PCCA RESEARCH & DEVELOPMENT

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Manual

Anhydrous SuspendIt®

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SuspendIt Anhydrous (PCCA #30-5176)

The new and innovative SuspendIt Anhydrous is an anhydrous oral suspension vehicle for use in oral suspension formulations. It is ideal for unstable APIs, offers improved taste, broader application and prolonged default beyond-use dates (BUDs). SuspendIt Anhydrous is preservative-free and thus has a broad use in pediatric patients.

Its unique self-emulsifying system potentially improves solubility, dispersibility and absorption of APIs, while its thixotropic effect potentially offers rapid redispersion of APIs with minimal sedimentation. And with water activity less than 0.6 (Aw<0.6), SuspendIt Anhydrous is classified as an anhydrous oral vehicle that allows pharmacy compounders to assign longer default BUDs.

Unique Self-Emulsifying Drug Delivery System (SEDDS)

- Combines surfactants within an anhydrous oral vehicle
- Provides smaller and more uniform emulsion droplet sizes to help promote the potential for improved absorption and bioavailability
- Potentially improves solubility and dispersibility of APIs
- May be used with hydrophilic or lipophilic drugs
- Easily mixes with water or juice without need of additional surfactants

Synergistic Thixotropic Effects

- Thins when shaken and thickens when standing
- Allows rapid redispersion of APIs with agitation and minimizes sedimentation once settled

Unlike traditional fixed oil suspensions and other oral suspensions, SuspendIt Anhydrous mixes easily with water or juice to improve patient compliance. It's also compatible with polyurethane feeding tubes for use in hospice, neonatal care and other healthcare settings.

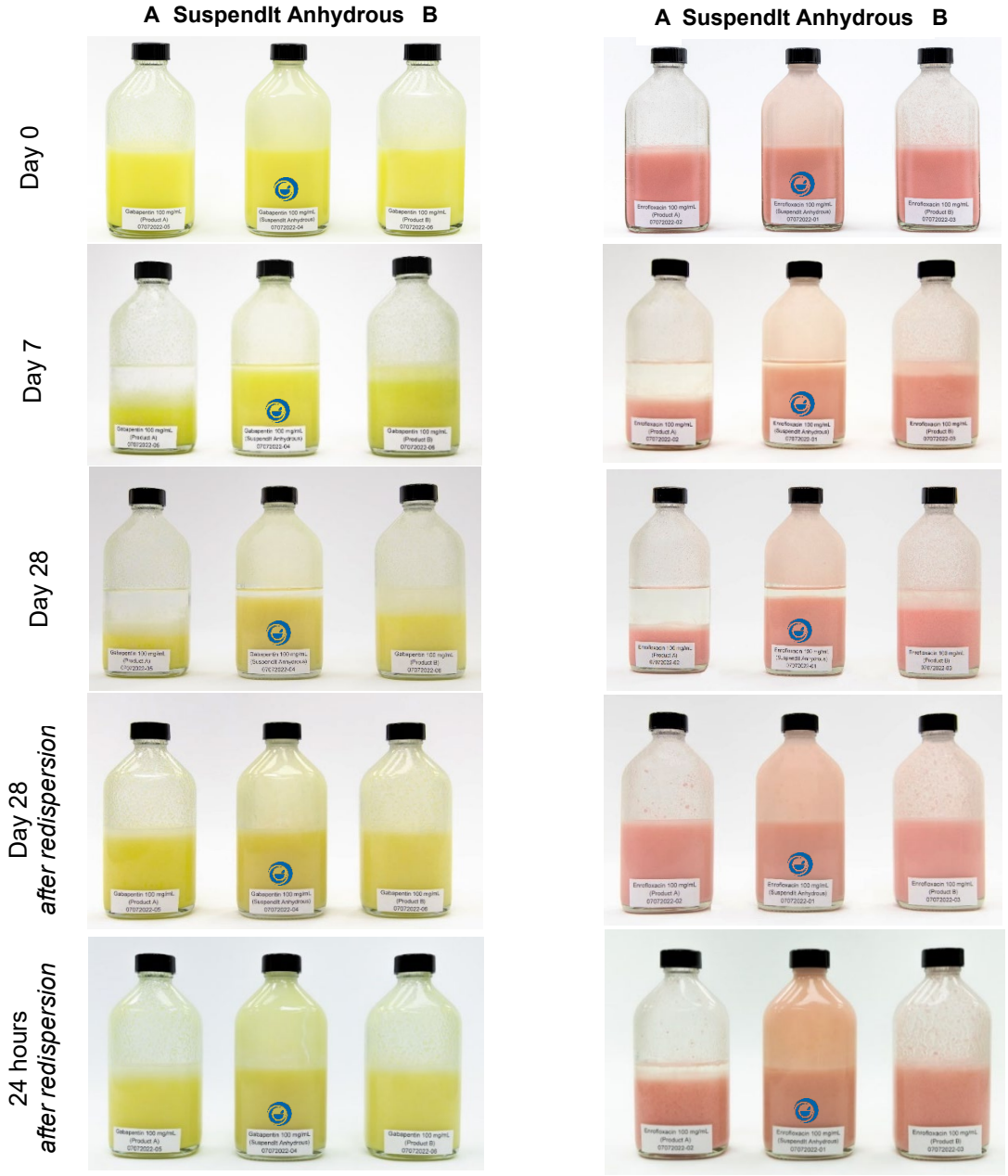
Mixing a single dose of medication with juice or other flavored liquids at time of administration helps disguise the medication's taste, which may possibly improve medication compliance in children, hospice patients and pets.

