Technical Report

Analysis of residual APIs in blister pack medication packaging – part 2

Prepared for: Global Self Care Federation

For the attention of:
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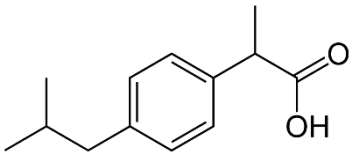
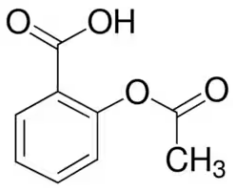
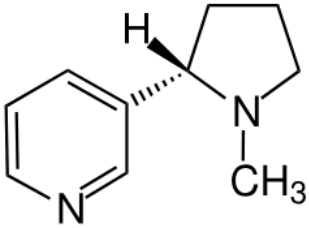
1. Introduction

The Global Self-Care Federation (GSCF) launched the "Charter for Environmentally Sustainable Self-Care", which is an industry wide action on behalf of the consumer healthcare industry designed to support environment sustainable development. One of the key focus areas is plastics and packaging recyclability concerning blister pack packaging.

Smithers carried out a small-scale proof of concept study to measure four active pharmaceutical ingredients (APIs) residual in PVC and PVC-free packaging, when subjected to differing simulated ageing and handling conditions. The GSCF wish to extend this study to test for additional APIs, summarized in Table 1 below, across various product types/formats and blister packaging combinations. A total of six packed products are to be tested. This proposal outlines the package of work that will be carried out for this phase.

The targeted products and APIs identified by the GSCF for testing in this trial are summarised in Table 1 below.

Table 1: API chemical information

API name	CAS #	Chemical structure
Ibuprofen	15687-27-1	
Paracetamol	103-90-2	
Nicotine	22083-74-5	

2. Test samples

The following test samples were received at Smithers, pictures included in Appendix 1.

Table 2: Test samples and descriptions

Smithers ID	Description	API	Form	Dose per tablet
S2998	Nicorette Gum PVC/PVDC - Alu	Nicotine	Uncoated Gum	4 mg
S3000	Nicorette Gum PVC/PVDC - Alu	Nicotine	Coated Gum	4 mg
S3007	Nurofen Tablets PVC - Alu	Ibuprofen	Coated Tablet	200 mg
S3008	Nurofen Express Capsules PVC/DC - Alu	Ibuprofen	Liquid Gel Capsule	200 mg
S3046	Panadol Actifast PVC – Alu	Paracetamol	Coated Tablet	500 mg
S3059	Panadol Zapp - PP	Paracetamol	Coated Tablet	500 mg

3. Experimental

The work was carried out in accordance with the work program reference 23-1006343HG v5 and as described below.

3.1 Method development

The analytical separation method developed in Part 1 using Liquid Chromatography with UV detection, initially designed for paracetamol, was extended to quantify ibuprofen with a detection limit of 10 ppb.

A separate method employing Gas Chromatography coupled with Mass Spectrometry (GC-MS) was established for the analysis of nicotine, also achieving a detection limit of 10 ppb.

Deionised water, recommended by the GSCF as the most representative solvent for industrial cleaning processes, was selected as the preferred extractant.

To support the development of the extraction and analysis procedures, recovery and stability studies were also conducted.

3.2 Extraction Analysis

The blister packs were separated into batches and tested as described below.

3.2.1 Extractables directly from blister packs

One batch of samples had contents removed and then the blister packaging was extracted into deionised water as received i.e. without conditioning. The two remaining batches were subjected to conditioning with pressure and vibration before removal of contents and subsequent analysis on the packaging.

Pressure conditioning: The packs were placed between two metal plates on a Specac press and subjected to 10psi pressure for 48 hours.

Vibration conditioning: A shipper box, containing the blister packs, was subjected to 60 minutes vibration using the ISTA 2A broadband random vibration profile, illustrated in Figure 2 below, (with an overall g_{RMS} of 1.15). Vibration was split evenly across all 6 orientations (10 minutes per orientation).

Figure 1: ISTA 2A broadband random vibration profile

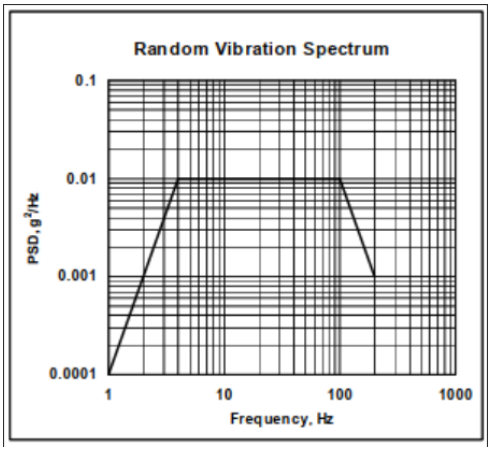


Figure 3: Images of shipper test subjected to 6 orientations vibration test.

		
1	2	3

		
4	5	6

The two batches of blister packs then had contents removed and were subsequently subjected to extraction using deionised water. The resulting extracts were analysed via HPLC-UV and GC-MS to quantify the total levels of API's adhered to or embedded within the plastic.

Additionally, the blister packs were imaged and weighed both before and after the extraction process to support the analysis.

Table 3: Test Conditions stage 1

Condition	Extracting solvent	Number of replicate packs tested
As received	Deionised Water	9
Packs subjected to pressure	Deionised Water	9
Packs subjected to vibration	Deionised Water	9

3.2.2 Extractables with pre-rinsing followed by extraction of blister packs

A set of blister packs were subjected to conditioning by vibration, which was selected as the worst-case conditioning regime. The packs were rinsed in deionised water and this extract was reserved for analysis. The packs were then subjected to extraction into deionised water, as before, for 24 hours. Both rinse and extraction liquids were analysed separately by HPLC-UV and GC-MS to compare the levels of API adhered to the surface compared to the quantity migrated into the plastic. This is intended to represent the proportion of physical vs. chemical contamination.

