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Research Article

Physicochemical and microbiological evaluation of ibuprofen suspension produced using *Detarium microcarpum* as suspending agent

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Abstract

Suspensions are two phase systems composed of solid materials dispersed in liquid. *Detarium microcarpum* gum (DMG) was obtained by acetone precipitation of filtrate obtained from maceration of *Detarium microcarpum* seed powder using distilled water. Ibuprofen was pulverized using a mortar and dispersed in distilled water to form ibuprofen suspension formulation (IS1). Five other ibuprofen suspension formulations were prepared using either DMG or acacia as the suspending agent (IS2-IS6). Benzoic acid was added during the preparation of formulations IS4 and IS6 as preservative. Physicochemical properties like pH, viscosity and the total microbial count for the suspensions were evaluated. Drug-excipient compatibility was studied using FTIR spectroscopy. The pH of the suspensions ranged from 3.7±0.0 -5.3±0.0 on day 0 to 3.9±0.0 - 6.3±0.0 on day 35. Flow rate was from 2.21±0.13 – 33.00±3.70 mls^{-1} on day 0 to 1.88±0.12 – 20.19±0.16 mls^{-1} on day 35. The viscosity at 25°C ranged from 2391.3 – 5702.2 mPas on day 0 to 3793.0 – 3828.2 mPas on day 35. It was a shear thinning system. Formulation IS6 was the most stable and IS1 was the least stable. The suspensions contained high level of bacteria on day 0 which increased significantly on day 35, with exception of formulations IS4 and IS6. Ibuprofen suspensions with good physicochemical properties were produced using DMG but the level of microbial contamination observed highlighted the need of having good environmental hygiene and use of preservatives when natural gums are used in formulations.

Keywords: ibuprofen, *Detarium microcarpum*, suspension, suspending agent, microorganisms

INTRODUCTION

Suspensions are two phase systems made up of solutes dispersed in liquid, which may be aqueous or oily. It can also be defined as a preparation containing finely divided insoluble material suspended in a liquid medium.[1] Different types of drugs such as paracetamol[2], antacids[3], ciprofloxacin[4] e.t.c. have been prepared as suspensions. Suspension is thermodynamically unstable; therefore, addition of suspending agent will reduce the rate of settling and ensure easy redispersion of any settled particulate matter. This allows for the withdrawal of uniform dose during administration. This is achieved by protective colloidal action and also by enhancing the viscosity of the suspending medium.[4] Suspending agents can be synthetic, semi-synthetic or of natural origin. Some natural gums like okra gum[5], tragacanth gum, *Sida acuta* gum[2], Aloe elegans Mucilage[6], Aloe weloensis mucilage[7], *Trigonella foenum graecum* mucilage[4], grewia polysaccharide gum[8], Grewia ferruginea mucilage[9] and *Brachystegia eurycoma* gum[10] were used as suspending agents in the formulation of suspensions. The advantages of the use of natural gums as suspending agents when compared to synthetic ones include biocompatibility, low cost, easy availability, biodegradable and environmental friendliness.[5] However, they have some drawbacks which include: reduced viscosity on storage, easy microbial contamination and uncontrolled rate of hydration.[5, 11] Suspensions can be grouped as flocculated or deflocculated due to the electrokinetic nature of their solid particles. In flocculated suspensions, the suspended particles aggregate loosely to form flocs or floccules which allow molecules of the dispersion medium to pass through them and sediment quick due to the reduced free energy. Therefore, flocculated suspensions are easier to be redispersed by shaking as compared to deflocculated suspensions. In deflocculated suspensions, the particles are not aggregated, they sediment more slowly and form a smaller but more compact sediments, called cake, that is harder to redisperse.[12, 13]

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) is utilized in the treatment of pain caused by headaches, toothaches, back pain, rheumatoid arthritis, osteoarthritis and slight injuries. It is used to relieve muscle spasm, and in reducing fever and any other nonspecific inflammation[14, 15]. It is a phenyl propionic acid derivative ((RS)-2-(4-(2-methylpropyl) phenyl) - propionic acid) and one of the best tolerated NSAIDs.[14, 15] It is a non-selective inhibitor of cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2). Ibuprofen is almost insoluble in water and this makes it a good candidate for suspension formulation.[16]

