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Development of simple and rapid method for estimation of low levels of docusate sodium from equipment surfaces

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Abstract: The objective of the present study was to develop a method for estimation of residual active substances with low RRF values from equipment surfaces, after cleaning of the equipment. Currently there is an increasing demand for rapid sample analysis along with low detection limits for verification of cleaning validation samples. UV/Vis spectroscopy or LC methods are routinely used in for the quantitative determination of product residues on equipment surface. Although several methods can potentially be used to estimate low levels of active drug substances, these are not suitable for quick estimation of residues during product change-over in a pharmaceutical manufacturing plant. Substances with low response factors present additional difficulty for estimation by traditional analytical methods. Although Docusate sodium [Dioctyl sodium sulfosuccinate (C20H37NaO7S)], may be estimated by analytical techniques such as LC-MS (at least low ppb), LC-Conductivity (~10 ppb and good selectivity), LC-CAD (~1 ppm) or ELSD (~5-10 ppm), LC-UV (10 - 50 ppm), an alternative method using conductivity measurements is proposed for estimation of Docusate sodium. On the basis of the results obtained, measurement of conductivity can be considered as a rapid and simple alternative to conventional chromatographic methods for verification of cleaning validation samples.

Introduction:

An essential part of any pharmaceutical manufacturing facility which operates under cGMP Guidelines, is the availability of well developed and effective cleaning procedures for all installed equipment. This will ensure that the cleaned equipment is free from residues of active ingredient from the previous product manufactured on that equipment and also from traces of detergent, if used in cleaning process. The equipment will also be free from microbial contamination which can be carried forward into the next batch. Consistent

Documented verification that the equipment cleaning procedure is effective and reproducible, and meets predetermined cleaning is termed as Cleaning validation[1].

In simple terms, validation is documented evidence that cleaning can be performed reliably and repeatedly to ensure a predetermined level of cleanliness of manufacturing equipment.

Current requirements[2-3] make it imperative that equipment cleaning procedures used in a manufacturing unit are simple, easy to implement and adequate to reduce concentrations of the previous product on the equipment surface to levels which are acceptable in terms of safety and purity of the product manufactured.

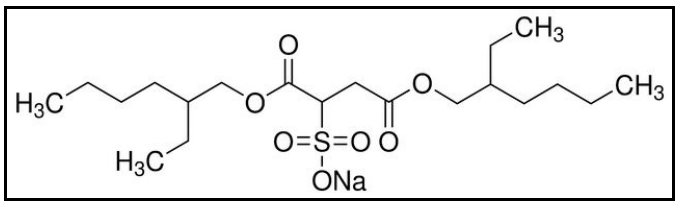
Swab (direct) or rinse (indirect) sampling is commonly used for sampling of residues on the equipment surface[4-6].

There are many analytical techniques available in cleaning validation. But choosing the appropriate analytical tool depends on a variety of factors[7]. The most important factor is to determine the specifications or parameters to be measured. The limit should always be established prior to the selection of the analytical tool.

The above details should be described in a cleaning validation protocol, which defines how the validation will be performed. Contents of the protocol include[8]:

The objective of the validation process; Responsibilities for performing and approving the validation study; Description of the equipment to be used; The interval between the end of production and the beginning of the cleaning procedures; Cleaning procedures to be used for each product, each manufacturing system or each piece of equipment; The number of cleaning cycles to be performed consecutively; Any routine monitoring equipment; Sampling procedures, including the rationale for why a certain sampling method is used; Clearly defined sampling locations; Data on recovery studies where appropriate; Analytical methods including the limit of detection and the limit of quantitation of those methods; The acceptance criteria, including the rationale for setting the specific limits; Other products, processes, and equipment for which the planned validation is valid according to the "bracketing" concept; and When Re-validation will be required.

Docusate sodium has a positively charged sodium ion that bond to a negatively charged sulfite group in the middle of a long carbon chain



It can be categorized based upon structure and includes nonionic, anionic, and cationic classes.

Docusate sodium can be detremined using LC. Chromatographic approaches can separate the molecules on the basis of carbon chain length, chain branching or positional isomer distribution.

As it does not contain a UV chromophore, it is usually measured using RP HPLC or conductivity. Literature survey indicated few methods for estimation of docusate sodium by conventional chromatographic methods. There is no reported method for estimation of docusate sodium using the conductivity method. Therefore, a method was developed for the same. Docusate sodium, due to its chemical properties is easily ionized and can be measured typically to low µg sensitivity using conductivity method.