Table 4: Test conditions stage 2

Condition	Rinsing solvent	Extracting solvent	Number of packs tested
Packs subjected to vibration	Deionised Water	Deionised Water	9

3.2.3 Extraction conditions, HPLC-UV and GC-MS analysis

Each blister pack was extracted in 80 ml of deionised water, sufficient to fully submerge the pack within the extraction tube.

The resulting extracts were analysed using High Performance Liquid Chromatography with UV detection (HPLC-UV). The method utilised a C18 column with a gradient elution, employing mobile phases of (A) acidified deionised water adjusted to pH 2.5 with phosphoric acid, and (B) acetonitrile. The detection limit for all extracts was established at 10 ppb.

For nicotine analysis, extracts were analysed using Gas Chromatography coupled with Mass Spectrometry (GC-MS), employing a DB5 column and a gradient oven temperature programme. The detection limit for nicotine was also set at 10 ppb.

4. Results and Discussion

4.1 Method development & validation

Method development was carried out using HPLC-UV and GC-MS to achieve a separation of the three APIs of interest. Example chromatograms showing the separation achieved is shown in Figures 2 and 3 below.

Figure 2: HPLC Chromatogram showing separation of Paracetamol and Ibuprofen for a 10ppb calibration standard.

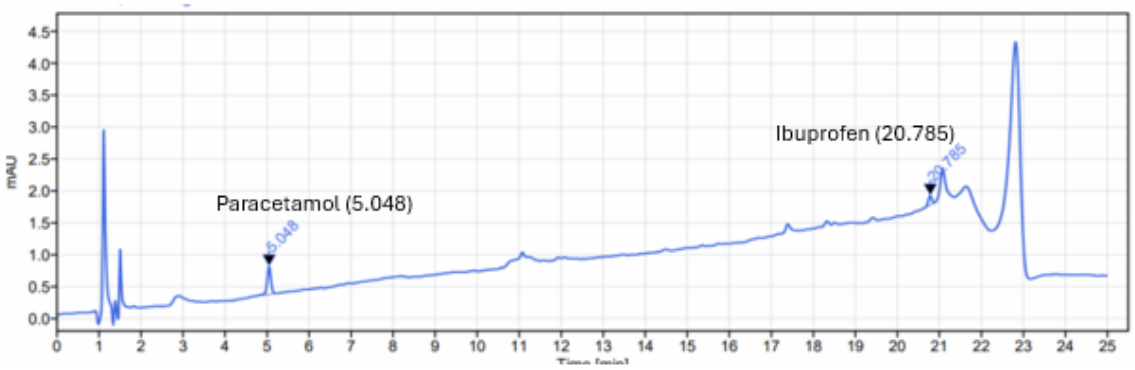
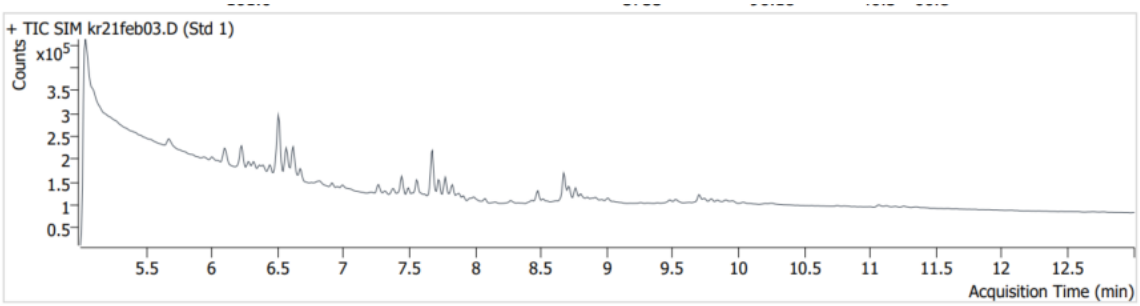
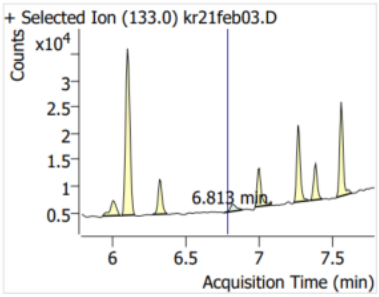
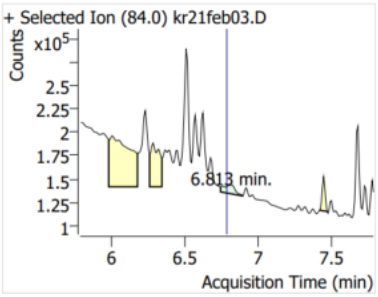


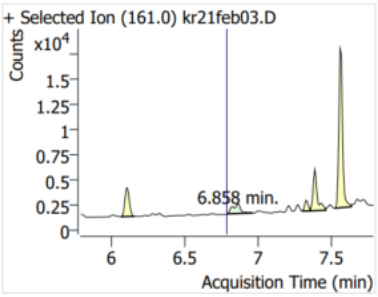
Figure 3: GC-MS Chromatogram showing separation of Nicotine for a 10ppb calibration standard.