Detarium microcarpum gum (DMG) is a polysaccharide isolated from *Detarium microcarpum,* Guill. and Perr. (Fam. Fabaceae) seeds.[17] *Detarium microcarpum* plant is found

uncultivated in some parts of the semi-arid sub-Saharan and tropical zones of Africa. The seeds are edible and are utilized in some towns in Nigeria for thickening of soups. In hot water, it exhibits a unique characteristic behaviour, displaying different degrees of the viscoelastic properties.[18] The Igbo people (South East, Nigeria) calls the tree, ofo while the English and the French call it sweet detar, sweet dattock or tallow tree and *petit détar* respectively.[17] The seeds are produced in abundance in some parts of Nigeria but are only utilized as soup thickeners. The low level of utilization of the seeds creates the need for expansion of its use as pharmaceutical raw material or excipients.

This study was conducted to determine the use of DMG as a suspending agent in the formulation of ibuprofen suspensions and to evaluate the effect that microorganisms have on the formulated suspensions.

MATERIALS AND METHODS

Materials

All the chemicals used were of analytical quality. Ibuprofen (Sigma-Aldrich, UK), benzoic acid (Central Drug House, India), acacia (Titan Biotech, India), acetone (JHD, Guangdang Guanghua Chemical Factory Co. Ltd, China), disodium hydrogen phosphate dodecahydrate (Xilong Chemical Co., Ltd, China), sodium dihydrogen phosphate dehydrate (Guangdong Guanghua Sci-Tech Co., Ltd, China),

Isolation of *Detarium microcarpum* gum

Detarium microcarpum seeds were purchased from Abakpa market, in Enugu, Enugu State, Nigeria. The seed was identified and issued voucher number PCG/UNN/0067 by Mr. Felix Nwafor a taxonomist working with the Department of Pharmacognosy and Environmental Medicine, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria. *Detarium microcarpum* gum (DMG) was extracted from the seeds using the method of Okafo *et al*..[17, 18] The seeds were pulverized and a 200 g of the powder was weighed and transferred into a small bucket. It was mixed properly with 3 liters of distilled water and macerated undisturbed for 24 h. The slurry was filtered using a clean muslin cloth and the produced filtrate was precipitated using equal volumes of acetone. Acetone was used to wash the crude gum twice before it was dried in an oven at 50°C for 6 h. The dried gum was pulverized in a mortar and passed through sieve with 300 µm mesh. The fine gum powder was stored in a tightly closed container.

Preparation of ibuprofen suspensions

The suspensions were prepared using the formula in Table 1. The suspending agent (acacia or DMG) was hydrated with water and turned into mucilage in a mortar. Ibuprofen with or without benzoic acid was added to the mucilage and triturated together thoroughly. Water was added to make it pourable. It was mixed properly and transferred into a 50 ml measuring cylinder. The various formulations were prepared using the same method and were kept on a stable undisturbed platform for 5 weeks.

Table 1: Composition of ibuprofen suspension formulations IS1 to IS6

Ingredient	IS1	IS2	IS3	IS4	IS5	IS6
Ibuprofen (g)	1	1	1	1	1	1
Detarium microcarpum gum (g)	-	-	1	1	2	2
Benzoic acid (g)	-	-	-	0.5	-	0.5
Acacia (g)	-	2	-	-	-	-
Water to (ml)	50	50	50	50	50	50

Physicochemical evaluation of ibuprofen suspensions

Physical examination (organoleptic studies)

Organoleptic properties such as colour and odour of the different ibuprofen suspensions were noted on day 0 and on day 35.[19, 20]

pH

A pH meter (model HI 2211 pH/ORP meter, Hanna Instruments, India) was utilized in the determination of the pH of the various paracetamol suspension formulations on day 0 and on day 35. The pH determinations were done in triplicate.[2, 21. 22]

Viscosity/ Flow Rate

The viscosity of the various ibuprofen suspension formulations was determined at 25°C using spindle 3 of a Brookfield viscometer (NDJ viscometer, India) set at 6, 12, 30 and 60 rpm respectively. The determinations were done three times on day 0 and on day 35 and results shown as mean ± standard deviation.[4, 23]

