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Formulation and stability study of an Ibuprofen oral suspension with a particular granulometry combining sodium CMC and xanthan gum as suspending agents

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Abstract

Objective: The aim of this study was to formulate a stable pediatric oral suspension of Ibuprofen (IBP) with particular granulometry using Sodium Carboxymethyl Cellulose (Na CMC) combined to Xanthan gum (XG)as suspending agents.

Materials and methods: Suspensions were prepared with Na CMC (2%; 2.25%), XG (0.75%; 1%) and the Na CMC-XG combination at the following ratios: 0.75%-0.25%; 1%-0.50%; 0.75%-0.75%. The suspensions developed underwent a stability study for organoleptic and physicochemical characteristics, sedimentation and redispersibility volumes, and biopharmaceutical properties. The microbiological quality of the high-performance suspension was also assessed.

Results: The stability study revealed that suspension of IBP, F6, with a predominance of particles in the [100-200 µm] granulometric class (62%), with an average size of 158 µm, prepared with the combination, 1%Na CMC-0.5%XG was demonstrated a stable optimum viscosity, equivalent to 0.8 cPs. F6 with satisfactory organoleptic characteristics (homogeneous, white with vanilla odor and taste, fluid), pH in the range 3.6-4.6, stable (F=1), with satisfactory dissolution kinetics, conforming to standards and with microbiological quality conforming to the acceptance criteria for the microbiological quality of non-sterile pharmaceutical forms was considered as a high-performance suspension.

Conclusion: It was concluded that F6 formulation containing Na CMC combined with XG at a concentration of 1%-0.5% appears to be the optimal formulation of a stable oral suspension of IBP with a coarse particle size and could be proposed for the formulation of other drugs with a similar particle size.

Keywords: Ibuprofen; Oral suspension; Sodium CMC; Xanthan gum; Stability

1. Introduction

Oral suspension, a pharmaceutical form of the liquid oral route, practical for administering insoluble or poorly soluble drugs, is widely used in geriatrics and pediatrics to solve the swallowing problem (difficulty swallowing) encountered with the tablet and capsule forms [1]. Oral suspension is a preferred dosage form for the geriatric and pediatric population [2]. Indeed, it is a drug delivery system offering numerous advantages such as acceptability and ease of administration, taste masking, control of drug absorption and better bioavailability than solid oral forms [3]. According to Delonca [4], pharmaceutical suspensions are heterogeneous systems consisting of a continuous liquid or semi-solid external phase and a fine dispersed internal phase in the form of solid particles that are insoluble or practically insoluble in the dispersing medium. It is also important to mention that the suspension is a thermodynamically unstable system [5, 6]. Depending on their electrokinetic nature, dispersed particles always end up sedimenting. Particle deposition can