+ TIC SIM kr21feb03.D (Std 1)
Counts
x10^5
Acquisition Time (min)

Nicotine


+ Selected Ion (133.0) kr21feb03.D
Counts
x10^4
6.813 min.
Acquisition Time (min)


+ Selected Ion (84.0) kr21feb03.D
Counts
x10^5
6.813 min.
Acquisition Time (min)


+ Selected Ion (161.0) kr21feb03.D
Counts
x10^4
6.858 min.
Acquisition Time (min)

4.2 Analysis results

4.2.1 Sample as received with extraction

Paracetamol, Ibuprofen and Nicotine were detected in some their respective product extracts. The results are summarised in the following table.

Table 5: Total extractable results for "As received" samples

Sample ID	Product/Pack Material	Tablets/blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol Content		Ibuprofen Content		Nicotine Content	
						µg/pack	µg/blister	µg/pack	µg/blister	µg/pack	µg/blister
S2998	**Nicotine (Uncoated) - PVC/PVDC**	**15**	**4mg**	**60mg**	1	ND	ND	ND	ND	TBC	TBC
					2	ND	ND	ND	ND	TBC	TBC
					3	ND	ND	ND	ND	TBC	TBC
					4	ND	ND	ND	ND	TBC	TBC
					5	ND	ND	ND	ND	TBC	TBC
					6	ND	ND	ND	ND	TBC	TBC
					7	ND	ND	ND	ND	TBC	TBC
					8	ND	ND	ND	ND	TBC	TBC
					9	ND	ND	ND	ND	TBC	TBC
					Mean	**ND**	**ND**	**ND**	**ND**	**TBC**	**TBC**
S3000	**Nicotine (Coated) - PVC/PVDC**	**15**	**4mg**	**60mg**	1	ND	ND	ND	ND	TBC	TBC
					2	ND	ND	ND	ND	TBC	TBC
					3	ND	ND	ND	ND	TBC	TBC
					4	ND	ND	ND	ND	TBC	TBC
					5	ND	ND	ND	ND	TBC	TBC
					6	ND	ND	ND	ND	TBC	TBC
					7	ND	ND	ND	ND	TBC	TBC
					8	ND	ND	ND	ND	TBC	TBC

Sample ID	Product/Pack Material	Tablets/blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol Content		Ibuprofen Content		Nicotine Content	
						µg/pack	µg/blister	µg/pack	µg/blister	µg/pack	µg/blister
					9	ND	ND	ND	ND	TBC	TBC
					Mean	**ND**	**ND**	**ND**	**ND**	**TBC**	**TBC**
S3007	**Ibuprofen (Coated Tablet) - PVC**	**10**	**200mg**	**2000mg**	1	ND	ND	<LOD	<LOD	ND	ND
					2	ND	ND	<LOD	<LOD	ND	ND
					3	ND	ND	<LOD	<LOD	ND	ND
					4	ND	ND	<LOD	<LOD	ND	ND
					5	ND	ND	<LOD	<LOD	ND	ND
					6	ND	ND	<LOD	<LOD	ND	ND
					7	ND	ND	<LOD	<LOD	ND	ND
					8	ND	ND	<LOD	<LOD	ND	ND
					9	ND	ND	<LOD	<LOD	ND	ND
					Mean	**ND**	**ND**	<LOD	<LOD	**ND**	**ND**
S3008	**Ibuprofen (Liquid Gel Capsule) - PVC/DC**	**10**	**200mg**	**2000mg**	1	ND	ND	2.62	0.26	ND	ND
					2	ND	ND	3.13	0.31	ND	ND
					3	ND	ND	2.54	0.25	ND	ND
					4	ND	ND	3.25	0.32	ND	ND
					5	ND	ND	2.11	0.21	ND	ND
					6	ND	ND	2.34	0.23	ND	ND
					7	ND	ND	2.31	0.23	ND	ND
					8	ND	ND	2.53	0.25	ND	ND
					9	ND	ND	3.06	0.31	ND	ND
					Mean	**ND**	**ND**	**2.65**	**0.27**	**ND**	**ND**
S3046	**Paracetamol (Coated Tablet) – PVC**	**10**	**500mg**	**5000mg**	1	1.18	0.12	ND	ND	ND	ND
					2	3.03	0.30	ND	ND	ND	ND
					3	1.90	0.19	ND	ND	ND	ND
					4	1.78	0.18	ND	ND	ND	ND

Sample ID	Product/Pack Material	Tablets/blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol Content		Ibuprofen Content		Nicotine Content	
						µg/pack	µg/blister	µg/pack	µg/blister	µg/pack	µg/blister
					5	1.84	0.18	ND	ND	ND	ND
					6	2.62	0.26	ND	ND	ND	ND
					7	2.23	0.22	ND	ND	ND	ND
					8	3.02	0.30	ND	ND	ND	ND
					9	2.76	0.28	ND	ND	ND	ND
					Mean	**2.26**	**0.23**	**ND**	**ND**	**ND**	**ND**
S3059	**Paracetamol (Coated Tablet) - PP**	**10**	**500mg**	**5000mg**	1	<LOD	<LOD	ND	ND	ND	ND
					2	1.47	0.15	ND	ND	ND	ND
					3	0.81	0.08	ND	ND	ND	ND
					4	<LOD	<LOD	ND	ND	ND	ND
					5	<LOD	<LOD	ND	ND	ND	ND
					6	<LOD	<LOD	ND	ND	ND	ND
					7	<LOD	<LOD	ND	ND	ND	ND
					8	0.90	0.09	ND	ND	ND	ND
					9	<LOD	<LOD	ND	ND	ND	ND
					Mean	**1.06**	**0.11**	**ND**	**ND**	**ND**	**ND**

LOD – Limit of detection of 0.80 ug/pack or 0.08 ug/blister using lowest calibration standard

Nicotine Data is tentative and requires further review. Smithers requested for more samples

4.2.2 Sample with Pressure conditioning extraction

Paracetamol, Ibuprofen and Nicotine were detected in some their respective product extracts. The results are summarised in the following table.