A slight modification of the method of Kolo et al[24] was used. A 10 ml quantity of the various ibuprofen suspensions were filled in respective burettes and the time it took the suspensions to flow through the orifice of the burettes were noted. The flow rate was calculated using equation 1:

$$Flow\ rate = \frac{Volume\ of\ burette\ (ml)}{Flow\ time\ (s)} \quad . \ . \ . \quad 1$$

Sedimentation volume

The various ibuprofen suspension formulations were kept on a flat undisturbed platform for 4 weeks. The volume of sediments was recorded daily for 4 weeks. This was carried out in triplicate. The sedimentation volume (F) was calculated using equation 2:

$$F = \frac{V_U}{V_O} \quad . \ . \ . \ . \ . \ . \quad 2$$

Where Vu = ultimate volume of sediment, Vo = initial volume of sediment.[2]

In vitro dissolution studies

This was performed by using a USP type II dissolution test equipment (Erweka Apparatebau GMBH, Heusengtamm, Germany) containing 500 ml of a pH 7.2 phosphate buffer maintained at 37 ± 0.5°C and the paddle rotated at a speed of 25 rpm for 30 min. A 10 ml quantity of ibuprofen suspension

formulation was carefully introduced using a 10 ml syringe into the bottom of the apparatus. Samples (5 ml) of the suspension were withdrawn at 5, 10, 15, 20, 25 and 30 min intervals for analysis and equal volumes of fresh dissolution medium were used to replenish them respectively. The samples were filtered, appropriately diluted and analyzed using a Spectrumlab SPM-752 pro UV-Vis spectrophotometer (Union Laboratories, England) at wavelength of 222 nm. The data obtained were used to determine the drug release.[2, 25]

Drug content

A 5 ml aliquot of suspension (20mg/ml) was measured and transferred into 100 ml volumetric flask. The volume was made up with phosphate buffer pH 7.2 and 1 ml of the diluted suspension was poured into a 10 ml measuring cylinder. It was made up to 10 ml with phosphate buffer pH 7.2. The final diluted suspension was analyzed using Spectrumlab SPM-752pro UV-Vis spectrophotometer (Union Laboratories, England) at wavelength of 222 nm. Drug content was calculated by comparing the absorbance with standard curve.[4]

Redispersibility

A 50 ml quantity of the various ibuprofen suspension formulations were poured into respective 100 ml bottles and kept on an undisturbed platform for 5 weeks. This was done in triplicate for all the formulations. On the thirty fifth day, each bottle was held with the thumb at the bottom of the bottle and the index finger on top of the bottle and rotated 180^0 clockwise and anti – clockwise until the sediments redispersed. A set of clockwise and anti – clockwise rotation was recorded as a cycle. The number of cycles taken for each suspension to redisperse was noted as its redispersion number.[2]

Drug/excipients compatibility: This was done by using Fourier transformed infra-red (FTIR) spectroscopy. The infra-red spectral analysis of pure ibuprofen and that of ibuprofen with DMG was carried out. The peaks and patterns obtained from the pure ibuprofen were compared with combination of DMG and pure ibuprofen.

Microbiological evaluation of ibuprofen suspensions

Enumeration of total viable bacterial and fungal count: For enumerating the total viable bacterial and fungal load, the method used by Dafale et al[26] and Anie and Okafo[3] were adopted. A 0.1 ml quantity of each ibuprofen suspensions was spread onto nutrient agar and Sabouraud dextrose agar respectively. The nutrient agar plates were then incubated for 24 hours at 37°C whereas the Sabouraud dextrose agar plates were incubated for 72 hours at 25°C. Typical colonies of microbial growth on plates were counted at the end of incubation and the result presented in colony forming unit per milliliter [CFU/ml]. [24, 27]

Data analysis: The experiments were done in triplicates and data were recorded as mean ± standard deviation. Statistical analysis was performed using Microsoft Excel.

RESULTS

Physicochemical evaluation of ibuprofen suspensions

Physical examination: Ibuprofen formulation IS1 was white in colour, formulation IS2 was light brown while formulations IS3, IS4, IS5 and IS6 were cream in colour on day 0. On day 35, formulation IS2 became dark brown, while formulations IS3 and IS5 were light brown in colour. There was no colour change for formulations IS1, IS4 and IS6. On day 0, all the ibuprofen suspension formulations were odourless but on day 35, formulations IS3 and IS5 had pungent odour.

pH: The pH values for the different ibuprofen suspensions are shown in Table 2.