Experimental:

Methods and materials:

API for the docusate sodium batches was procured from Cytec Labs, USA. Detergent used for the cleaning cycle was Teepol®, is a mixture of linear alkylbenzene sulfonates (LAS). It consists of a mixture of homologues of different alkyl chain lengths (C10-C13 or C14) and isomers differing in the phenyl ring positions (2 to 5 phenyl). A 1% solution at 25°C in de-ionized water was used in this study for equipment cleaning.

Cleaning cycle:

Equipment cleaning cycle for RMG after manufacture of docusate sodium enema is as given below:

- Hot water (100L, 60°C) was used to prewash the RMG.
- After discharging the prewash water, the RMG was cleaned using hot water and detergent. The swinging bowl was filled with detergent, and both the bowl and lid were cleaned with the mixer and chopper operating at 100RPM. The solution was discharged and the discharge valve was cleaned with hot water and detergent. The total volume of hot water (60°C) used was 100L.

- Cold water (50L, 25°C) was used to remove any residual detergent followed by a final rinse with de-mineralized water (50L, 25 °C). Finally, the machine was dried by using the heated jacket.
- The total cleaning cycle is of 90 minutes, including 30 minutes for drying the machine for next batch processing.
- Two batches were produced to evaluate the cleaning procedure reproducibility. The system was cleaned immediately after production run in case of first batch and after a "dirty hold time" of 24 hours in case of second batch.
- After the cleaning cycle, samples of the final rinse water were collected to ensure elimination of the detergent.

Sampling:

Following each batch production, samples were taken from five locations of the RMG - the impeller, chopper, bowl and lid, and discharge chute. These locations were selected because they represent difficult to clean areas it is essential that they are cleaned between production runs. Both the stainless steel surfaces of the areas and their surrounding gaskets were visually examined for cleanliness. Samples were taken using the swab method, wetting a swab tissue with 10 mL of purified water. Swab surfaces were predetermined and an area of approximately 100 sq cm was swabbed.

The total surface in contact with the product is 2400sq cm. The swab sample was taken from a surface area of 100sq cm of the equipment surface for each location.

Analytical determination by HPLC

Method:

The chromatographic system comprised an isocratic pump and a variable wavelength UV detector. The analytical column (250mm x 4.6mm) was packed with 5 µm RP-C18 particles (Inertsil ph). The mobile phase consisted of a mixture of 60% (v/v) acetone and 40% (v/v) 0.01M Tetrabutyl ammonium hydrogen sulfate; its flow rate was 1.2 mL/min. The UV detector monitored the docusate sodium concentration at 214 nm and the coluimn temperature was maintained at a constant 40°C. The system suitability was verified with standard solutions of 225 µg/mL (225ppm).-In order to determine detection levels of docusate sodium, sample solutions at 10 µg/mL (10ppm) and 45 µg/mL (45ppm) were chromatographed on the system. The results of the study are presented in table 1 & 2 below. Specimen chromatograms are presented in Fig 1, 2 and 3.

Table 1: System suitability determination for docusate sodium

S.No.	Standard solution (225ppm)	RSD
Injection-1	177598	Average: 177534
Injection-2	177682	
Injection-3	177337	RSD: 0.1%
Injection-4	177629	
Injection-5	177426	

Table 1: Results of study at 10 µg/mL **and 45**µg/mL

Sr.No.	**Solution of concentration 10** µg/mL	**Solution of concentration 45** µg/mL
Injection-1	Peak not detected	50514
Injection-2	Peak not detected	42789
Injection-3	Peak not detected	48333
Injection-4	Peak not detected	48384
Injection-5	Peak not detected	50605
Injection-6	Peak not detected	40429
Mean	NA	46842
%RSD (Relative standard deviation)	NA	9.0%
Remarks	Not suitable	High RSD; not suitable

The results at concentrations of 10µg/mL and 45µg/mL indicate that chromatographic method is not suitable for determination of low levels of docusate sodium.