Table 6: Total extractable results for samples subjected to pressure pre-conditioning

Sample ID	Product/Pack Material	Tablets/blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol Content		Ibuprofen Content		Nicotine Content	
						µg/pack	µg/blister	µg/pack	µg/blister	µg/pack	µg/blister
S2998	**Nicotine (Uncoated) - PVC/PVDC**	**15**	**4mg**	**60mg**	1	ND	ND	ND	ND	TBC	TBC
					2	ND	ND	ND	ND	TBC	TBC
					3	ND	ND	ND	ND	TBC	TBC
					4	ND	ND	ND	ND	TBC	TBC
					5	ND	ND	ND	ND	TBC	TBC
					6	ND	ND	ND	ND	TBC	TBC
					7	ND	ND	ND	ND	TBC	TBC
					8	ND	ND	ND	ND	TBC	TBC
					9	ND	ND	ND	ND	TBC	TBC
					Mean	**ND**	**ND**	**ND**	**ND**	**TBC**	**TBC**
S3000	**Nicotine (Coated) - PVC/PVDC**	**15**	**4mg**	**60mg**	1	ND	ND	ND	ND	TBC	TBC
					2	ND	ND	ND	ND	TBC	TBC
					3	ND	ND	ND	ND	TBC	TBC
					4	ND	ND	ND	ND	TBC	TBC
					5	ND	ND	ND	ND	TBC	TBC
					6	ND	ND	ND	ND	TBC	TBC
					7	ND	ND	ND	ND	TBC	TBC
					8	ND	ND	ND	ND	TBC	TBC
					9	ND	ND	ND	ND	TBC	TBC
					Mean	**ND**	**ND**	**ND**	**ND**	**TBC**	**TBC**

Sample ID	Product/Pack Material	Tablets/blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol Content		Ibuprofen Content		Nicotine Content	
						µg/pack	µg/blister	µg/pack	µg/blister	µg/pack	µg/blister
S3007	**Ibuprofen (Coated Tablet) - PVC**	**10**	**200mg**	**2000mg**	1	ND	ND	<LOD	<LOD	ND	ND
					2	ND	ND	<LOD	<LOD	ND	ND
					3	ND	ND	<LOD	<LOD	ND	ND
					4	ND	ND	<LOD	<LOD	ND	ND
					5	ND	ND	<LOD	<LOD	ND	ND
					6	ND	ND	<LOD	<LOD	ND	ND
					7	ND	ND	<LOD	<LOD	ND	ND
					8	ND	ND	<LOD	<LOD	ND	ND
					9	ND	ND	<LOD	<LOD	ND	ND
					Mean	**ND**	**ND**	**<LOD**	**<LOD**	**ND**	**ND**
S3008	**Ibuprofen (Liquid Gel Capsule) - PVC/DC**	**10**	**200mg**	**2000mg**	1	ND	ND	3.23	0.32	ND	ND
					2	ND	ND	3.07	0.31	ND	ND
					3	ND	ND	3.38	0.34	ND	ND
					4	ND	ND	3.50	0.35	ND	ND
					5	ND	ND	2.90	0.29	ND	ND
					6	ND	ND	2.52	0.25	ND	ND
					7	ND	ND	3.56	0.36	ND	ND
					8	ND	ND	7.96	0.80	ND	ND
					9	ND	ND	2.11	0.21	ND	ND
					Mean	**ND**	**ND**	**3.58**	**0.36**	**ND**	**ND**
S3046	**Paracetamol (Coated Tablet) - PVC**	**10**	**500mg**	**5000mg**	1	2.71	0.27	ND	ND	ND	ND
					2	2.94	0.29	ND	ND	ND	ND
					3	3.04	0.30	ND	ND	ND	ND
					4	5.91	0.59	ND	ND	ND	ND
					5	3.22	0.32	ND	ND	ND	ND
					6	2.44	0.24	ND	ND	ND	ND

Sample ID	Product/Pack Material	Tablets/blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol Content		Ibuprofen Content		Nicotine Content	
						µg/pack	µg/blister	µg/pack	µg/blister	µg/pack	µg/blister
					7	1.64	0.16	ND	ND	ND	ND
					8	2.77	0.28	ND	ND	ND	ND
					9	4.88	0.49	ND	ND	ND	ND
					Mean	**3.28**	**0.33**	**ND**	**ND**	**ND**	**ND**
S3059	**Paracetamol (Coated Tablet) - PP**	**10**	**500mg**	**5000mg**	1	<LOD	<LOD	ND	ND	ND	ND
					2	<LOD	<LOD	ND	ND	ND	ND
					3	<LOD	<LOD	ND	ND	ND	ND
					4	<LOD	<LOD	ND	ND	ND	ND
					5	<LOD	<LOD	ND	ND	ND	ND
					6	<LOD	<LOD	ND	ND	ND	ND
					7	<LOD	<LOD	ND	ND	ND	ND
					8	<LOD	<LOD	ND	ND	ND	ND
					9	<LOD	<LOD	ND	ND	ND	ND
					Mean	**<LOD**	**<LOD**	**ND**	**ND**	**ND**	**ND**

LOD – Limit of detection of 0.80 ug/pack or 0.08 ug/blister using lowest calibration standard

Nicotine Data is tentative and requires further review. Smithers requested for more samples

4.2.3 Sample with Vibration conditioning with extraction

Paracetamol, Ibuprofen and Nicotine were detected in some their respective product extracts. The results are summarised in the following table.