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lead to two types of sediment: flocculated sediment that is voluminous, porous and easy to redisperse, and deflocculated sediment that is not very voluminous, compact and difficult to redisperse [7]. Consequently, the formulation of suspensions remains delicate and stability studies remain important to meet the pharmaceutical requirements of these forms and guarantee product quality. A suspension with ideal characteristics should settle slowly, ensure uniform particle dispersibility, be easily dispersible after agitation, flow easily and uniformly from the container (low viscosity) and should not form a "hard cake" (caking phenomenon) [8]. In this way, a stable suspension provides the patient with the intended amount of drug in the administered dose. Suspension agents are normally added to stabilize these delivery systems and, consequently, keep the drug in suspension at the time of administration, thus guaranteeing dosage. Stability is achieved through a protective colloidal action of the particles and an increase in the viscosity of the dispersing liquid induced by the addition of suspending agents [9]. They can be synthetic, semi-synthetic or natural [10]. Among suspension agents, Xanthan gum (XG) and Sodium Carboxymethyl Cellulose (Na CMC) are widely used in the development of stable dispersed systems, particularly suspensions. Xanthan gum, a natural anionic polysaccharide, gives the suspension a gel-like texture. Due to its pseudo-plastic rheological behavior that is stable to acids, temperature and enzymes, XG is able to maintain a constant viscosity over a wide range of temperatures and pH. Its gelling power is manifested at low concentrations [11]. Similarly, the negatively charged, water-soluble polyelectrolyte Sodium Carboxymethyl Cellulose, characterized by its high capacity to bind to water via its Carboxymethyl functional groups provides excellent stability to the dispersed system without phase separation [12]. Ibuprofen (IBP), a non-steroidal anti-inflammatory drug (NSAID) on the World Health Organization (WHO) list of essential medicines [13], attracted the authors' attention. Due to its peripheral anti-inflammatory action, Ibuprofen is widely prescribed for inflammatory pain conditions. It is also used to relieve muscle spasms and reduce fever and other non-specific inflammation [14, 15]. Derived from phenylpropionic acid ((RS)-2-(4-(2-methylpropylphenyl)-propionic acid), it is one of the best-tolerated NSAIDs [16, 17]. Its low solubility in water at neutral pH (25 mg/L) [18] can be used to prepare an oral suspension, which in this case remains an interesting system of administration. This makes Ibuprofen suspension one of the leading analgesic, antipyretic and non-steroidal anti-inflammatory drugs available for pediatric care. The aim of this study was to formulate a stable pediatric oral suspension of IBP with a particular granulometry. As the literature on the use of combined suspending agents for the formulation of IBP suspensions is sparse, the authors propose a combination of two suspending agents, a semi-synthetic derivative like Sodium Carboxymethyl Cellulose (Na CMC), and a natural product as Xanthan gum (XG), for the preparation of suspensions. Suspension formulations were prepared with Na CMC and XG, used separately or in combination, at different concentrations. To meet the challenge of physical stability suspension, the authors looked for the best combination of Na CMC and XG to obtain the ideal suspension qualities, especially as the IBP used in this study has a large particle size. In this case, an optimum viscosity was required to obtain flowability and flocculation and, consequently, slow sedimentation of the particles. Finally, to complete the study, a pediatric oral suspension of IBP (reference specialty) was used for comparison purposes.

2. Materials and methods

2.1. Materials

Ibuprofen (IBP), active pharmaceutical ingredient was obtained as a gift sample from Alpha Pharma Belgium, Sodium Carboxymethyl Cellulose (Na CMC) and Xanthan gum (XG), suspending agents were obtained from Sigma-Aldrich France, Sodium benzoate was purchased from Verdugt bv Holland, Glycerin was procured from Sigma-Aldrich Germany, Polysorbate 80 (Tween 80) was purchased from Sigma-Aldrich France, Citric acid was obtained from Sigma-Aldrich USA, vanillin flavor was obtained from Fluka Chemie AG CH Switzerland. The reference specialty "AdvilMed oral suspension" marketed product (MP), France. All other chemicals/solvents used were of analytical grade.

2.2. Methods

2.2.1. Preliminary test pre-formulation

Preliminary studies were carried out in order to define, firstly, the optimal concentration of the wetting agent (Tween 80), and secondly, the ideal range of suspending agent concentrations (Na CMC, XG and Na CMC-XG combination).

2.2.2. Formulation and manufacturing of test suspensions

A series of formulations were prepared with Na CMC and XG, used as suspending agents, separately or in combination (Na CMC-XG), at various concentrations. The test suspensions as given in Table 1 were prepared according to the following protocol:

Table 1 Formulation and composition of test suspensions of Ibuprofen

Formulation code							
Composition	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
IBP	2 g	2 g	2 g	2 g	2 g	2 g	2 g
Na CMC	2%	2.25%	-	-	-	-	-
XG	-	-	0.75%	1%	-	-	-
Na CMC-XG	-	-	-	-	0.75%-0.25%	1%-0.50%	0.75%-0.75%
Polysorbate 80 (1%)	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml
Sucrose syrup	10 g	10 g	10 g	10 g	10 g	10 g	10 g
Glycerin	06 g	06 g	06 g	06 g	06 g	06 g	06 g
Sodium benzoate	0.2 g	0.2 g	0.2 g	0.2 g	0.2 g	0.2 g	0.2 g
Flavor	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Distilled water qs to	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml
Citric acid*	qs	qs	qs	qs	qs	qs	qs

*to adjust pH 3.6-4.6 IBP; Ibuprofen XG; Xanthan gum Na CMC; Sodium Carboxymethyl Cellulose

2.2.3. Preparation of suspending agent solutions

The suspending agent solutions were prepared before 24 hours. The required concentration of suspending agents was added, under agitation, to distilled water placed if necessary under a heat source (55°C) to facilitate its dispersion (case of Na CMC). Stirring was maintained until homogenization and complete swelling.