Evaluation of the Physical Properties of SuspendIt Anhydrous – *Part 1: Sedimentation*

Introduction: Sedimentation is the simple process in which suspended particles separate from a liquid upon settling on the bottom because of gravity. The sedimentation properties of SuspendIt Anhydrous were evaluated and compared to the performance of competitor products.

Methodology: A gabapentin 100 mg/mL anhydrous suspension (banana cream, yellow color) and an enrofloxacin 100 mg/mL anhydrous suspension (raspberry flavor, pink color) were prepared using SuspendIt Anhydrous, Competitor A and Competitor B. The suspensions were placed in a standing position at room temperature for 30 days. On day 28, the glass containers were shaken vigorously with the same amount of force and duration, and allowed to settle again.

Results and Discussion: On day 0, the three suspensions exhibited similar appearance, although a little separation was evident at the top for the Competitor A and B products. By days 7 and 28, the settling of suspended particles was remarkable for the Competitor A and B products. The sedimentation volumes were as follows: 40% (Competitor A), 88% (SuspendIt Anhydrous) and 70% (Competitor B). All suspensions resuspended after shaking on day 28. Then 24 hours following redispersion (day 29), the SuspendIt Anhydrous remained a homogenous suspension with no signs of separation, as opposed to the Competitor A and B products.



Evaluation of the Physical Properties of SuspendIt Anhydrous – *Part 2: Thixotropic Properties*

Introduction:

Thixotropic properties of suspensions refer to the time-dependent, reversible changes in viscosity (resistance to flow). Ideally, suspensions are thixotropic and exhibit stable viscous properties at rest but become fluid when agitated.

Methodology:

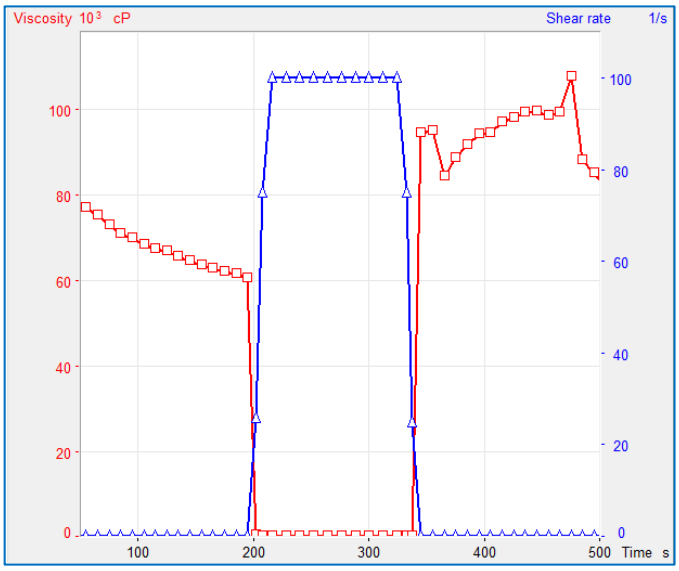
The thixotropic properties of SuspendIt Anhydrous were evaluated and compared to the industry-standard PCCA SuspendIt. The viscosity instrument used was the Brookfield Viscometer DV-II + Pro. SuspendIt Anhydrous and SuspendIt were added to a 600 mL beaker and mixed for 5 minutes at 700 rpm. The suspensions were then allowed to rest for 10 minutes. The shear rate applied was 0.1 – 100 1/s.