Table 7: Total extractable results for samples subjected to vibration pre-conditioning

Sample ID	Product/Pack Material	Tablets/blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol Content		Ibuprofen Content		Nicotine Content	
						µg/pack	µg/blister	µg/pack	µg/blister	µg/pack	µg/blister
S2998	**Nicotine (Uncoated) - PVC/PVDC**	**15**	**4mg**	**60mg**	1	ND	ND	ND	ND	TBC	TBC
					2	ND	ND	ND	ND	TBC	TBC
					3	ND	ND	ND	ND	TBC	TBC
					4	ND	ND	ND	ND	TBC	TBC
					5	ND	ND	ND	ND	TBC	TBC
					6	ND	ND	ND	ND	TBC	TBC
					7	ND	ND	ND	ND	TBC	TBC
					8	ND	ND	ND	ND	TBC	TBC
					9	ND	ND	ND	ND	TBC	TBC
					Mean	**ND**	**ND**	**ND**	**ND**	**TBC**	**TBC**
S3000	**Nicotine (Coated) - PVC/PVDC**	**15**	**4mg**	**60mg**	1	ND	ND	ND	ND	TBC	TBC
					2	ND	ND	ND	ND	TBC	TBC
					3	ND	ND	ND	ND	TBC	TBC
					4	ND	ND	ND	ND	TBC	TBC
					5	ND	ND	ND	ND	TBC	TBC
					6	ND	ND	ND	ND	TBC	TBC
					7	ND	ND	ND	ND	TBC	TBC
					8	ND	ND	ND	ND	TBC	TBC
					9	ND	ND	ND	ND	TBC	TBC
					Mean	**ND**	**ND**	**ND**	**ND**	**TBC**	**TBC**
S3007		**10**	**200mg**	**2000mg**	1	ND	ND	1.30	0.13	ND	ND

Sample ID	Product/Pack Material	Tablets/blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol Content		Ibuprofen Content		Nicotine Content	
						µg/pack	µg/blister	µg/pack	µg/blister	µg/pack	µg/blister
	Ibuprofen (Coated Tablet) - PVC				2	ND	ND	1.29	0.13	ND	ND
					3	ND	ND	1.24	0.12	ND	ND
					4	ND	ND	1.33	0.13	ND	ND
					5	ND	ND	1.61	0.16	ND	ND
					6	ND	ND	1.29	0.13	ND	ND
					7	ND	ND	1.15	0.12	ND	ND
					8	ND	ND	1.12	0.11	ND	ND
					9	ND	ND	1.30	0.13	ND	ND
					Mean	**ND**	**ND**	**1.29**	**0.13**	**ND**	**ND**
S3008	**Ibuprofen (Liquid Gel Capsule) - PVC/DC**	**10**	**200mg**	**2000mg**	1	ND	ND	6.10	0.61	ND	ND
					2	ND	ND	5.96	0.60	ND	ND
					3	ND	ND	5.85	0.58	ND	ND
					4	ND	ND	4.20	0.42	ND	ND
					5	ND	ND	5.07	0.51	ND	ND
					6	ND	ND	4.23	0.42	ND	ND
					7	ND	ND	10.40	1.04	ND	ND
					8	ND	ND	5.87	0.59	ND	ND
					9	ND	ND	5.98	0.60	ND	ND
					Mean	**ND**	**ND**	**5.96**	**0.60**	**ND**	**ND**
S3046	**Paracetamol (Coated Tablet) - PVC**	**10**	**500mg**	**5000mg**	1	4.31	0.43	ND	ND	ND	ND
					2	9.55	0.95	ND	ND	ND	ND
					3	5.83	0.58	ND	ND	ND	ND
					4	4.50	0.45	ND	ND	ND	ND
					5	4.32	0.43	ND	ND	ND	ND
					6	3.80	0.38	ND	ND	ND	ND
					7	5.79	0.58	ND	ND	ND	ND

Sample ID	Product/Pack Material	Tablets/blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol Content		Ibuprofen Content		Nicotine Content	
						µg/pack	µg/blister	µg/pack	µg/blister	µg/pack	µg/blister
					8	4.44	0.44	ND	ND	ND	ND
					9	4.18	0.42	ND	ND	ND	ND
					Mean	**5.19**	**0.52**	**ND**	**ND**	**ND**	**ND**
S3059	**Paracetamol (Coated Tablet) - PP**	**10**	**500mg**	**5000mg**	1	<LOD	<LOD	ND	ND	ND	ND
					2	1.47	0.15	ND	ND	ND	ND
					3	<LOD	<LOD	ND	ND	ND	ND
					4	<LOD	<LOD	ND	ND	ND	ND
					5	<LOD	<LOD	ND	ND	ND	ND
					6	1.24	0.12	ND	ND	ND	ND
					7	0.82	0.08	ND	ND	ND	ND
					8	<LOD	<LOD	ND	ND	ND	ND
					9	<LOD	<LOD	ND	ND	ND	ND
					Mean	**1.18**	**0.12**	**ND**	**ND**	**ND**	**ND**

LOD – Limit of detection of 0.80 ug/pack or 0.08 ug/blister using lowest calibration standard

Nicotine Data is tentative and requires further review. Smithers requested for more samples

