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Particulate contamination in plastic ampoules

RICHARD C. OPPENHEIM* AND I. ROSS GILLIES†

*Victorian College of Pharmacy Ltd, Parkville, Victoria, 3052 and †Goulburn Valley Base Hospital, Shepparton, Victoria, 3630 Australia

Plastic ampoules of Water for Injections, JP, and Injection Sodium Chloride, JP, were investigated to determine their particle load. Four batches were studied. The ampoules were twist-opened as they would be in the clinical setting and the total particle load, both inherent and that created in opening, was determined by reading the contents with a HIAC 420 particle counter with a CMB 60 sensor. The total particle content was found to be minimal, easily complying with world L.V.P. standards and the S.V.P. standard of the USP XXI. The number of particles found in these opened plastic ampoules was significantly lower than that found in clinically snap-opened glass ampoules and also slightly lower than that found in laboratory heat-opened glass ampoules. Whilst the plastic ampoule has a restricted application because it is not suitable for all drugs, it is concluded that when they are used as the immediate container for Water for Injections and Injection Sodium Chloride they are highly effective in reducing the particulate contamination generated in opening.

Small volume parenteral products have traditionally been presented in all-glass ampoules. In contemporary manufacture, a sealed glass ampoule is bought by the manufacturer and then opened, filled and sealed under good manufacturing conditions. The ampoule is opened by cutting the elongated top in such a way as to minimize the entry of particulate contamination. The liquid product is then filled into the ampoule and the ampoule is flame sealed. Hence a relatively clean product is available for use in the clinical setting (Gillies et al 1986). If clear glass is used as the container material, each finished ampoule can be inspected for particulate contamination. Inspection is much more difficult with amber or coloured glass containers.

For access to the product inside the glass ampoule, the ampoule must be snapped open. This leads to a great increase in the level of particulate contamination of the contents (Davies & Smart 1982; Gillies et al 1986). Hence, although the sealed manufactured production can have little contamination, the opened product can be severely contaminated. The USP XXI small volume parenteral particulate contamination limit test is performed on snap-opened products and must lead to variable results depending on the intrinsic level of contamination as well as the variably introduced contamination from the snap-opening procedure (Oppenheim & Gillies 1986). However, any opened product, tested for particulate contamination, cannot be used clinically. Hence, the quality assurance of any injected product must be extrapolated from other tested products. Confidence in this extrapolation procedure is increased if the opening procedure can be shown reproduceably to contribute very little contamination to the inherent contamination already in the product. This can only be achieved by the use of an ampoule container material other than glass.

Recognizing this problem, Otsuka Pharmaceutical has been manufacturing ampoules made from low density polyethylene since 1977. The major advantage claimed for these ampoules is that upon twist-opening, very little contamination is added to the liquid product.

In manufacture, as the ampoule is blow moulded, the previously sterilized liquid product is aseptically filled almost instantaneously and then the top is aseptically pressed rapidly into shape whilst the plastic is still warm. This product therefore meets the requirements of Distilled Water for Injections JP10 and those of Water for Injections USP XXI. Provided the product meets the various tests of the BP monograph, it also complies with the requirements for Water for Injections BP 1980 (and addenda) with regard to sterility. Although autoclaving is the method of choice for sterilization specified in the monograph, the general notices of the BP 1980 state: 'The use of other procedures is not however precluded provided that the final product complies with the requirements of the monograph'. Autoclaving clearly is not appropriate for plastic ampoules. The only point of contention is whether the plastic container could be said to meet all the BP 1980 (Appendix XVIIIC) requirements for Containers of Water for Injections. In particular it might be argued

* Correspondence.

that the containers are not clear enough to see any visible particles. The plastic ampoules used by Otsuka Pharmaceutical are translucent but meet the JP10 requirements and the notice issued by the Japanese Ministry of Health and Welfare requiring more than 55% transmission of light through such plastic containers. There does not appear to be any analogous BP 1980 requirement. A major objective of the work reported here was to determine the particulate load of these ampoules.