2.2.4. Preparation of test suspensions

The required amount of the suspending agent solution was introduced into a beaker containing portion of dispersing phase and stirred. Syrup solution previously mixed with glycerol was added into preparation, into small fractions, under constant stirring. Then, still under stirring, Ibuprofen was added into mixture, after suspending it in a few ml of distilled water containing the optimal concentration of Tween 80. Preservative previsiouly dissolved in water was transferred to obtained mixture after its homogenization. Then, flavor was added and the preparation was stirred for 5 minutes. Finally, volume of preparation was made up to 100 ml with distilled water, and pH was adjusted in the range 3.6-4.6 with citric acid solution according to USP [19]. For each formulation, 300 g of suspension were prepared. After being homogenized, the prepared suspensions were transferred into graduated cylinders (100 ml) and stored at room temperature (room t°) (25°C).

2.3. Evaluation of formulated suspensions

Evaluation of organoleptic characteristics (color, odor, taste, appearance and consistency), pH, sedimentation volume, redispersibility, fluidity and viscosity were carried out at 24, 72 hours and 1 week (1W). Microscopic analysis, drug content and *in vitro* dissolution kinetics were performed on flocculated suspensions after one week.

2.3.1. Organoleptic characteristics

The color, odor, taste, appearance (heterogeneous; homogeneous) and consistency were carefully checked by observation and direct perception.

2.3.2. pH measurement

The pH was determined by direct reading using the Inolab PH 7110 digital pH meter previously calibrated at pH 4 and 7. The determination of pH was carried out in triplicate.

2.3.3. Sedimentation volume and redispersibility

For each formulated suspension, 50 ml was taken into stoppered graduated measuring cylinder (100 ml). The suspension was carefully dispersed by inverting it several times. Then it was allowed to settle for a few minutes and the

volume of sediment, considered as the original volume before sedimentation (V_0) was noted. The test suspensions were analyzed after 24, 72h and one week to record the ultimate sediment volume (Vu). The sedimentation volume (F) was determined according to the formula:

$$F=\frac{Vu}{Vo}$$

Where,
F; Sedimentation volume
Vu; Ultimate volume of sediment
Vo; Original volume of suspension before sedimentation

At regular intervals, 24, 72h and 1 week, the graduated cylinders were rotated 180° in a semicircle (clockwise and counterclockwise) and the number of redispersion cycles of the suspensions until there was no sediment at the bottom of cylinder was also determined. The determination of Sedimentation volume and redispersibility was performed three times.

2.3.4. Rheological study

The rheological study of the pediatric suspensions was carried out at 25°C using the Fungilab viscoelite-H viscometer. The viscosity was measured using the R2 spindle, at the rotation of 60 rpm. The rheogical profiles of the suspensions at 10, 20... 100 rpm as well as viscosity at constant shear speed (60 rpm) versus time were also performed. The viscosity measurements were determined in triplicate and the results were expressed as the mean values in centipoises (cPs).

2.3.5. Flow rate

For each suspension, a sample of 10 ml is taken in a graduated pipette, then, let flow freely in a recipient. The time required for the free flow of this volume is noted. The test was repeated three times. The flow rate is then calculated as follows [20]:

$$\text{Flow rate (ml/s)}=\frac{\text{Volume of pipette (ml)}}{\text{Flow time (s)}}$$

2.3.6. Microscopic analysis

Knowing the significant impact of particle size distribution in the finished drug dosage form on bioavailability and pharmacokinetics [21], a particle size analysis was conducted. The flocculated suspensions (1W) were examined under optical microscope (Optika B-352A microscope) by placing a drop of diluted suspension between a glass slide and a cover slip. Particle size was measured with a calibrated ocular micrometer. The analysis was performed on 100 particles. For each size range, the percentage of particles and the mean size were determined. A similar test was performed for the marketed product (MP) for comparison.