Viscosity/flow rate: The viscosity of the different ibuprofen suspensions on day 0 and 35 is shown in Figure 1, while the flow rate is shown in Table 2.

Redispersibility: This ranged between 1.33 ± 0.58 and 12.67 ± 2.52 as shown in Table 2.

Drug content: This ranged between 98.5 and 101.2% as shown in Table 2.

Table 2: Some physicochemical properties of ibuprofen suspensions

Formulation	pH		Redispersibility index	Drug content (%)	Flow Rate (ml/s)	
	day = 0	day = 35			day = 0	day = 35
IS1	4.5 ± 0.0	4.6 ± 0.0	1.33 ± 0.58	100	2.21 ± 0.13	1.88 ± 0.12
IS2	4.6 ± 0.0	5.1 ± 0.0	6.33 ± 3.06	98.5	2.34 ± 0.18	2.21 ± 0.09
IS3	5.2 ± 0.0	4.9 ± 0.0	2.33 ± 0.58	99.3	3.61 ± 0.34	2.04 ± 0.04
IS4	3.8 ± 0.0	3.9 ± 0.0	3.33 ± 0.58	98.7	3.77 ± 0.11	2.81 ± 0.10
IS5	5.3 ± 0.0	6.3 ± 0.0	6.00 ± 3.46	101.2	32.93 ± 0.66	1.98 ± 0.09
IS6	3.7 ± 0.0	6.2 ± 0.0	12. ± 2.52	99.4	33.00 ± 3.70	20.29 ± 0.16

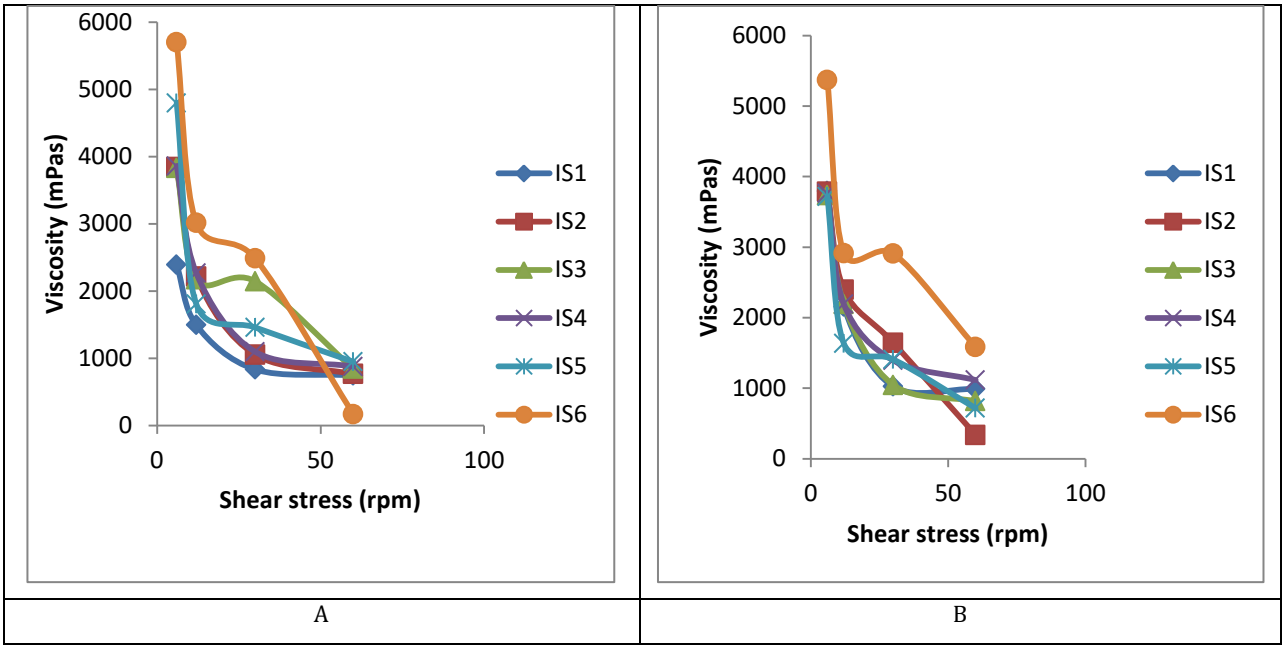


Figure 1: Viscosity curve of ibuprofen suspensions formulations IS1 to IS6 at (A) day 0 and (B) day 35

Sedimentation volume: The sedimentation volume for the different ibuprofen suspensions are shown in Figure 2.

