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Cleaning Validation and Analytical Method Development for Estimation of Terbutaline Sulphate by HPLC

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ABSTRACT

The cleaning validation is to validate whether the cleaning procedure used at the liquid oral department can limit the drug residues to a predetermined acceptable level. The cleaning validation is to address the amount of cross-contamination, which is a major concern about multipurpose pharmaceutical formulation plants. This study addressed difficulties in swab recovery studies. The candidate drug, Terbutaline sulfate, is selected as per the MACO study employed in the liquid oral production line. Terbutaline sulphate has a MACO value of 131.25 mg, is found to contaminate more in the group. The HPLC method is developed and validated by using various method validation parameters like accuracy, precision, specificity, linearity and range, intermediate precision, and robustness. The recovery studies are carried out using a Texwipe swab made of the polyester tip. Swabbing time and swabbing pattern are developed and the method is validated by using the method validation parameters as mentioned earlier.

INTRODUCTION:

Cleaning Validation[1] is a documented process that proves the effectiveness and consistency in the cleaning of pharmaceutical equipment. It is necessary to have effective cleaning programs in place because of the regulatory and compliance requirements to do so. There is however more fundamental reason and that is a moral requirement to produce products that are as pure and free of contamination to the extent that is possible and feasible. Cleaning programs are necessary to prevent manufactured products from being contaminated. There are basically two types of contamination[2,3].

- Cross-contamination of one product into another.
- Product contamination by foreign material.

Cross-contamination is usually in terms of an active ingredient from one product carrying over into a subsequently manufactured product. However, the carryover of other product components such as excipients can also be problematic and may degrade the final quality of the product[3].

By definition, Validation requires the accumulation of documentary evidence relating to a process, item of equipment, or facility. This is achieved utilizing "Validation Protocol", which details the tests to be carried out, the frequency of testing, and the results accepted (the acceptance criteria). There are different approaches for validation, Prospective Validation, Concurrent process Validation, Retrospective Validation and Re-Validation[4,5].

Prospective Validation is defined as the establishment of documented evidence that a system does what it purports to do based on a pre-planned protocol. This Validation is usually carried out before the introduction of new drugs and their manufacturing process and this approach to Validation is normally undertaken whenever a new formula, process or facility must be validated before routine pharmaceutical formulation commences. Validation of process by this approach often leads to transfer of the manufacturing process from the development function to production[4,5].

Concurrent Validation is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price. This Validation involves in-

process monitoring of critical processing steps and product testing and this helps to generate documented evidence to show that the production process is in a state of control[4].

Retrospective Validation is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control[4].

Re-validation is the repetition of a Validation process[6-13]. This is carried out when there is any change or replacement in formulation, equipment plant or site location, batch size and in the case of sequential batches that do not meet product and process specifications.

MATERIALS AND EQUIPMENT USED

Chemicals: (HPLC grade)

Methanol, Hexane sulphonic acid sodium salt, Ammonium formate, Formic acid, Millipore water and Terbutaline Sulphate WRS.

Instrument: Instrument: HPLC Agilent 1100 series, Detector wavelength is 276nm, Column used is Kromasal 100 A-5C18, 5 µm, 120 x 4.6 mm and Mobile phase is as follows- Dissolve 4.23 g of Hexane sulphate acid sodium salt in 750 ml of 0.05 M of Ammonium Formate solution and add 250ml Methanol and mix. Filter the solution through 0.45 µ membrane filter and degas in the sonicator for two minutes.

0.05 M Ammonium Formate solution: Weigh 3.15 g of Ammonium Formate into a 1000 ml volumetric flask. Add 975 ml of water. Adjust pH to 3.0±0.1by Formic acid and dilute to volume with Milli-Q water and mix. The flow rate is 1.2 ml/minute, with an Injection volume: of 20 µl.

Selection of column

Kromasil 100 A-5C18, 5 µm, 120 x 4.6 mm

Selection of mobile phase

For the selection of the mobile phase, the following solvents were taken into consideration

- Methanol.
- Hexane sulphonic acid sodium salt with Ammonium phosphate solution of PH-3.0.

Different proportions of solvents were mixed and run for the analysis until good resolution of the analyte chromatogram was obtained. It was found that Methanol and Hexane sulphonic acid sodium salt with Ammonium phosphate solution in 25:75 ratio provided better resolution.

λ- Max determination

It was found that the λ- max of the analyte Terbutaline Sulphate in methanol was 276 nm.

Flow rate

The flow rate was set to 1.2 ml per minute throughout the experimental analysis.

Retention time

The retention time of the analyte Terbutaline Sulphate was about 11 minutes at the flow rate of 1.2 ml per minute.

VALIDATION OF ANALYTICAL METHOD DEVELOPED:-

The method developed for the analysis of Terbutaline sulphate was validated by using various parameters: -

- Accuracy
- Precision
- Linearity
- Specificity
- Limit of detection
- Limit of quantification
- Intermediate precision

- Robustness

An analytical method for the determination of Terbutaline sulphate was developed for the cleaning validation studies. The developed analytical method for Terbutaline sulphate was validated by the validation parameters like specificity, precision, accuracy, linearity and range, intermediate precision, ruggedness, robustness. Moreover, data obtained are found to be within the intended specifications. In addition, the method can be used for routine validation analysis.

The recovery studies for Terbutaline sulphate are carried out using the swab technique. The swabs used are Texwipe made of the polyester tip. The swabs are able to recover more than 90% of the spiked amount from the stainless steel -316 coupons. , which are within the acceptance criteria.