2.3.7. Drug content

A 1 ml sample of flocculated suspension (1W) was introduced into a volumetric flask (100 ml). Then, the volume was made up to 100 ml with phosphate buffer pH 7.2. The prepared sample was shaken for 5 minutes, then filtered (syringe filter; 0.45µm) and the absorbance was measured at 225 nm with a UV-Vis Thermo Scientific Evolution 201 spectrophotometer. The IBP content was calculated using the equation of calibration curve ($y=0.0512x$; $R^2=0.9957$). The test is replicated 3x. This assay was also performed on the marketed product.

2.3.8. In vitro dissolution

In vitro dissolution was performed according to USP II dissolution apparatus [19] (paddle type) (Erweka DT 80). Sample (1 ml) of suspension was placed into 900 ml of phosphate buffer pH 7.2 maintained at 37±0.5ºC under stirring at 50 rpm. At specific time intervals (5, 10, 15, 20, 30, 45, 60 min); a 5 ml aliquot of dissolved medium was removed through 0.45 µm filter and replaced with fresh pre-warmed buffer (equal quantity). The collected samples were then analyzed by UV spectroscopy at $\lambda=225$ nm. The percentage of drug release was determined using the calibration curve ($y=0.0512x$; $R^2=0.9957$). The results represent the average of three trials. This test was carried out only for flocculated suspensions after the one-week evaluation. Similar test was carried out for marketed product (MP) for comparison.

2.3.9. Stability study

After the one-week evaluation, selected suspensions (packaged in 100 ml glass test tubes) were stored for 6 months at room t° (real-time) and at 40±2 °C (75±5% RH) (accelerated stability) [22] to carry out a stability study. Samples were taken at intervals of 1, 3 and 6 months to assess organoleptic characteristics (appearance, color, odor and taste), pH, viscosity, sedimentation volume, redispersibility, drug content and *in vitro* dissolution kinetics.

2.3.10. Microbiological quality

To evaluate the microbiological quality, the optimized suspension was subjected to the total viable aerobic germs and total fungi and moulds enumeration tests, and the test for absence of Escherichia coli according to the European Pharmacopoeia [23, 24].

2.3.11. Compatibility of active substance and excipients

For any formulation, drug-excipient compatibility is very important. The chemical interaction between the drug and the suspending agent was performed by FTIR spectroscopy. The infrared analysis was carried out on pure Ibuprofen (IBP), freshly prepared physical mixtures (IBP-Na CMC; IBP-XG; IBP-Na CMC-XG) and the performance formulation, in the spectral region from 4000 to 500 cm^{-1} with a resolution of 4 cm^{-1} using a Shimadzu IRAffinity-1S FTIR spectrometer. The compatibility was then verified by comparing the recorded spectra.

3. Results and discussion

3.1. Evaluation of formulated suspensions

3.1.1. Organoleptic characteristics and pH measurement

With the exception of suspensions containing Na CMC (F1 and F2) and the formulation F4 (XG), for all other suspensions, F3, F5, F6 and F7, a homogeneous appearance, white color, vanilla flavor and taste and acceptable consistency were noted at 24, 72h and 1 week. F1 and F2 exhibited heterogeneous appearance at 72h and instability at 1 week (caking). F4 showed an unacceptable consistency, certainly due to the high concentration of XG (1%). For all formulations, F1 to F7, the pH was between 4.33±0.04 and 4.52±0.01, in accordance with the USP standards (3.6-4.6) [19] (Figure 1) (Table 2).