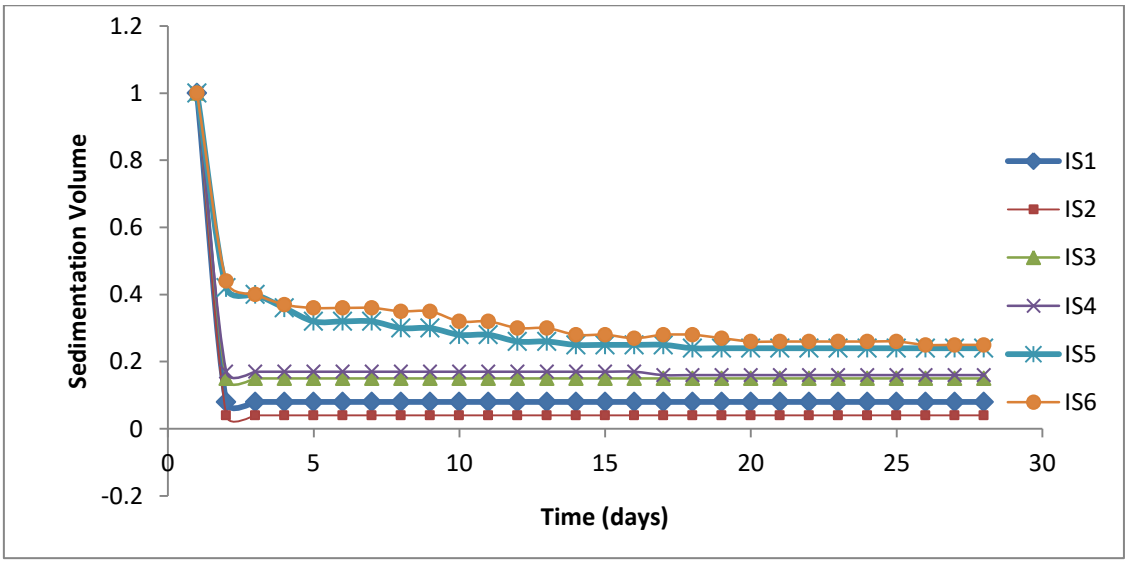


Figure 2: Sedimentation volume of ibuprofen suspension formulations IS1 to IS6

In vitro drug release: The cumulative % drug release of ibuprofen from the various suspension formulations after 30 min is shown in Figure 3.

