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COMMUNICATION

CHOICE OF FILTRATION METHODS FOR MONITORING THE DISSOLUTION OF FRUSEMIDE

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ABSTRACT

Although the British Pharmacopoeia indicates the need for filtration during the removal of samples in the course of dissolution tests, there is little guidance as to the type of filters that should be used to clarify fluids during their removal. On the basis of results obtained using frusemide as a model drug, the following recommendations are made regarding the use of filters in dissolution testing.

[1] If membrane filters are to be used to clarify dissolution fluids, filters with the smallest diameter and the highest pore size as practically permissible should be utilized to minimise drug loss into the filters.

[2] Whatman Paper filters, or equivalent, are probably to be preferred to membrane filters since they do not seem susceptible to drug sorption.

[3] The membrane type should be varied to the pH of the dissolution fluid. At pH 5.8, cellulose acetate filters sorbed less frusemide than cellulose nitrate filters but with 0.1M HCl more sorption occurred into the cellulose acetate filters.

INTRODUCTION

Dissolution tests for tablets and capsules are now very common with 481 tests in the United States Pharmacopoeia XXII. The procedures for dissolution tests have been reviewed (Cartwright, 1979; Hansen, 1982; Ford, 1990). Even after standardization of the official pharmacopoeial procedures many diverse factors affect the results obtained during dissolution tests. These include aeration of media (Cox et al, 1983), flask shape (Cox et al, 1982), cleaning procedures (Cox & Furman, 1984), sampling probe (Wells, 1981) and stirrer alignment (Cox & Furman, 1982).

However, filtration of post-dissolution samples is necessary to remove any remaining solid aggregates or undissolved drug particles and thereby allow assay, by whatever methods adopted, to be carried out meaningfully and accurately. It is important that the quantity of dissolved drug measured is that which has dissolved in the dissolution apparatus and not during the sampling procedures themselves. The British Pharmacopoeia (1988) recommends filtration of samples following removal and states 'the filter used is inert, causes no significant absorption of the active ingredient from the solution, contains no material extractable by the dissolution medium that would interfere with the prescribed analytical procedures and has a pore size not exceeding 1μm'. No guidance is however given on the type of filter and whether it may be used for repeated sampling or whether

a fresh filter should be used for each sample. The United States Pharmacopoeia XXII implies that all parts of the apparatus that come into contact with the preparation being examined or with the dissolution media are chemically inert and do not adsorb, react or interfere with the preparation being examined. Additionally the dissolution process continues from the time at which the sample is withdrawn into the syringe until it is forced through the filter (Hanson, 1982). Consequently filtration shold proceed as rapidly as possible.

Cartwright (1979) showed that certain materials may be released from the filter during the test. Many membranes contained iso-octylphenoxypolyethoxyethanol as a wetting agent and to facilitate the manufacture of membrane filters. It has significant absorbance at 220 to 240 nm (Cartwright, 1979) and may thus interfere with the assay of drugs. Additionally Liu et al (1977) have shown that some drugs may be adsorbed from solution by various membrane filters. The choice of filter should therefore be preceeded by an investigation of the sorption characteristics of the drug and the particular filter specifications being employed.

The aims of this study are to investigate the suitability of a number of membrane filters for use as potential clarifiers of frusemide solutions during dissolution tests. Although Furosemide Tablets U.S.P. are tested at a pH of 5.8, a comparison of filter performances at this pH and using 0.1M HCl is made.

MATERIALS AND METHODS

Materials

Table 1 shows the specifications of the filters used throughout the study. The membrane filters were held in Millipore Swinnex Filter Holders of 13, 25 or 47 mm diameter.

Frusemide Tablets B.P. and Frusemide B.P. were used throughout the study. Dissolution studies of the tablets were

TABLE 1

Types, Manufacturers and Specifications of Filters

MANUFACTURER	TYPE	PORE SIZE	DIAMETER
Oxoid Nuflow NS47/22G	Cellulose acetate	0.22 µm	47 mm
Oxoid Nuflow NHS47/45G	Hydrophobic edged Cellulose acetate	0.45 µm	47 mm
Courtaulds Nuflow N25/22UP	Cellulose acetate	0.22 µm	25 mm
Millipore HA	Mixed esters of cellulose acetate and cellulose nitrate	0.45 µm	47 mm
Millipore EH	Cellulose acetate	0.50 µm	47 mm
Millipore GS	Mixed esters of cellulose acetate and cellulose nitrate	0.22 µm	47 mm
Millipore SM	Mixed esters of cellulose acetate and cellulose nitrate	5.0 µm	25 mm
Whatman WCN	Cellulose nitrate	1.0 µm	47 mm
Whatman WCN	Cellulose nitrate	0.45 µm	47 mm
Whatman WCN	Cellulose nitrate	0.2 µm	47 mm
Whatman WCN	Cellulose nitrate	1.0 µm	25 mm
Whatman WCN	Cellulose nitrate	0.45 µm	25 mm
Whatman WCN	Cellulose nitrate	0.2 µm	25 mm
Whatman WCN	Cellulose nitrate	0.45 µm	13 mm
Whatman WCN	Cellulose nitrate	0.2 µm	13 mm
Micro Filtration Systems	Plain Surface Cellulose nitrate	1.2 µm	13 mm
Sartorious SM 11307	Cellulose nitrate	0.2 µm	47 mm
Whatman No. 1 medium fast	Paper		11 cm