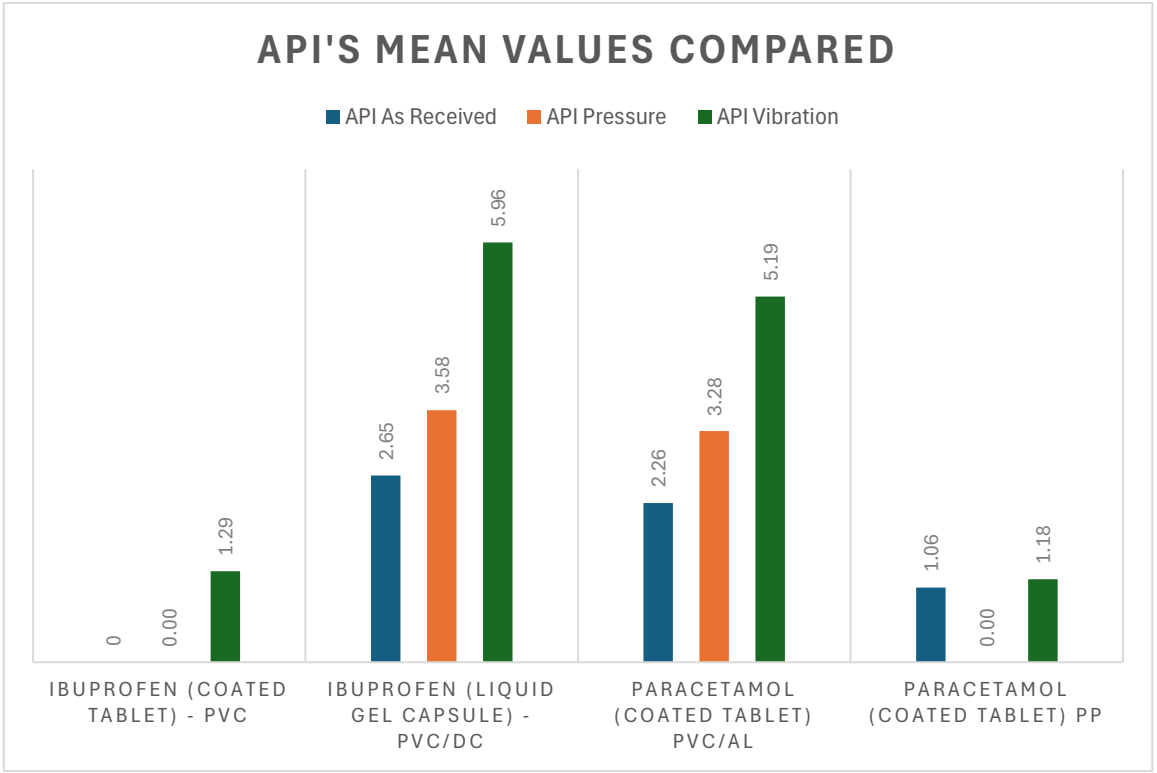
4.2.4 Discussion

The levels of extractables contaminations were compared to the original dose of API available in the tablets in the packs supplied and expressed as percentages of the available dose. The levels calculated show that the percentage contamination is trace level (see table 8).

Table 8: Extractable API as Percentage of Total Dose in Pack

Sample ID	Product/Pack Material	Blisters per pack	API product dose level per tablet	API product dose per pack	API As Received		API Pressure		API Vibration	
					ug/pack	% of pack dose	ug/pack	% of pack dose	ug/pack	% of pack dose
S2998	Nicotine (Uncoated) - PVC/PVDC	15	4mg	60mg	TBC	0.00000%	TBC	0.00000%	TBC	0.00000%
S3000	Nicotine (Coated) - PVC/PVDC	15	4mg	60mg	TBC	0.00000%	TBC	0.00000%	TBC	0.00000%
S3007	Ibuprofen (Coated Tablet) - PVC	10	200mg	2000mg	<LOD	<LOD	<LOD	0.00000%	1.29	0.00006%
S3008	Ibuprofen (Liquid Gel Capsule) - PVC/DC	10	200mg	2000mg	2.65	0.00013%	3.58	0.00018%	5.96	0.00006%
S3046	Paracetamol (Coated Tablet) - PVC	10	500mg	5000mg	2.26	0.00005%	3.28	0.00007%	5.19	0.00010%
S3059	Paracetamol (Coated Tablet) - PP	10	500mg	5000mg	1.06	0.00002%	<LOD	0.00000%	1.18	0.00002%

Figure 1: API's Mean Values Compared Chart



The results from the analysis of total contamination levels were measured under three different conditions; As Received, Pressure, and Vibration, across various pharmaceutical formulations of Ibuprofen and Paracetamol.

The data reveals that vibration consistently results in the highest contamination levels, particularly in Ibuprofen (liquid gel capsule – PVC/DC) and Paracetamol (coated tablet PVC/Al). These show a clear and substantial increase in contamination from the "As Received" state through to "Pressure" and peaking under "Vibration," indicating a strong sensitivity to mechanical stress.

In contrast, Ibuprofen (coated tablet – PVC) shows no or less than the LOD, contamination under "As Received" or "Pressure," with only a minimal amount observed under "Vibration," suggesting that this API and packaging combination is more resistant to external influences.

A second set of results for Paracetamol (coated tablet PP) shows low contamination in the "As Received" and "Vibration" states, with less than the LOD contamination under “Pressure”, further emphasising variability based on packaging and formulation.

Overall, the results suggest that both the physical form (e.g., gel capsule vs. tablet) and the packaging material (e.g., PVC, PVC/DC, PVC/Al, PP) significantly influence the number of contaminations released. Vibration poses the greatest risk for contaminations release, followed by pressure, while some formulations remain largely unaffected under certain conditions. This highlights the importance of evaluating packaging and handling conditions when assessing contaminations in pharmaceutical products.