Results and Discussion:

SuspendIt Anhydrous exhibited similar synergistic thixotropic properties to SuspendIt, as shown in Figure 1 (left versus right). When low shear (0.1/s) was applied for the first 200 seconds, both suspensions maintained their viscosity at rest (blue lines). Viscosity dropped to around 0 cp (red lines) immediately after shear rate was increased (100/s). Later when shear was back to low rate (0.1/s), both suspensions regained their viscosity at rest within seconds.

The thixotropic properties of both suspensions are described as: thinning when shaken and thickening upon standing. Thinning when shaken is an important property that allows for a rapid redispersion of APIs and thus ensures dose uniformity. It also facilitates the measurement and administration of each dose. Thickening upon standing minimizes sedimentation of APIs once the suspensions settle. This property ensures superior physical stability of the suspensions.

PCCA SuspendIt Anhydrous



PCCA SuspendIt

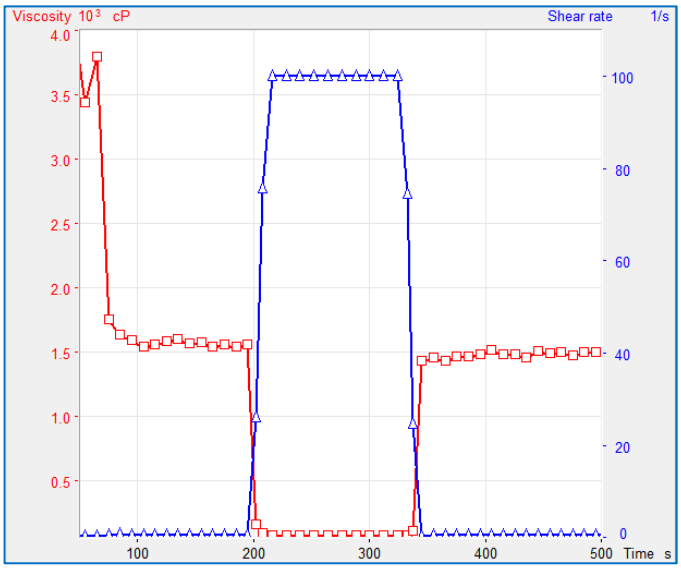


Figure 1. Thixotropic properties of SuspendIt Anhydrous (left) and PCCA SuspendIt (right) at room temperature. Red lines represent the change of viscosity and blue lines represent the change of shear rate.

Evaluation of the Physical Properties of SuspendIt Anhydrous – *Part 3: Droplet Size*

Introduction:

Droplet size is an important parameter when evaluating an anhydrous suspension which is also a self-emulsifying drug delivery system. When in contact with an aqueous phase and under gentle mixing (i.e., the gastric fluid and the gastrointestinal movements), the anhydrous suspension will generate a fine emulsion. The small and uniform droplets generated in emulsions are known to contribute to improved intestinal absorption and drug bioavailability.

Methodology:

Compounded anhydrous oral suspensions were prepared for ibuprofen 40 mg/mL in PCCA SuspendIt Anhydrous, and also for ibuprofen 40 mg/mL in the anhydrous vehicle by Competitor B. The purpose of this study was to compare the droplet size of ibuprofen in the compounded anhydrous oral suspensions versus the commercial product of reference for ibuprofen 40 mg/mL.

The test samples were prepared by shaking the containers vigorously for about 30 seconds. The analysis consisted of dispersing 10 g of each suspension in 15 mL of simulated gastric fluid, followed by 1 hour of stirring. The droplet size detector used was the Saturn DigiSizer II 5205 V1.04. Sampling conforms to PTA SOP 001/44053/00 and the tests were run in accordance with ISO 13320. The droplet size testing was performed by Particle Testing Authority, Norcross, GA.

Results and Discussion:

Most of the ibuprofen droplets in the PCCA SuspendIt Anhydrous presented a diameter of about 48.5 – 65.4 µm. These results are very similar to those obtained for the ibuprofen 40 mg/mL commercial product of reference, as shown in Table 1. In the contrary, most of the ibuprofen droplets in the Competitor B presented a much larger diameter of about 192.7 – 255.3 µm.