conducted in either 0.1M HCl or in Phosphate Buffer, pH 5.8, as prescribed in the United States Pharmacopoeia XXII in the dissolution test for Furosemide tablets, using the paddle apparatus. In 0.1M HCl frusemide levels were determined following 45 minutes of dissolution at 276 nm. In phospate buffer samples were determined after 15 minutes monitoring at 330 nm. Dilution of samples prior to analysis was not required.

Samples were removed with a plastic, 10 ml. Gillette Surgical Syringe and passed immediately through the filter attached to the syringe or passed through paper filters placed in glass funnels.

Samples were collected in triplicate and passed consecutively through the filters. The quantity of frusemide in each 10 ml sample was determined in order to estimate the amount of frusemide lost onto the filter.

Standardisation of Techniques

A 40 mg/l solution of frusemide in phosphate buffer, pH 5.8, was used to validate the procedures used. It was shown that by using ten replicate samples the coefficient of variation of the assay technique was very low (0.17%) when assays were performed from the same batch solution.

Additionally by recycling the same sample, ten times, into the sampling syringe and by determining the absorbance following each expulsion no change in absorbance occurred. The coefficient of variation was low (0.28%) again indicating that no sorption of frusemide to the syringe occurred.

Likewise samples were recycled into the sampling syringe and passed, ten times, through the Millipore Swinnex Membrane Filter Holders containing no membrane. The coefficients of variation for the solutions passed through 13mm, 25mm and 47mm units were again low (0.20%, 0.21% and 0.34% respectively) and no determinable sorption of frusemide to the syringe occurred.

Finally ten samples were recycled through the Whatman Filter Number 1. No significant sorption of frusemide occurred although the coefficient of variation (1.36%) for the replicates was higher. Consequently the values of frusemide dissolved during the dissolution studies were determined against samples filtered through Whatman Filter Paper and taken concurrently with the membrane-filtered samples to determine the amount of frusemide sorbed to the membrane filters.

RESULTS AND DISCUSSION

The results obtained from the two different dissolution media gave somewhat contrasting results. In 0.1M HCl the loss of

TABLE 2

Quantities of Frusemide Adsorbed onto various Filters following Filtration of successive 10 ml Aliquots of Solutions in 0.1M HCl, prepared by Subjecting Frusemide Tablets 40 mg to 45 minutes Dissolution.

TYPE	DIAMETER	PORE SIZE	FRUSEMIDE ADSORBED (µg) 1st PASSAGE	2nd	3rd	TOTAL
Whatman WCN	13mm	0.2µm	5.3	2.0	0.0	7.3
Whatman WCN	13mm	0.45µm	3.2	1.3	0.0	4.5
Whatman WCN	25mm	0.2µm	12.3	9.3	8.4	30.0
Whatman WCN	25mm	0.45µm	5.6	7.3	6.7	19.6
Whatman WCN	25mm	1.0µm	5.4	8.4	8.4	22.2
Whatman WCN	47mm	0.2µm	29.8	14.6	11.3	55.7
Whatman WCN	47mm	0.45µm	12.3	12.6	7.7	32.6
Whatman WCN	47mm	1.0µm	7.6	8.4	8.4	24.4
Micro Filtration Systems	13mm	1.2µm	2.1	11.6	10.1	23.8
Courtaulds Nuflow	25mm	0.22µm	36.7	32.0	23.6	92.3
Millipore SM	25mm	5.0µm	5.9	20.2	18.5	44.6
Sartorius SM	47mm	0.2µm	15.3	6.1	1.0	22.4
Millipore GS	47mm	0.22µm	29.8	9.1	6.7	45.6
Oxoid Nuflow	47mm	0.22µm	24.6	34.6	37.5	96.7
Oxoid Nuflow	47mm	0.45µm	10.6	15.7	19.0	44.3
Millipore HA	47mm	0.45µm	13.2	0.3	2.9	16.4
Millipore HE	47mm	0.45µm	29.8	33.1	34.0	96.9

frusemide into the Whatman WFN filters was easily quantified. Sorption increased with both an increase in area of the filter and a decrease in pore size (Table 1). Both increase the area of a filter exposed to drug solution passing through it with concomitant increase in sorption of the drug. On the basis of these results it would appear that the smallest possible filter, with largest pore size should be used to avoid drug loss into the filter. Additionally considerable sorption occurred on first pass through the filters indicating that, in practice, these filters should be saturated with frusemide prior to their use in clarifying dissolution fluids. The Whatman filters are composed of cellulose nitrate and in comparison with filters produced by

TABLE 3

Quantities of Frusemide Adsorbed onto various Filters following Filtration of Successive 10 ml Aliquots of Solutions in Phosphate Buffer, pH 5.8, Prepared by Subjecting Frusemide Tablets 40 mg to 15 Minutes Dissolution.

