE AND TRIMETHOPRIME TABLETS

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Abstract - The purpose of this work is to present a validation protocol of the cleaning method at the end ofcontained Sulfamethoxazole and Thrimetoprimemanufacturing tablets. After cleaning, the new tablets to be produced contained Amoxycilline as Active Ingredient Products. Acceptance criteria used health-based data such as Maximum Allowable Carryover (MACO) and No Observable Effect Level (NOEL).Validation of the cleaning method was carried out using swab technique. HPLC was applied as analytical method with Symmetry C18 column and UV detection at 254 mm. Validation parameters were : recovery from spiked swab media, precision, linearity/range, limit of detection and limit of quantitation, specificity, stability of samples and solutions, system suitability criteria, robustness.

Keywords - Cleaning, Sulfamethoxazole and Thrimetoprime, Amoxycilline, Swab, Validation, HPLC.

I. INTRODUCTION

This work describes the principles to be applied to the development, validation of analytical methods, which are used to evaluate the cleanliness of processing equipment used to manufacture pharmaceutical materials.Swab analysis is employed to confirm the cleanliness of processing. FDA defines the recommended criteria for development and validation of swab method used to confirm cleanliness of processing equipment and covers both limit test and quantitative methodologies. Equipment to be cleaned was used to produce Sulfamethoxazole and Thrimetoprime Tablets, it will be used to produceAmoxycilline after cleaning. HPLC is the analytical method employed to quantify Sulfamethoxazole and Thrimetoprime after using swab.Limits and acceptance criteria should be :

• Practical
• Verifiable
• Achievable
• Scientifically sound

Residues should be :

• Active Drug
• Cleaning agents
• Microbial
• Endotoxin
• Toxic Excipients
• Degradants

II. ACCEPTANCE CRITERIA

Acceptance criteria using health-based data is applied in this study. In the beginning, classical parameters must be calculated. First, the Maximum Allowable Carryover (MACO) should be based upon the Acceptable Daily Exposure (ADE) when this data is available. Calculations of NOEL and MACO are important factors in cleaning validation of pharmaceutical equipments.NOEL is “No Observed Effect Level” of any pharmaceutical drug. It is determined to calculate the MACO (Maximum Allowable Carry Over) in cleaningvalidation. NOEL is the amount of drug in mg that does not have any effect on the human health.NOEL is calculated by using Lethal Dose 50 (LD50) of the drug.

NOEL = (LD50 x 70kg)/2000
70kg – Average adult weight
2000 – Constant
For Sulfamethoxazole and Thrimetoprim : LD50 are6370 and 2764 mg/kg respectively, their NOEL will be calculated as below.
NOEL = 6370x70/2000= 222.95 mg
NOEL = 2764 x70/2000= 96.74 mg
The value of NOEL is used to calculate the MACO (Maximum Allowable Carry Over) as follow :
MACO = (NOEL x MBS)/ (SF x TDD)
Where,
MBS – Maximum Batch Size
SF – Safety Factor (1000 for oral drugs)
TDD – Total Daily Dose of Next Product
In our case, MBS = 100 kg, TDD of Amoxycillin= 2000 mg
MACO = 14866 mg = 14.9 g and 6.5 g for Sulfamethoxazole and Trimethoprime respectively.
It shows that the drugs with 6370 and 2764 mg/kg as DL50 should not be carried over more than 14.9gand6.5g in next batch having 100 kg batch size.This values correspond to 14.9 and 6.5 ppm. This criterion is used to calculate the cleaning validation limits.

Health authorities do not require shared equipment to be cleaned to 10 ppm of the next product.The 10-ppm criterion for the acceptable concentration of potential API in cleaning validation is no longer necessary and a risk-based approach should be universally adopted (1-11).

III. EXPERIMENTAL

3.1. The Swabbing Method

This method is based on the physical removal of residue left over on a piece of equipmentafter it has been cleaned and dried. A swab wetted with a solvent is rubbed over a previously determined sample surface area to remove any potential residue, and thereafterextracted into a known volume of solvent in which the contaminant active ingredient residue is soluble. The amount of contaminant per swab is then determined byan analytical method of adequate sensitivity.

Sample surface is 10 X 10 cm², swab surface (Origin : Texwipe alpha swabs) of 5 cm square is used.Prior to swabbing, the swab media is typically moistened with extraction ethanol. The solvent is selected based on known contaminant solubility and stability along with consideration of operator safety- and compatibility of the solvent with the technique to be employed for analysis.The area to be sampled- should be the wiped in two directions in a systematic way to insure complete coverage. See figure 1 below.

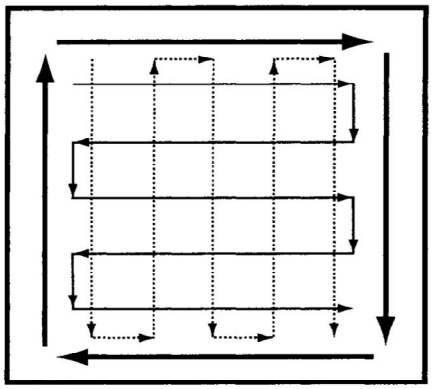


Fig.1. Swab Sampling

Sample preparation involves an extraction step to remove the adsorbed Sulfamethoxazole and Thrimetoprime from the swab. 5 ml of ethanol is used.Sonication is used for extraction of swabs.