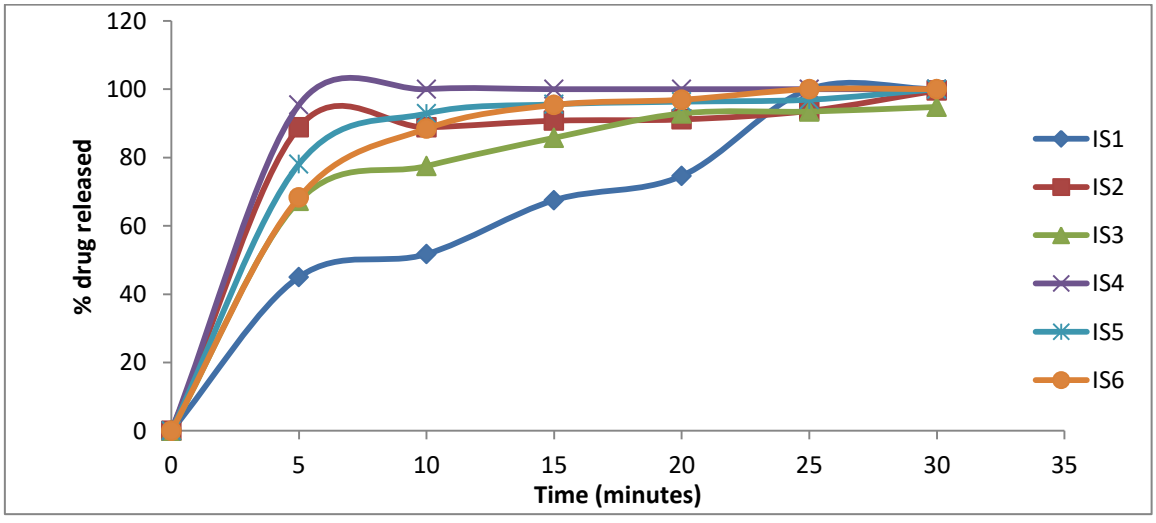
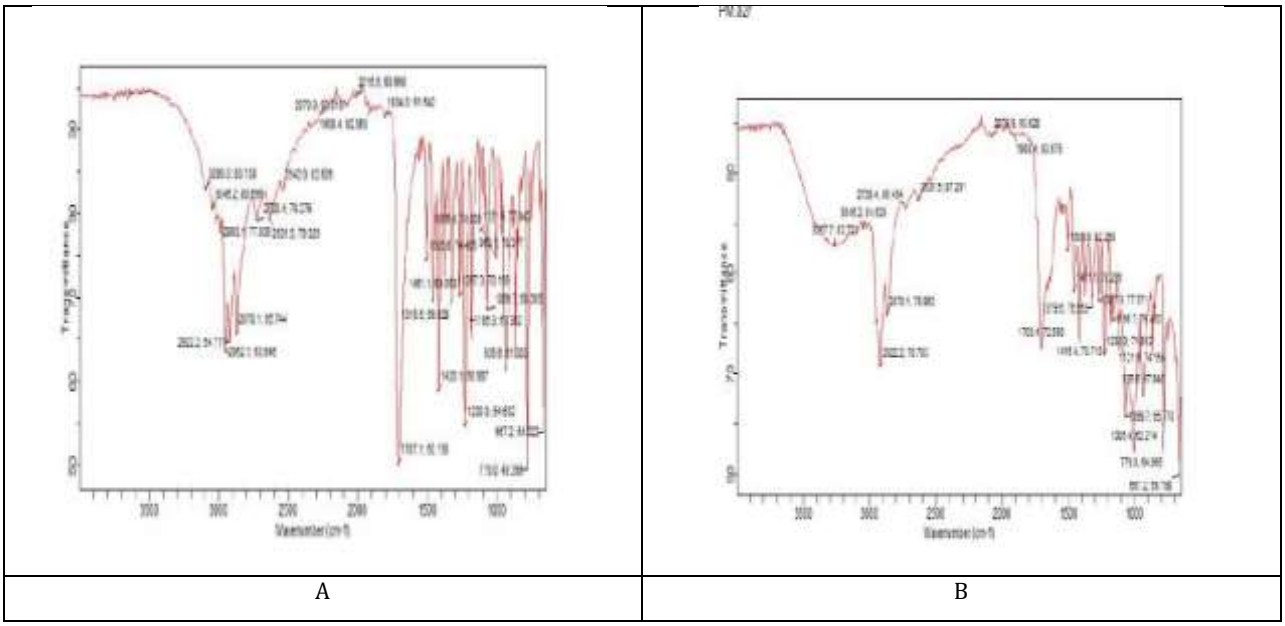


Figure 3: *In vitro* drug release for ibuprofen suspension formulations IS1 to IS6

Drug/excipients compatibility: The FTIR spectrum in Figures 4 showed that there was no drug/excipients incompatibility between ibuprofen and DMG.



A B

Figure 4: (A) Ibuprofen FTIR spectrum (B) Ibuprofen + DMG FTIR spectrum

Enumeration of total viable bacterial and fungal count:

There was no growth in the Sabouraud dextrose agar plates but that of the nutrient agar plates is shown on Table 2.