It is concluded that SuspendIt Anhydrous contributed to a small droplet size diameter for ibuprofen, comparable to the commercial product of reference, potentially facilitating improved absorption and bioavailability of the compounded anhydrous oral suspensions.

Table 1. Droplet size diameter distribution by selected percentiles for ibuprofen 40 mg/mL in two compounded anhydrous oral suspensions versus the commercial product of reference.

Suspensions	Droplet Size Diameter (µm)			
	90%	50%	10%	Mean ± Std Dev
Ibuprofen 40 mg/mL (PCCA SuspendIt Anhydrous)	65.422	48.519	8.097	43.162 ± 0.898
Ibuprofen 40 mg/mL (Reference Commercial Product)	73.228	36.356	9.891	38.652 ± 0.142
Ibuprofen 40 mg/mL (Competitor B)	255.273	192.657	96.671	183 ± 0.034

Evaluation of the Content Uniformity of 13 SuspendIt Anhydrous Formulations

Introduction:

Suspensions are pharmaceutical dosage forms consisting of insoluble Active Pharmaceutical Ingredients (APIs) dispersed in a liquid medium (suspending vehicle). The content uniformity is defined as the consistency in the amount of APIs among dosage units. An ideal suspension should be uniform in content so that each dose is equivalent in the amount of APIs. Content uniformity within a suspension is highly dependent on the characteristics of the suspending vehicle. If a suspending vehicle is too viscous, the APIs will not be easily dispersed. In contrast, if the suspending vehicle is too thin, the APIs will settle at the bottom of the container.

The purpose of this study was to evaluate the content uniformity of 13 suspensions, each containing one API dispersed in SuspendIt Anhydrous.

Methodology:

The evaluation of the content uniformity was divided in two stages:

1. Elaboration of the 13 anhydrous suspensions according to the corresponding PCCA Formulas (see Table 1). Some formulas were prepared in the PCCA laboratory using the FlackTek SpeedMixer® (indicated below).

2. Potency testing by Ultra-Performance Liquid Chromatography (UPLC) assay. The test samples were stored at room temperature and were analyzed by the analytical laboratory in the PCCA Research & Development department or by Eagle Analytical Services, Inc. For each sample, 10 sampling points were taken for analysis and the value reported is the average of all sampling points.

Results and Discussion:

The potency testing showed that none of the anhydrous suspensions were outside of the 90.0%-110.0% potency specification (USP <621> chapter: Chromatography). As such, the new proprietary vehicle SuspendIt Anhydrous successfully contributed to the content uniformity of multiple APIs in variable strengths.

Table 1. Mean potency (percentage of recovery) at room temperature for 13 SuspendIt Anhydrous formulations.

Oral Suspensions (SuspendIt Anhydrous)	*PCCA Formula*	*Mean Potency (%)*	*Standard Deviation*
Chloroquine Phosphate 100 mg/5 mL	14216	104.0	1.054
Doxycycline 50 mg/mL	14222	101.0	1.323
Doxycycline 100 mg/mL	14223	100.0	1.50
Doxycycline 100 mg/mL (FlackTek SpeedMixer)	14424	102.0	1.889
Enrofloxacin 10 mg/mL (Vet)	14224	99.0	0.812
Enrofloxacin 100 mg/mL (Vet)	14225	100.0	0.569
Ketotifen 1 mg/mL	14241	101.1	1.000
Metronidazole 50 mg/mL	14243	104.6	1.381
Metronidazole 50 mg/mL (Alternate)	14244	104.2	1.497
Nifedipine 4 mg/mL	14247	96.6	0.686
Phenoxybenzamine HCl 2 mg/mL	14252	95.5	1.595
Tretinoin 10 mg/mL	14260	100.74	0.875
Tretinoin 10 mg/mL (FlackTek SpeedMixer)	14429	102.0	1.197

Conclusion:

This study has demonstrated that all 13 SuspendIt Anhydrous formulations were uniform in content. By following the corresponding PCCA formulas, compounding pharmacists are likely to meet the requirements of content uniformity and, as a result, dispense anhydrous oral suspensions in accordance to the labeled claim.