TYPE	DIAMETER	PORE SIZE	FRUSEMIDE ADSORBED (µg) 1st	2nd	3rd PASSAGE	TOTAL
Whatman WCN	13mm	0.2µm	6.9	6.9	6.9	20.7
Whatman WCN	13mm	0.45µm	7.6	6.9	6.2	20.7
Whatman WCN	25mm	0.2µm	11.7	10.3	6.2	28.4
Whatman WCN	25mm	0.45µm	6.9	4.8	2.1	13.8
Whatman WCN	25mm	1.0µm	8.3	4.1	5.5	17.9
Whatman WCN	47mm	0.2µm	19.3	6.9	0.0	25.2
Whatman WCN	47mm	0.45µm	21.3	6.9	4.1	32.3
Whatman WCN	47mm	1.0µm	12.3	2.1	3.2	17.6
Micro Filtration Systems	13mm	1.2µm	4.1	5.5	6.2	15.8
Courtaulds Nuflow	25mm	0.22µm	10.3	6.9	6.9	24.1
Millipore SM	25mm	5.0µm	6.2	4.1	3.4	13.7
Sartorius SM	47mm	0.2µm	0.0	0.0	0.0	0.0
Millipore GS	47mm	0.22µm	11.7	0.0	0.0	11.7
Oxoid Nuflow	47mm	0.22µm	0.0	6.9	0.0	6.9
Oxoid Nuflow	47mm	0.45µm	1.4	0.0	0.0	1.4
Millipore HA	47mm	0.45µm	3.4	0.0	0.0	3.4
Millipore EH	47mm	0.45µm	0.0	0.0	0.0	0.0

other manufacturers (Table 2) it appears that cellulose nitrate filters are less susceptible to frusemide sorption from its solution in 0.1M HCl than filters composed of cellulose acetate. Additionally those filters composed of mixed esters of cellulose acetate and nitrate gave performances intermediate to those accomplished by the filters containing homogenous esters.

In reality dissolution into 0.1M HCl for 45 minutes resulted in drug concentrations of ~10 mg/litre. Therefore for a 10 ml sample containing 10 mg frusemide per litre, the loss of 10 µg on first pass onto the filter represents an under-estimate of 10% of the active. Consequently, on a single pass with uncharged filters ~30% of the drug in solution was lost using Whatman WCN 47mm,

0.2µm filters and >35% was lost with the Courtaulds Nuflow filters. However, the unsuitability of other filters is readily apparent and filters based solely on cellulose acetate performed poorly and generally did not approach saturation even following three passes of drug solution.

In contrast the sorption onto filters from the pH 5.8 buffer solutions (Table 3) was considerably less than in the more acidic conditions provided by 0.1M HCl.

The solutions analysed at pH 5.8, even though were only 15 minute samples contained the whole quantity of drug, i.e., 40 mg/litre. In a simple analogy to the acidic conditions for a 10ml sample containing 40 mg frusemide per litre, the loss of 10 µg, in table 3, on first pass onto the filter represents an under-estimate of 2.5% of the active. Generally the Whatman WCN filters were more readily saturated at this higher pH and pore size did not seem to be so great a controlling factor. Consequently, at this higher pH these filters would not contribute to errors as great as those observed in 0.1M HCl. Additionally the filters based on cellulose acetate performed better at this higher pH with very low levels of frusemide generally being sorbed to them.

The explanation of the results probably cannot be divorced from the influence imposed by the pKa of frusemide which is 3.9. Consequently in 0.1M HCl the drug would be mostly in its unionised form. It would appear from the results that this form is more readily adsorbed to cellulose acetate. At pH 5.8, when the drug would be predominantly ionised, more adsorption occured to the cellulose nitrate filters.

CONCLUSIONS

The data shows that while pore size and membrane diameter may control sorption of drugs to filters pH plays an important role by modifying the proportions of ionised and unionised forms of the

drug. The consequence of this is that these forms may be differently sorbed onto filters thus rendering filters suitable or unsuitable depending on the ionised form of the drug. It therefore cannot be assumed that a particular filter, although suitable at one pH may be as suitable at a different pH in clarifying dissolution fluids. When different pH's are used to monitor drug dissolution, the filter must be accordingly altered.

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