4.2.5 Sample with Vibration conditioning with rinse and extraction

A stepped process incorporating a wash step prior to extraction was used to try to separate the physically adhered API from the migrated portion in the plastic. The extractable contamination results are given in the table below.

Table 9: Quantities of API in deionised water rinse (physically adhered contaminant) and deionised water extraction (chemically migrated into plastic)

Sample	Product/Pack Material	Tablets/ Blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol				Ibuprofen				Nicotine			
						µg/pack	µg/blister	Rinse extract µg/pack	Rinse extract µg/blister	µg/pack	µg/blister	Rinse extract µg/pack	Rinse extract µg/blister	µg/pack	µg/blister	Rinse extract µg/pack	Rinse extract µg/blister
S2998	**Nicotine (Uncoated) - PVC/PVDC**	**15**	**4mg**	**60mg**	1	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					2	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					3	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					4	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					5	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					6	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					7	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					8	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					9	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**TBC**	**TBC**	**TBC**	**TBC**
S3000	**Nicotine (Coated) - PVC/PVDC**	**15**	**4mg**	**60mg**	1	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					2	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					3	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					4	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					5	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					6	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					7	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					8	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					9	ND	ND	ND	ND	ND	ND	ND	ND	TBC	TBC	TBC	TBC
					Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**TBC**	**TBC**	**TBC**	**TBC**
S3007	**Ibuprofen (Coated Tablet) - PVC**	**10**	**200mg**	**2000mg**	1	ND	ND	ND	ND	<LOD	<LOD	ND	ND	ND	ND	ND	ND
					2	ND	ND	ND	ND	<LOD	<LOD	ND	ND	ND	ND	ND	ND
					3	ND	ND	ND	ND	<LOD	<LOD	ND	ND	ND	ND	ND	ND
					4	ND	ND	ND	ND	<LOD	<LOD	ND	ND	ND	ND	ND	ND

Sample	Product/Pack Material	Tablets/ Blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol				Ibuprofen				Nicotine			
						µg/pack	µg/blister	Rinse extract µg/pack	Rinse extract µg/blister	µg/pack	µg/blister	Rinse extract µg/pack	Rinse extract µg/blister	µg/pack	µg/blister	Rinse extract µg/pack	Rinse extract µg/blister
					5	ND	ND	ND	ND	<LOD	<LOD	ND	ND	ND	ND	ND	ND
					6	ND	ND	ND	ND	<LOD	<LOD	ND	ND	ND	ND	ND	ND
					7	ND	ND	ND	ND	<LOD	<LOD	ND	ND	ND	ND	ND	ND
					8	ND	ND	ND	ND	<LOD	<LOD	ND	ND	ND	ND	ND	ND
					9	ND	ND	ND	ND	<LOD	<LOD	ND	ND	ND	ND	ND	ND
					Mean	**ND**	**ND**	**ND**	**ND**	**<LOD**	**<LOD**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
S3008	**Ibuprofen (Liquid Gel Capsule) - PVC/DC**	**10**	**200mg**	**2000mg**	1	ND	ND	ND	ND	2.28	0.23	<LOD	<LOD	ND	ND	ND	ND
					2	ND	ND	ND	ND	3.46	0.35	<LOD	<LOD	ND	ND	ND	ND
					3	ND	ND	ND	ND	4.52	0.45	<LOD	<LOD	ND	ND	ND	ND
					4	ND	ND	ND	ND	3.71	0.37	<LOD	<LOD	ND	ND	ND	ND
					5	ND	ND	ND	ND	4.35	0.44	<LOD	<LOD	ND	ND	ND	ND
					6	ND	ND	ND	ND	3.08	0.31	<LOD	<LOD	ND	ND	ND	ND
					7	ND	ND	ND	ND	3.82	0.38	<LOD	<LOD	ND	ND	ND	ND
					8	ND	ND	ND	ND	3.63	0.36	<LOD	<LOD	ND	ND	ND	ND
					9	ND	ND	ND	ND	6.06	0.61	<LOD	<LOD	ND	ND	ND	ND
					Mean	**ND**	**ND**	**ND**	**ND**	**3.88**	**0.39**	**<LOD**	**<LOD**	**ND**	**ND**	**ND**	**ND**
S3046	**Paracetamol (Coated Tablet) – PVC**	**10**	**500mg**	**5000mg**	1	1.25	0.12	2.66	0.27	ND	ND	ND	ND	ND	ND	ND	ND
					2	<LOD	<LOD	3.62	0.36	ND	ND	ND	ND	ND	ND	ND	ND
					3	1.21	0.12	3.98	0.40	ND	ND	ND	ND	ND	ND	ND	ND
					4	2.11	0.21	3.03	0.30	ND	ND	ND	ND	ND	ND	ND	ND
					5	1.16	0.12	1.42	0.14	ND	ND	ND	ND	ND	ND	ND	ND
					6	1.01	0.10	2.83	0.28	ND	ND	ND	ND	ND	ND	ND	ND
					7	0.95	0.09	2.41	0.24	ND	ND	ND	ND	ND	ND	ND	ND
					8	1.34	0.13	3.18	0.32	ND	ND	ND	ND	ND	ND	ND	ND
					9	1.64	0.16	1.70	0.17	ND	ND	ND	ND	ND	ND	ND	ND
					Mean	**1.33**	**0.13**	**2.76**	**0.28**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Sample	Product/Pack Material	Tablets/ Blisters per pack	API product dose level per tablet	API product dose per pack	Replicate	Paracetamol				Ibuprofen				Nicotine			
						µg/pack	µg/blister	Rinse extract µg/pack	Rinse extract µg/blister	µg/pack	µg/blister	Rinse extract µg/pack	Rinse extract µg/blister	µg/pack	µg/blister	Rinse extract µg/pack	Rinse extract µg/blister
S3059	Paracetamol (Coated Tablet) - PP	10	500mg	5000mg	1	<LOD	<LOD	<LOD	<LOD	ND	ND	ND	ND	ND	ND	ND	ND
					2	0.90	0.09	<LOD	<LOD	ND	ND	ND	ND	ND	ND	ND	ND
					3	1.01	0.10	<LOD	<LOD	ND	ND	ND	ND	ND	ND	ND	ND
					4	<LOD	<LOD	<LOD	<LOD	ND	ND	ND	ND	ND	ND	ND	ND
					5	<LOD	<LOD	1.28	0.13	ND	ND	ND	ND	ND	ND	ND	ND
					6	<LOD	<LOD	<LOD	<LOD	ND	ND	ND	ND	ND	ND	ND	ND
					7	1.15	0.11	0.89	0.09	ND	ND	ND	ND	ND	ND	ND	ND
					8	1.10	0.11	<LOD	<LOD	ND	ND	ND	ND	ND	ND	ND	ND
					9	10.83	1.08	3.20	0.32	ND	ND	ND	ND	ND	ND	ND	ND
					Mean	**3.00**	**0.30**	**1.79**	**0.18**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