Evaluation of the Self-Emulsifying Properties of SuspendIt Anhydrous – *Part 1: Microscopic Evaluation*

Introduction:

PCCA SuspendIt Anhydrous is a Self-Emulsifying Drug Delivery System (SEDDS) that creates a spontaneous emulsion when it comes into contact with water. This emulsion then releases the Active Pharmaceutical Ingredients (APIs) from the oral base, potentially achieving increased drug solubility, dispersibility, absorption and bioavailability. SuspendIt Anhydrous combines surfactants within an anhydrous oral vehicle, and it easily mixes with water or juice without need of additional surfactants. The self-emulsifying properties are likely to improve dispersibility of water-soluble drugs and drug release of lipophilic drugs.

Methodology:

The self-emulsifying properties of SuspendIt Anhydrous were evaluated in 2 Parts: Microscopic Evaluation and Fluorescence Microscopy. In both tests, SuspendIt Anhydrous was compared to competitor products. For the microscopic evaluation, a metronidazole 50 mg/mL anhydrous suspension was prepared using SuspendIt Anhydrous, Competitor A and Competitor B. The three suspensions were mixed in water at 1:1 ratio (v/v). Afterwards, a sample of each suspension was observed under a light microscope with a total magnification of 100x for evaluation of the droplet size formation.

Results and Discussion:

When the metronidazole 50 mg/mL anhydrous suspensions were mixed with water, the suspension using the PCCA SuspendIt Anhydrous formed a uniform emulsion, which is a good indicator for drug absorption. On the other hand, the suspensions using the competitor products were immiscible with water, and thus formed two separate phases (Figure 1).

When the samples were observed under the microscope at 4x magnification, the suspension using the PCCA SuspendIt Anhydrous showed, once again, a homogeneous dispersion (Figure 2). In the contrary, the Competitor A suspension displayed aggregation of metronidazole (Figure 3, highlighted with arrow) and the competitor B suspension showed separation of the water and oily phases (Figure 4, highlighted with arrow).

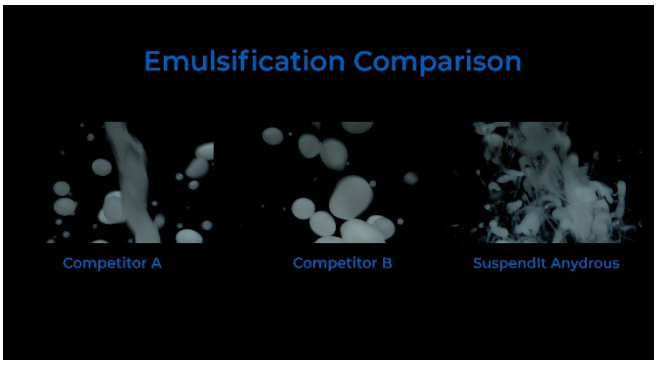
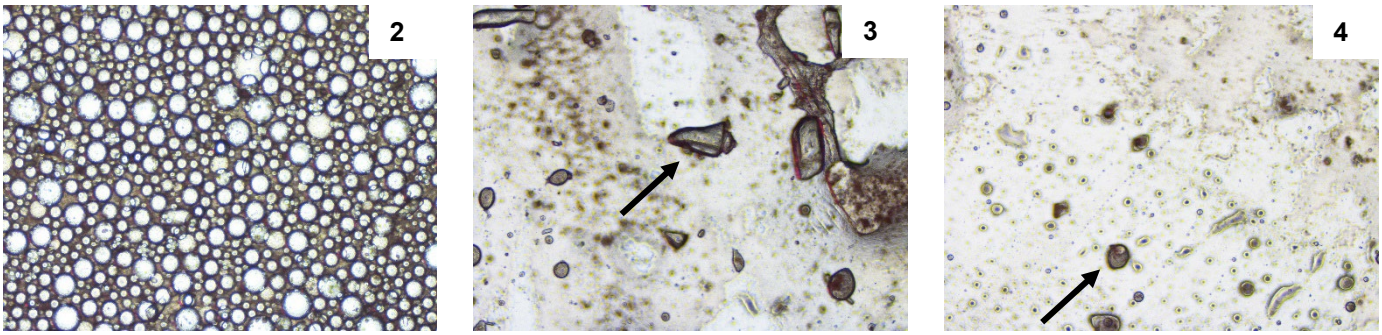


Figure 1. Video illustration of the emulsification properties of SuspendIt Anhydrous versus Competitors A and B: *https://player.vimeo.com/video/762054101*

The SEDDS in SuspendIt Anhydrous allows for the formation of a uniform emulsion, characterized by small and homogeneous droplets. As a result, it is expected that the self-emulsifying properties of SuspendIt Anhydrous are likely to promote increased drug solubility, dispersibility, absorption and bioavailability.