Table 2: Bacterial count

Formulation	Bacterial count (CFU/ml)	
	Day 0	Day 35
IS1	5 x 10^3	2.5 x 10^4
IS2	7 x 10^3	TNTC*
IS3	3.7 x 10^4	TNTC*
IS4	1.6 x 10^4	2.2 x 10^4
IS5	TNTC*	TNTC*
IS6	1.3 x 10^4	1.2 x 10^4

Key: TNTC = Too numerous to count

DISCUSSION

The colour and odour of some of the ibuprofen suspension formulations (IS2, IS3 and IS5) changed probably due to deterioration as a result of microbial contamination. The contamination may be from the natural suspending agent or water used in preparation of the suspensions. Microbial contamination is one of the drawbacks of the use of natural gums.[5, 11]

The pH values of the suspensions were between 3.7 and 5.3 when formulated and between 3.9 and 6.3 on the 35th day. The pH was within the acceptable limit (2-6) for oral administration.[28] The formulations made using DMG as the suspending agent has higher pH values except formulations IS4 and IS6 that also contained benzoic acid as preservative. The pH of formulations IS2, IS5 and IS6 increased on storage which may be connected to the effects of the microbial contamination.

The viscosity curve in Figure 1 showed that the suspension formulations are shear thinning systems. Their viscosities decrease with increasing shear stress. Their viscosities slightly decreased during the 35 days storage. However, flow rate results showed that there was slight increase in flow rate for formulations IS1, IS2 and IS4, moderate increase for IS3 but remarkable increase in the flow rate for formulations IS5 and IS6. Flow rate depends inversely on viscosity, therefore, the higher the viscosity, the slower the flow rate, vice versa. Viscosity of gums and mucilages has been found to reduce upon storage due to their complex nature.[5, 11] Also, the decreased viscosity may be due to breakdown of structures as a result of microbial contamination, especially formulations IS3 and IS5 that were prepared without preservatives.

The redispersibility results as shown in Table 2 indicate that the different formulation can easily be redispersed after period of settling. One of the acceptable features of an ideal suspension is that the suspended particles should not form hard cake as they settle and that they should be easily redispersed with moderate shaking or agitation of the container.[12] This gives room for withdrawal of the desired dose and resultant therapeutic effectiveness.

The drug content ranged between 98.5 and 101.2% and this was within acceptable limits for ibuprofen.[29]

The sedimentation volume result shown in Figure 2 indicates that Formulation IS6 and IS5 are the most stable formulations, followed by IS3 and IS4 while IS1 and IS2 was the least stable. Increasing viscosity of the dispersion medium results in decrease in sedimentation rates of the particles.[6] This may be the reason formulations IS5 and IS6 with high viscosity may be more stable than the rest formulations.

The cumulative % drug release from all the formulations were up to or close to 100% after 30 min of in vitro dissolution (Fig. 3) but the release of ibuprofen from formulation IS1 that contained no suspending agent was the least.

The FTIR spectrum in Figures 4 showed that there was no drug/excipients incompatibility between ibuprofen and DMG. The band characteristic to ibuprofen at 1720 cm^{-1} (carbonyl stretching of isopropionic acid group) was intense at 1707.1 cm^{-1} for ibuprofen spectrum and 1703.4 cm^{-1} for ibuprofen +DMG spectrum while the hydroxyl stretching band (3000 cm^{-1}) was intense at 2972.2 cm^{-1} for ibuprofen and 2922.2 cm^{-1} for ibuprofen +DMG spectrum.[30, 31]

There was no fungal growth. The bacterial count on day 0 and day 35 showed that the ibuprofen suspensions contained high level of microorganisms and that the level of contamination increased drastically upon storage except for formulation IS4 that recorded marginal increase and formulation IS6 that showed marginal reduction in microbial level. Oral drugs do not have sterility requirement, however, the level of contamination should be minimal. Contamination in oral dosage forms is usually due to unhygienic production environment, contamination from workers or raw materials. Natural gums suffer the disadvantage of microbial contamination. The use of preservatives helps to control microbial deterioration of suspensions formulated using natural suspending agents as shown by formulations IS4 and IS6.[32]

CONCLUSION

Ibuprofen suspensions that had good physicochemical properties were prepared successfully utilizing *Detarium microcarpum* gum as suspending agent. Formulations containing 1% of DMG (IS5 and IS6) produced more stable suspension than those that contained 0.5% of DMG (IS3 and IS4) and 1% of a standard suspending agent, acacia (IS2) respectively. The formulations that contain preservative (IS4 and IS6) had less microbial burden and deteriorated less than those without preservative (IS3 and IS5).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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