3.2. High performance liquid chromatography (HPLC).

A Waters chromatograph with a 600E pump, 7625i Rheodyne injector with a 20 µL sample loop, and a Waters diode array detector 996 are used. Separations are carried out on a Symmetry C18 column (150 mm × 4.6 mm) from Waters (USA). Mobile phase consisted of 700 ml of water, 200 ml of acetonitrile and 1 ml of triethylamine in a 1000 ml flask, adjust with 0.2N NaOH solution, or dilute with glacial acetic acid 1/100 to pH = 5.9 ± 0.1. Fill with water. Filter with a 0.45 µm membrane and degass.

Flow rate is fixed at 1 mL min^{-1}. Data are collected using the Millenium 32 program (Waters) Quantitation is carried out at 254nm.

Standard Solution: Dissolve an exactly weighed amount of trimethoprim and standard sulfamethoxazole in methanol, dilute with the same solvent to obtain a solution containing 0.32 mg / ml and 1.6 mg / ml, respectively. Take 5 ml of this solution in a 50 ml flask, complete with the mobile phase, mix to obtain a standard solution of 0.032 mg / trimethoprime et 0.16 mg/ml of sulfamethoxazole.

Swab Solution:3 swabs are each impregnated with 0.1 ml of solvent (ethanol) and serve to wipe the surface 10 * 10 cm as described in Fig.1. Introduce the 3 swabs in an amber bottle. Subject it to a stream of nitrogen to evaporate the solvent. Take up with 10 ml of mobile phase. Stir magnetically for 15 min.Take 2 ml, filter, inject 20µl. The same procedure without wiping is applied to obtain a blank solution.

3.3. Validation procedure

Validation of swabbing method is carried out with the determination of different parameters:

Specificity:samples with and without the analyte are tested.

Linearity: 5 concentrations across the range of the procedure (dilute standard stock solution or prepare synthetic mixtures) are measured. Plot the signals as function of concentration and evaluate the plot.

- Accuracy : 9 determinations over a minimum of 3 concentration levels covering the specific range are performed.
- Precision: A minimum of 6 determinations at 100 % of the test concentration are performed.
- Intermediate Precision: is established on different days, for different analysts.
- Limit of detection (LOD) and quantification (LOQ) : They are calculated from signal to noise (s/n), LOD = 3.3 x s/n ; LOQ = 10 x s/n.

IV. RESULTS AND DISCUSSION

Validation procedure described in 3.3 is applied.

Specificity of the method is determined byanalysing blank and real swab solutions. Fig. 2 shows there corresponding chromatograms.No substances interfered with the assay are observed.

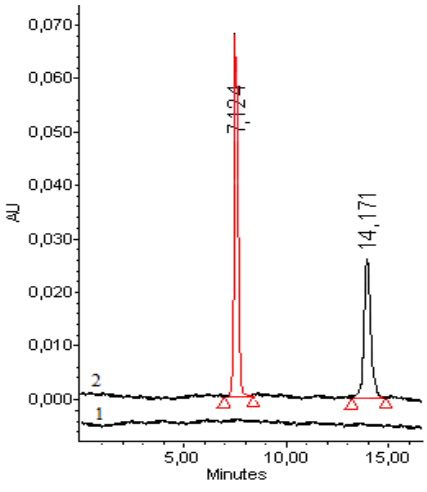


Fig.1. Typical chromatogram of blank (1) and sample solutions (sulfamethoxazole 7 min, Trimethoprime 14 min).

Linearity is expressed vith calibration curve obtained by the least-squares linearregression analysis of the peak area of analytevs. its concentration (mg L^{-1}). For the two compounds, the curves are linear as shown in Table 1. Other validation parameters appearing in Table 1 are convenient.

Table 1. Validation parameters

	Sulfamethoxazole	Trimethoprim
linearity slope	22945	8184
intercept	1295	358
Correlation coefficient	0.999	0.998
Range mg.L^{-1}	1-20	1-10
Accuracy %	2.54	4.23
Precision %	3.81	3.98
Intermediate precision	4.11	4.32
LODmg.L^{-1}	0.227	0.045
LOQmg.L^{-1}	0.750	0.150

The proposed method was applied successfully and many times to clean the production line of tablets.

CONCLUSION

In this study, NOEL (No Observed Effect Level) and MACO(Maximum Allowable Carry Over) arethe important factors used as acceptance criteria in cleaning validation of pharmaceutical equipment from Sulfamethoxazole and Trimethoprime. Swab method is used and the samples are analyzed by HPLC with Symmetry C18 column (150 mm × 4.6 mm) and UV detection. The technique is completelyvalidated.

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