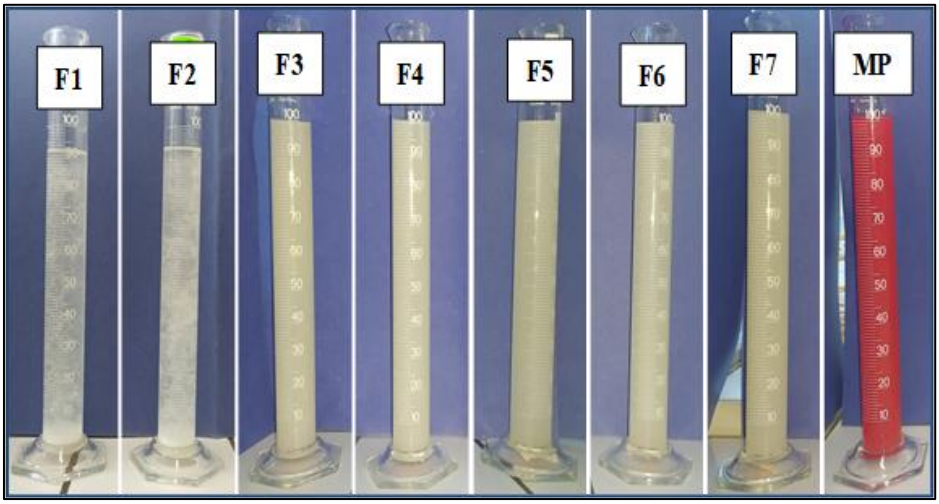

Figure 1 Macroscopic appearance of formulated suspensions "One week"

3.1.2. Sedimentation volume and redispersibility

No sedimentation was observed for formulations F3 to F7. The sedimentation volume was determined to be 1 after 24, 72h and 1 week. Therefore, redispersibility tests were not necessary for these formulations. For F1 and F2, prepared with Na CMC as suspending agent, it was noted complete sedimentation (F<0.1) with difficulty in redispersing the sediment due to the caking phenomenon (Figure 1) (Table 2).

Table 2 The one-week evaluation of formulated suspensions

Characteristics of suspensions	Formulation code							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**MP**
Color	White	White	White	White	White	White	White	Red
Odor & Taste	Vanilla	Vanilla	Vanilla	Vanilla	Vanilla	Vanilla	Vanilla	strawberry
Appearance[a]	+	+	+++	+++	+++	+++	+++	+++
Consistency[b]	+	+	+	+++	+	+	++	+
pH	4.43±0.02	4.33±0.04	4.48±0.01	4.51±0.02	4.46±0.02	4.48±0.01	4.52±0.01	4.54±0.01
Sediment	Compact	Compact	No S[c]	No S[c]	No S[c]	No S[c]	No S[c]	No S[c]
Supernatant	Cloudy	Cloudy	-	-	-	-	-	-
V_u/V_o	<0.1[d]	<0.1[d]	1	1	1	1	1	1
Redispersibility	> 10 cycles Caking	> 10 cycles Caking	✓	✓	✓	✓	✓	✓
Viscosity (cP)	700	900	600	900	400	800	1100	800
Flow rate (mls^{-1})	0.034	0.028	0.021	Too viscous[e]	0.052	0.023	0.015	0.024
Drug content (%)	-	-	104.33±1.95	97.53±1.50	100.36±7.62	94.24±3.08	101.66±4.23	98.42±2.37

[a] + Heterogeous; +++Homogenous [b]+ Less consistence ; ++ Consistence; +++ More consistence

[c] No sediment formation was observed [d] Complete sedimentation ✓ No needed redispersibility [e] Poor flow