The cleaning validation is carried out on the equipment in the production line, which is common for the entire manufacturing operation. Swabs and rinse samples are collected from hot spots on the contact surfaces of the equipment. The samples are analyzed by using the validated HPLC method. However, in the retention time of Terbutaline sulphate, no characteristic peaks are detected. Therefore, the concentration of the drug, which could be present, was taken as less than 0.15 ppm (LOD concentration). The amount, which can be transferred into the next batch, is found to be 4.50 mG as per the swab technique and 0.46 mG for the rinse sample analysis. The values are well within the acceptable limits of MACO (131.25 mG). Thus, the cleaning procedure followed in the liquid oral department is capable of limiting the residues to a predetermined acceptance level for a continuous process.

SUMMARY

The worst case is selected as per the MACO studies carried out on the products in the liquid oral production line and the difficulty in cleaning. Bricanyl syrup, which contains Terbutaline sulphate, is found to be the product, which can contaminate more among the group. The MACO value for Terbutaline sulphate was found to be 131.25 MG for the entire contact surface area.

TABLE NO. 1: SUMMARIZED RESULTS OF ANALYTICAL METHOD VALIDATION OF TERBUTALINE SULPHATE

Sr. No	Parameters	Acceptance criteria	RSD	Results
1	Specificity	A placebo should not interfere in the analysis	-	Complied
2	Limit of Detection (LOD)	The signal to noise ratio should be 3:1	-	The LOD = 0.15 ppm/ml S/N Ratio = 3:1
3	Limit of Quantification	The signal to noise ratio should be 10:1 and RSD should be within 3 %	1.06	The method was found to comply.
4	Precision	Relative standard deviation (RSD) for three injections each of the standard solution S_1, S_2, S_3 should not be more than 3.0%	0.23	The value RSD was well under the limits. .
5	Linearity and Range	Percentage curve fitting should not be less than 100% across the range of 0.5 – 48µg/ml	-	The percentage curve fitting was found to be 100%.
6	Accuracy	Should be accurate across 97- 103% recovery	-	The method was found to be accurate across 97-103% of the recovery limit.
7	Intermediate precision	The difference in RSD between the two analysts should not be more than 2%	0.16	Compiled
8	Robustness	Relative standard deviation (RSD) for three injections of	0.49	The method was found to comply.

		the standard solution S_1, S_2, S_3 should not be more than 3.0%		

TABLE NO. 2: SUMMARISED RESULTS FOR SWAB RECOVERY STUDY

Sr. No.	Parameters	Acceptance criteria	RSD	Results
1	Specificity	A placebo should not interfere in the analysis	-	Complied
2	Limit of Detection (LOD)	The signal to noise ratio should be 3:1	-	The LOD = 0.15 ppm/ml S/N Ratio = 3:1
3	Limit of Quantification	The signal to noise ratio should be 10:1 and RSD should be within 3 %	2.6 %	The method was found to comply.
4	Precision	Relative standard deviation (RSD) for two injections each of the standard solution S_1, S_2, should not be more than 3.0%	0.24	The value RSD was well under the limits.
5	Linearity and Range	Percentage curve fitting should not be less than 100% across the range of 0.5 – 48µg/ml	-	The percentage curve fitting was found to be 100%.
6	Accuracy	Should be able to recover amount less not than 90%	-	The method was found to be accurate for the recovery

7	Intermediate precision	The difference in RSD between the two analysts should not be more than 2%	0.14	Compiled

TABLE NO. 3: SUMMARISED RESULTS OF CLEANING VALIDATION

Sr. No.	Equipment	Sampling method	Acceptance criteria (mg)	MACO (ppm/equipment)	Total residual carry over(mg)	Result
1	Jacketed Tank	**Swab Method**	**131.25**	**977.825**	**4.50**	It was found to be within the acceptance limit. So the cleaning procedure was found to be validated.
2	Non Jacketed Tank			**1855.365**		
3	Sparkler Pressure Filter			**78.54**		
4	Cylindrical Holding Tank			**319.455**		
5	Rectangular Holding Tank			**111.2925**		
6	Alfa Helical Pump			**20.108**		
7	Roto Pump			**5.198**		
8	Filling Machine			**31.185**		

TABLE NO. 4

Sr. No.	Equipment	Sampling method	Acceptance criteria(mg)	MACO (ppm/equipment)	Total residual carry over(mg)	Result
1	JACKETED TANK	**Rinse method (purified water)**	131.25	150	**0.461**	It was found to be within the acceptance limit. So the cleaning procedure was found to be validated.
2	NON JACKETED TANK			150		
3	CYLINDRICAL HOLDING TANK			150		

CONCLUSION:

The cleaning validation samples are collected from the hot spots in the equipment, which are difficult to clean, and probably contaminate more. The samples are analyzed by the validated HPLC method. The analytical method validation for Terbutaline sulphate is carried out and the data are found well within the limits. The method is able to detect drug residue up to a level of 0.15 ppm. The swab recovery studies are carried out and are found to recover more than 90% from the stainless steel coupons, which are well within the acceptance criteria. The cleaning validation samples showed no characteristic peak in the retention time window of Terbutaline sulphate. Moreover, on doing cleaning validation, results showed that the cross-contamination was found well within the acceptance criteria.

The validated analytical method can be used for the routine analysis of Terbutaline sulphate. The analytical method is found, able to detect drug residue up to 0.15 ppm. Thus, the method is

capable of performing the cleaning validation studies carried out. The swab recovery studies gave recovery above 90% for the spiked amount in stainless steel coupon. Therefore, the swab recovery studies are suitable to produce reproducible and precise results. The cleaning validation conducted showed that the cross-contamination is well within the set acceptance limit. The cleaning procedure followed, is able to limit the drug residues to an acceptable level.

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