Imperfectly sealed glass ampoules will fail if terminally autoclaved. Hence, in principle, the requirements of the BP should ensure a lower incidence of unsterile products in glass ampoules in the market place than the USP requirements. We are unaware of any data to support this hypothesis. Imperfectly welded or sealed plastic ampoules could be detected by subjecting them to a standard test such as placement in a vacuum. There has been no example of any product in a plastic ampoule made by Otsuka Pharmaceutical which has been shown to be non-sterile when about to be used in the clinical situation (private communication, Otsuka Pharmaceuticals 1985). Hence the various codes of good manufacturing practice are sufficiently rigorous to prevent microbiologically contaminated products being marketed.

When the Otsuka type plastic ampoule is twist-opened, a large hole is made at the top of the ampoule and the product can be withdrawn in an analogous way to that from snap-opened glass ampoules. Hence such opened plastic ampoules are unlikely to be put aside and reused at a later time unlike those plastic ampoules in which the product is removed from the unopened ampoule by puncturing the ampoule wall with a needle.

The other major advantage of plastic ampoules when compared to glass ampoules is that plastic ampoules are said not to shatter upon dropping.

The disadvantages of plastic ampoules include oxygen ingress preventing oxidizable drugs being presented, carbon dioxide egress preventing sodium bicarbonate solutions being incorporated and finally some drugs are known to adsorb to or diffuse through plastics and hence could not be presented. Presumably for these and commercial reasons, only Water for Injections, Sodium Chloride Injection, and Dextrose Injection are presented in plastic ampoules by Otsuka Pharmaceutical.

This paper presents the results of a study on the particulate contamination found in Water for Injections and Normal Saline Injection in twist-opened Otsuka-type plastic ampoules.

MATERIALS AND METHODS

Methods

Ampoules (20 ml) of Water for Injections and 0·9% Sodium Chloride Injection supplied by Otsuka Pharmaceutical Factory, Inc. Japan were investigated. Four batches of each product were investigated. Ten ampoules from each batch were randomly selected from randomly selected shipments of ampoules sent from Japan to the Australian group.

The ampoules were cleaned before opening in a laminar flow cabinet, using the principles described by de Luca et al (1980). They were then shaken for 30 s and opened by the recommended twist technique and then placed vertically in a cleaned stainless steel grid stand in a cleaned 2000 ml glass vacuum dessicator. The products were degassed at about 50 kPa absolute pressure for 4 min. Air was returned to the dessicator through a 0·22 μm Millex filter.

A HIAC 420 light blockage counter connected to a CMB 60 sensor was used to determine the extent of particulate contamination of each ampoule. A 20G stainless steel needle had its Luer fitting removed and the resultant 8 cm long tube was inserted into the end of the plastic probe of the sensor. The needle and sensor combinations were thoroughly cleaned with 0·22 μm filtered Water for Injections until no contamination was recorded. The sensing equipment was similarly cleaned between batches of ampoules.

Using the procedure described earlier (Gillies et al 1986) the liquid flow rate through the sensor was established at 8 ml min^{-1}. The counter settings were adjusted to correspond to 5 and 20 μm and the number of particles equal to or greater than these size were counted in aliquots of 0·66 ml over 5 s. The USP standard requires sample aliquots to be not less than 1 ml. The 0·66 ml used to sample the contents of the small ampoules in the previous study (Gillies et al 1986) was chosen for experimental convenience. So that the experimental protocols in the two studies were as close as possible, the same sampling volume was used.

The opened ampoules were held vertically in a cleaned stainless steel grid in the laminar flow hood and the needle inserted so that it reached to within 1·0 mm of the base of the ampoule. At least 16 determinations of particulate contamination were made on each ampoule.

Over 500 plastic ampoules filled with either Water for Injections or Normal Saline Injection were subjected to 15 min at about 50 kPa absolute pressure.

Twenty ampoules selected at random from each batch of products tested were dropped 3 m onto a

concrete floor. The ampoules were visually inspected for breakage and macroscopic cracking. Any fine breaks in the seals were investigated by subjecting the ampoules to the reduced pressure test.

RESULTS

Table 1 lists the contamination found in four batches each of Water for Injections and Normal Saline Injection presented in plastic ampoules.

No ampoule showed any signs of fine breaks or pinholes in the seals either before or after dropping. No ampoules broke or were macroscopically cracked as a result of the drop test. Table 1 also lists the contamination found in each batch after dropping each ampoule onto the floor and subjecting it to the reduced pressure test. The Student's *t*-test with unequal variance was used to determine whether there was a significant difference between the before and after dropping results.