LOD – Limit of detection of 0.80 ug/pack or 0.08 ug/blister using lowest calibration standard

Nicotine Data is tentative and requires further review. Smithers requested for more samples

Table 10: Extractable levels as percentage of dose in pack for physical contamination (rinse extract) vs chemical contamination (plastic extraction)

Sample ID	Product/Pack Material	Blisters per pack	API product dose level per tablet	API product dose per pack	API Rinse		API Plastic	
					ug/pack	% of pack dose	ug/pack	% of pack dose
S2998	**Nicotine (Uncoated) - PVC/PVDC**	15	4mg	60mg	TBC	TBC	TBC	0.00000%
S3000	**Nicotine (Coated) - PVC/PVDC**	15	4mg	60mg	TBC	TBC	TBC	0.00000%
S3007	**Ibuprofen (Coated Tablet) - PVC**	10	200mg	2000mg	ND	0.00000%	<LOD	0.00000%
S3008	**Ibuprofen (Liquid Gel Capsule) - PVC/DC**	10	200mg	2000mg	<LOD	0.00000%	3.88	0.00019%
S3046	**Paracetamol (Coated Tablet) – PVC**	10	500mg	5000mg	2.76	0.00006%	1.33	0.00003%
S3059	**Paracetamol (Coated Tablet) - PP**	10	500mg	5000mg	1.79	0.00004%	3.00	0.00006%

The results show that Ibuprofen (S3007) in coated tablet form had no detectable contaminations, while Ibuprofen gel capsules (S3008) released a small amount from plastic extraction. Paracetamol samples (S3046, S3059) showed low but measurable contaminations in both rinse and plastic, with batch-to-batch variability. All contaminations were extremely low, with the highest being 0.00019%, indicating there are some variations with the contamination levels as percentage of dose in pack for physical contamination (rinse extract) vs chemical contamination (plastic extraction).

5. Conclusion

The extractables study has demonstrated clear evidence that handling conditions and the duration of pack lifecycle can significantly influence the level of active pharmaceutical ingredient (API) contamination observed on blister surfaces and within packaging systems. Specifically, mechanical stresses such as vibration were shown to induce a greater degree of API migration and surface adherence compared to pressure conditioning and the “as received” analysis.

The investigation evaluated four pharmaceutical products: Ibuprofen and Paracetamol, each in different dosage forms and packaging configurations. Test conditions included as received, pressure, and vibration, with each sample comprising 10 units per pack and total drug content per pack ranging from 2,000 mg to 5,000 mg. As agreed with GSCF, deionised water was used as the rinse and extraction solvent. Extractable API contamination was detected in four out of the six samples, highlighting that under certain conditions, measurable migration can occur.

The results show that vibration conditioning consistently resulted in the highest levels of contaminations, particularly for Ibuprofen (Liquid Gel Capsule – PVC/DC) and Paracetamol (Coated Tablet, PVC/Al) packs. These dosage forms, due to their softer or encapsulated nature, appear to be more susceptible to mechanical stress, allowing trace amounts of API to leach or adhere to the pack materials. In contrast, Ibuprofen (Coated Tablet – PVC) demonstrated the greatest resistance to contaminations, with either no detectable API contamination or values below the limit of detection across all test conditions. Furthermore, the study confirms that product format (coated tablet vs. gel capsule) and packaging composition (PVC vs. PVC/DC, PVC/Al, PP) are critical factors influencing the contaminations profile. More flexible or permeable systems tend to exhibit a higher inclination for contamination under simulated stress conditions.

Although the contamination levels identified in all cases were extremely low, less than 0.0002% of the total pack dose, the findings underline the importance of evaluating packaging materials and handling conditions for this type of packaging. Even when initial contamination levels are undetectable, post-handling scenarios like transportation or prolonged vibration can trigger a measurable increase in API migration.

Nicotine results and discussions will be shared later due to continued discussion with GSCF regarding the recent data.

Analysed by:

08/08/2025

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Appendix 1 – Sample Pictures:

Nicorette Gum PVC/PVDC- Alu Coated (top) and Nicorette Gum PVC/PVDC- Alu Uncoated (bottom)

Nurofen Tablets PVC- Alu (left) and Nurofen Express Capsules PVC/DC- Alu (right)

Panadol Actifast - PVC (left) and Panadol Zapp - PP (right)