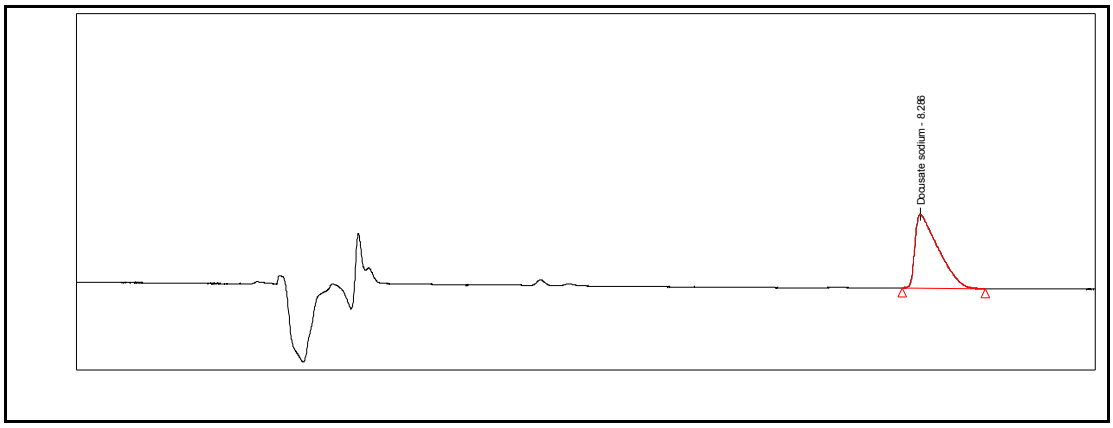


Figure 1: Specimen Chromatogram of Standard

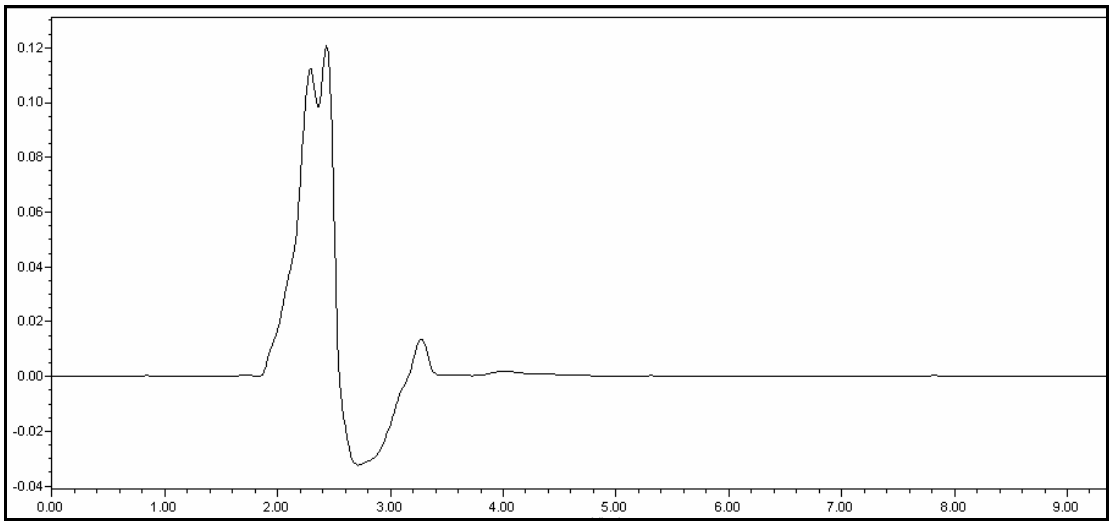


Figure 2: Specimen Chromatogram of Diluent

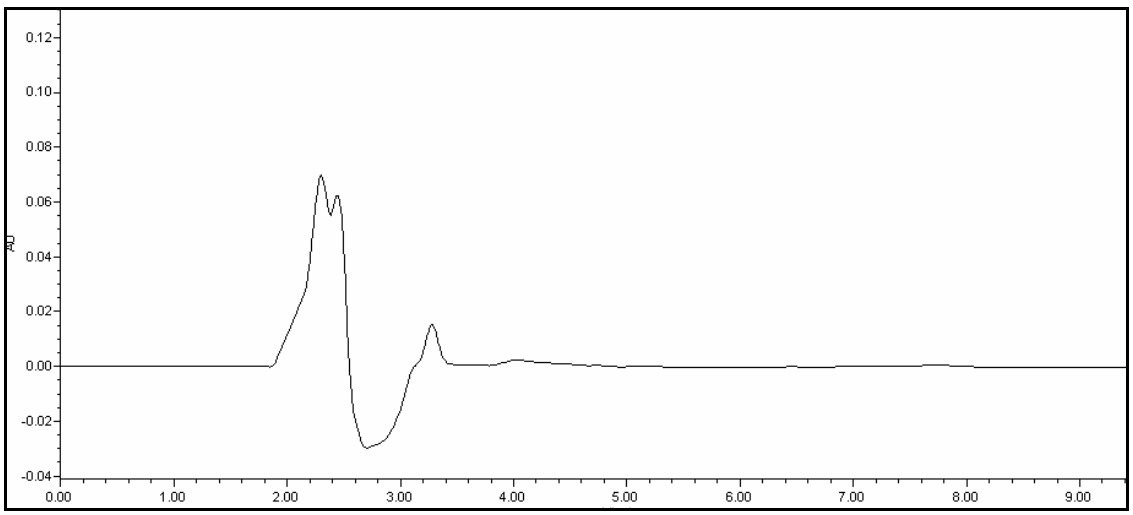


Figure 3: Specimen Chromatogram for dosusate sodium at 10 µg/mL

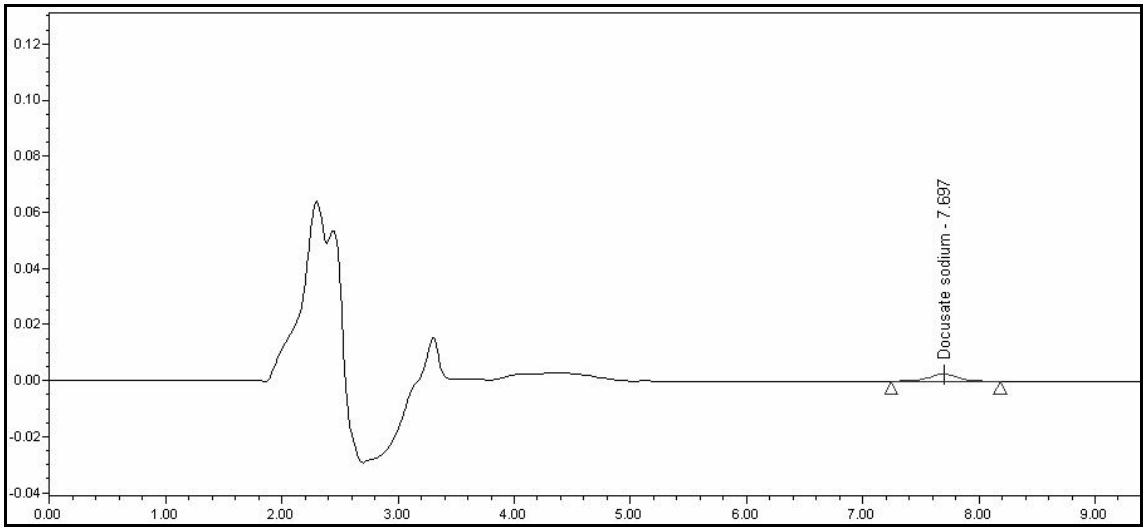


Figure 4: Specimen Chromatogram for dosusate sodium at 45 µg/mL

Analytical determination by Conductivity:

As Docusate sodium does not have satisfactory response on HPLC at low ppm level (i.e. below 10 µg/mL), an alternative method for estimation, i.e. conductivity may be utilized for qualification of the active ingredient at levels of 10 µg/mL or below.

Standard docusate sodium:

All experiments were run at ambient temperature. Stock solution of docusate sodium at a concentration of 100µg /mL (100ppm) was prepared in distilled water and stored below 10°C in stoppered flasks. The solution was then used to prepare a set of six calibration standards; concentrations varied (1µg/ml–10µg/mL).

The method was linear across the concentration range (R^2 0.9) and the qualification threshold was 2 µg/swab.

Procedure for Standard Stock preparation:

Weigh about 25mg of Docusate sodium standard and transfer to 250ml volumetric flask. Add 200ml of water, sonicate to dissolve with intermittent shaking and diluted upto the mark with diluent, mix well. Final concentration of standard is 100 µg/mL. From stock solution prepare 1, 2, 4, 6, 8 and 10ppm standard solution as presented in Table 3. The conductance values are reported in Table 4.