SuspendIt Anhydrous **Competitor A** **Competitor B**



Figures 2-4. Microscopic evaluation of droplet size formation (4x objective lens) for metronidazole 50 mg/mL anhydrous suspension prepared using SuspendIt Anhydrous (left) and Competitor B (right) mixed with water.

Evaluation of the Self-Emulsifying Properties of SuspendIt Anhydrous – *Part 2: Fluorescence Microscopy*

Introduction and Methodology:

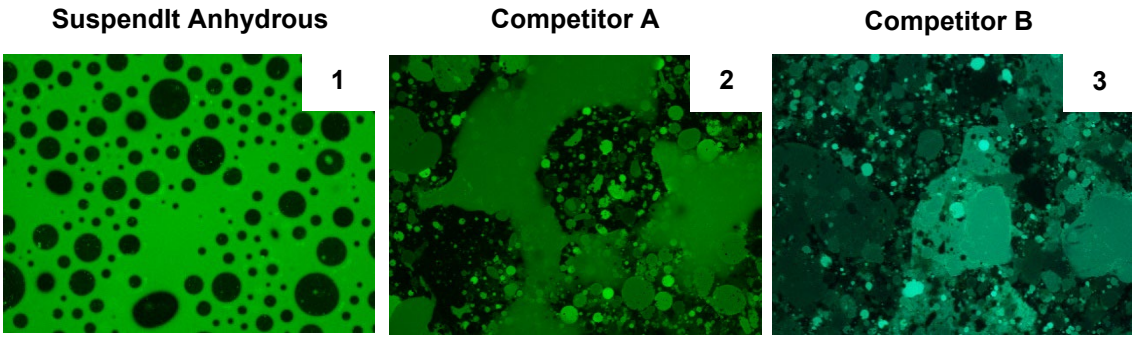
The purpose of this study is to explore further the self-emulsifying properties of SuspendIt Anhydrous by evaluating the distribution pattern of the hydrophilic substance fluorescein sodium (high solubility), and also the lipophilic substance curcumin (low solubility and high permeability), in comparison to the performance of competitor products. Fluorescein sodium 1% anhydrous suspensions and curcumin 1% anhydrous suspensions were prepared including PCCA SuspendIt Anhydrous, as well as the Competitor A and the Competitor B anhydrous vehicles. All suspensions were gently mixed with water at 1:1 ratio (v/v).

A fluorescence microscopy test was performed on all suspensions using fluorescent light and, when applicable, white light at 4x and 10x objective lens. Photographs were taken with a Nikon Eclipse TS100 inverted phase microscope coupled with the NIS-Elements imaging software.

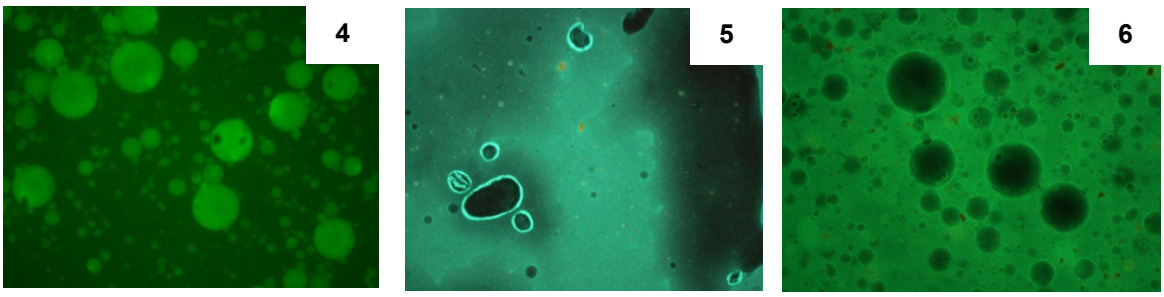
Results and Discussion:

Fluorescein sodium and curcumin were selected in this study for research purposes only to represent the hydrophilic and lipophilic APIs that are commonly used in clinical practice. Results show that upon mixing of the anhydrous suspension with water at 1:1 ratio (v/v), the PCCA SuspendIt Anhydrous exhibits its unique self-emulsifying properties by creating an emulsion, i.e., dispersed lipophilic droplets in an aqueous continuous phase. Fluorescein sodium was solubilized in the water phase which resulted in a uniform emulsion (Figure 1). In the contrary, for the competitors A and B, no uniform emulsion was formed. Most of the fluorescein sodium was soluble in water, and there was separation between the water and oily phases (Figures 2 and 3).