DISCUSSION

The results show that both types of opened products exhibit very low levels of particulate contamination. On average the 5 μm contamination is about 50% of that which we found in Australian glass heat-opened ampoules and roughly comparable at the 20 μm contamination level. Snap-opened glass ampoules, ready for clinical use, were, as shown in Table 2, even more contaminated (Gillies et al 1986). The USP XXI small volume parenteral contamination test has limits (per ml) of 500 and 50 at the 10 μm and 25 μm levels, respectively, for 20 ml ampoules. It is clear that the twist-opened plastic ampoules ready for clinical use have extremely low levels of contamination. Any contamination found is likely to be clinically insignificant compared with that introduced from the administering needle and syringe.

The levels of particulate contamination in the twist-opened plastic ampoules are so low that it is probably unrealistic from a clinical point of view to perform detailed statistical analysis of the data. However, as with our earlier study (Gillies et al 1986), we believe that the sampling within one ampoule had no time dependent effects, allowing the data to be treated as replicates. Experimentally this means that particle settling during the analysis of any individual ampoule is not a problem.

Using MULTCOMP, a multicomparison of the means program and the STATPAK statistical package, there generally was no significant difference, at the 10% level, between any pair of mean particulate contamination at either the 5 μm or the 20 μm level in ampoules within any given batch.

As might be expected there generally was an increase in the particulate load after the somewhat drastic test of dropping the ampoules 3 m onto a concrete floor. However, two batches of sodium chloride ampoules showed a significant decrease for

Table 1. Contamination per ml in ten twist-opened 20 ml plastic ampoules from each batch, before and after dropping.

			≥5 μm			≥20 μm		
Product	Batch	State[a]	$\bar{X}$	$\bar{X}+2s$	Prob.[b]	$\bar{X}$	$\bar{X}+2s$	Prob.[b]
Water for Injections								
	K4E84T	Before	7·83	15·84	0·1	0·41	2·66	0·1
		After	9·86	19·91		0·95	3·68	
	K3E88T	Before	11·01	22·86	NS	0·59	2·81	0·1
		After	11·31	20·61		1·23	4·38	
	K4A87T	Before	8·25	16·08	0·1	0·12	1·08	0·1
		After	11·64	20·46		1·11	4·56	
	K3I81T	Before	8·91	17·40	0·1	0·21	1·53	0·1
		After	10·86	19·71		1·14	3·81	
0·9% NaCl Injection								
	K4F76T	Before	1·04	3·86	0·1	0·24	1·53	2·0
		After	3·48	9·15		0·48	3·00	
	K4F73T	Before	2·19	6·63	0·1	0·42	2·34	1·0[c]
		After	3·86	9·44		0·17	1·52	
	K2J87T	Before	1·17	3·75	0·1	0·41	2·15	0·1
		After	4·34	14·36		0·78	3·33	
	K3F79T	Before	1·19	14·76	0·2	0·60	3·06	5·0[c]
		After	1·85	6·26		0·35	2·12	

[a] Before or after dropping 3 m onto a concrete floor.
[b] Limiting percentage point of *t* value.
[c] Note lower contamination after dropping.
$\bar{X}$ = mean; s = standard deviation.

Table 2. Contamination per ml in ten heat-opened and ten snap-opened 20 ml Water for Injections glass ampoules (David Bull Laboratories, DBL, Batch B067605) (Gillies et al 1986).

	≥5 μm		≥20 μm	
	$\bar{X}$	$\bar{X}$ + 2s	$\bar{X}$	$\bar{X}$ + 2s
Heat-opened	6·68	13·67	0·29	1·64
Snap-opened	192	488	0·89	3·17

the >20 μm data which probably reflects the difficulty in working with the low number of counts recorded for this type of ampoule.

CONCLUSIONS

We found that the particulate contamination at the 5 μm and 20 μm levels in twist-opened plastic ampoules of Water for Injections and Normal Saline Injection, ready for clinical use, were extremely low. With good manufacturing procedures it is clear that such ampoules readily conform with the only official pharmacopeial standard, that of the USP XXI. Such ampoules, although limited in the range of active drugs they may contain, are superior to snap-opened glass ampoules.

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