Table 3: Standard Stock solution preparation

Concentration of Docusate Sodium (µg/ml)	Volume taken from stock solution (ml)	Volume made in ml
1	1	100
2	2	100
4	4	100
6	6	100
8	8	100
10	10	100

Table 4: Conductivity values for Docusate Sodium

Concentration (µg/ml)	Conductivity
10	3.05
8	2.51
6	2.32
4	2.00
2	1.92

1	1.69
Blank	1.29
Co-relation Coefficient	0.920

A graph of the conductance values versus concentrations of docusate sodium was plotted. The graph is presented in Figure 5.

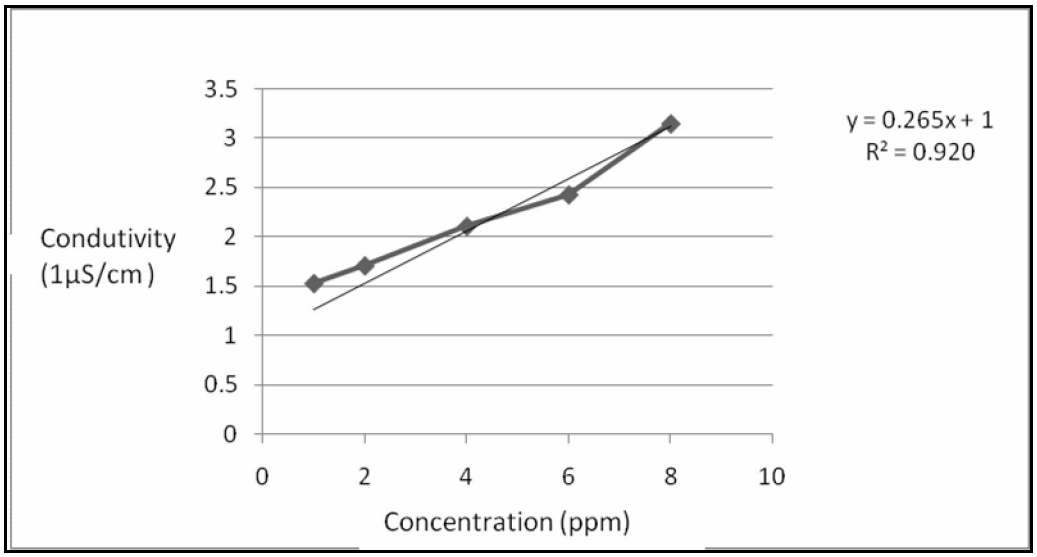


Figure 5: Linearity graph for docusate Sodium

Note: Blank reading was considered if the docusate sodium reading was within ±0.1µS/cm of blank. This proves that docusate sodium at 1µg/ml level is not detected.

Swab recovery

Trials conducted for recovery on the swab determined that the docusate sodium recovery was between 90–95%. However, to account for any operator influence, a factor of 75% for swab recovery was maintained in the formula for calculating the acceptance criteria.

Swab sample analysis.

After transfer of the swab to a borosilicate tube, 10 mL of distilled water was added. The tube was vortex-mixed for 10 seconds, and the swab was discarded. The conductivity was then measured using Thermo scientific conductivity meter.

Conductivity of swab blank was measured by treating swab identically to negate effects of the blank on conductivity readings.

The conductivity of the swab water samples collected after equipment cleaning was consistently lower than the conductivity of the 10µg/mL docusate solution dilution and equalled the conductivity of the swab blank samples. These results indicate that the equipment cleaning procedure is capable of removing all residues of docusate sodium from the equipment. Conductivity values for swab samples are reported in Table 5.

Table 5: Conductivity values for swab samples

Equipment	**Conductivity µS**
Impeller	1.44
Chopper	1.51
Bowl	2.02
Discharge chute	2.00
Blank	1.34

It is observed that the conductivity procedure can be used to determine low levels of active ingredient Docusate sodium from equipment surfaces, after cleaning. The conductivity method is a good qualitative method to determine low levels of docusate sodium with linearity over the range 1ppm to 10ppm.

Conclusion:

From the results obtained, it may be concluded that the HPLC method is not suitable for estimation of substances having a low relative response factor and may only be used if the residual levels of the substance is well above 10ppm. In comparison, the conductivity method provides a simple, rapid and effective method for estimation of low levels of docusate sodium over the range 1ppm to 10ppm and easily be used for routine analysis.

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