As expected, the insoluble curcumin was enclosed inside the oil droplets and a uniform emulsion was formed for the SuspendIt Anhydrous (Figure 4). For the Competitors A and B, the curcumin mainly dispersed in the oil phase but not in water and, once again, there was separation between the oil and water phases (Figures 5 and 6).



Figures 1-3. Fluorescence microscopy (fluorescent light) at 4x objective lens for fluorescein sodium 1% in the PCCA SuspendIt Anhydrous, as well as the Competitor A and the Competitor B anhydrous vehicles.



Figures 4-6. Fluorescence microscopy (fluorescent light) at 10x objective lens for curcumin 1% in the PCCA SuspendIt Anhydrous, as well as the Competitor A and the Competitor B anhydrous vehicles.

In Vitro Nasogastric Feeding Tube Testing for SuspendIt Anhydrous

Introduction:

Nasogastric feeding tubes are commonly used in patients when enteral nutrition is required. However, tube clogging remains a significant barrier to the delivery of the nutritional support and attention must always be paid to this potential complication. It is also essential that drug administered via a nasogastric tube preserves the correct dose when exiting from the tube. The purpose of this study was to evaluate the likelihood of compounded anhydrous suspensions (metronidazole 50 mg/mL, tretinoin 10 mg/mL and nifedipine 4 mg/mL) to block or leave residues in nasogastric feeding tubes, as well as to determine the corresponding drug recovery rates.

Methodology:

A nasogastric feeding tube (Polyurethane, 6.5 Fr x 90cm, NEOMED) for use in neonatal and pediatric patients was set up for testing. The tube was prepared by flushing 5 mL of deionized water. Formulations were prepared using either PCCA SuspendIt Anhydrous or the corresponding Competitor A and Competitor B anhydrous vehicles. With an oral syringe, each dose was pushed through the nasogastric feeding tube at a rate of 5 mL / 25s into a graduated cylinder, followed by flushing with 10 mL of water (Figure 1). The resulting volume was measured, and potency testing was determined by HPLC. The tube was then checked for any signs of residues or clogging after air drying and photographs were taken.

Results and Discussion:

The amount of metronidazole, tretinoin and nifedipine recovered from the feeding tubes was >95% for SuspendIt Anhydrous, as shown in the table below. On the day after the recovery test, it was observed that there were no significant drug residues throughout the nasogastric tube, nor at the exit of the tube, for the oral suspensions in SuspendIt Anhydrous (Figure 2). On the contrary, there was visible accumulation of drug residues for the corresponding Competitor A and Competitor B oral suspensions, which suggests potential tube clogging (Figures 3 and 4).

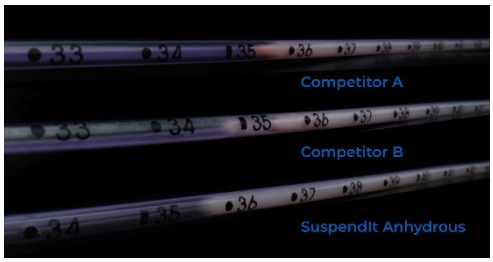


Figure 1. Video illustration of the nasogastric feeding tube testing: *https://player.vimeo.com/video/762054335*

	Potency (mg/mL)	Volume (mL)	Total amount (mg)	Drug recovery
Metronidazole 50 mg/mL SuspendIt Anhydrous				
Delivered	52.28	5.0	261.4	96.02%
Recovered	50.20	5.0	251.0	
Tretinoin 10 mg/mL SuspendIt Anhydrous				
Delivered	10.07	10.0	100.7	100%
Recovered	10.30	9.9	102.0	
Nifedipine 4 mg/mL SuspendIt Anhydrous				
Delivered	3.93	10.0	39.3	100%
Recovered	4.25	9.9	42.1	

SuspendIt Anhydrous **Competitor A** **Competitor B**

Figures 2-4. Nasogastric feeding tubes (exit) on the day after the recovery test for the metronidazole oral suspensions in PCCA SuspendIt Anhydrous and the corresponding Competitor A and Competitor B products.