3.1.3. Rheological study and flow rate

All test suspensions were demonstrated to decreasing viscosity at increase shear rates. The rheological study depicted in Figure 2, showed a pseudoplastic non-Newtonian flow type behavior for flocculated suspensions, F3 to F7. The rheological properties were dependent on the nature of the suspending agent and its concentration. On the one hand, increasing the concentration of the suspending agent leads to an increase in viscosity. On the other hand, when the concentration of XG in the polymer combination (Na CMC-XG) increases, the viscosity increases significantly. The viscosity was in the range of 400 to 1100 cPs. F4 and F7 recorded the highest viscosities, 900 and 1100 cPs respectively. For F4, this high viscosity is due to the high concentration of XG (1%), compared to F3 (0.75%). For F7, the increase in viscosity is due, on the one hand, to the high concentration of the Na CMC-XG combination (1.5%), compared to F5 (1%), and, on the other hand, to the high concentration of XG in the polymer's combination (0.75%), compared to F6 (0.5%). The increase in viscosity follows the order: F7>F4>F6>F3>F5 (Table 2). Also, it is noted that F6 and MP recorded similar rheological profiles (Figure 2). Therefore, identical viscosities at 60 rpm were demonstrated for F6 and MP (800 cPs). At last, for flocculated suspensions, the flowability decreases as the concentration of XG increases. The ease of flowability of flocculated suspensions is in the order: F5>F6=MP≥F3>F7>>>F4 (Table 2). It should also be noted that due to its high viscosity and consistency, F4 has exhibited very poor flow or no free flow, which is not acceptable for oral administration. This is certainly due to its high XG concentration (1%). In the end, it is clear that as the concentration of XG increases, whether used separately or in combination, the consistency and viscosity increase and free flow is less easy.

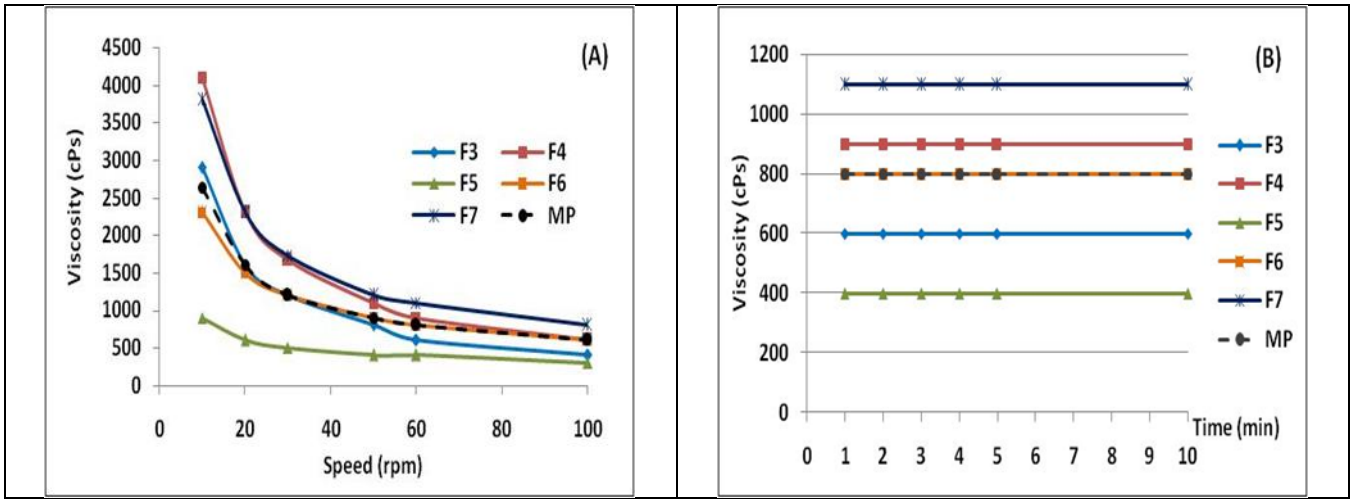

Figure 2 Rheological study of flocculated suspensions "F3 to F7" (A) Viscosity versus speed (B) Viscosity at constant speed versus time

3.1.4. Microscopic analysis

The observations of the microscopic analysis were depicted in Figure 3A (Percent of particles per size range) and Figure 3B (mean size per size range). All flocculated suspensions, F3 to F7, as well as the IBP used in the study, showed a non-negligible percent of particles with a size greater than 200 µm (13-16%), in contrast to MP which showed zero percent of particles ≥ 200 µm. In addition, MP showed only 17% of particles in the size range [100-200] with a mean size not exceeding 121 µm. While for this same size interval, F3 to F7 and pure IBP recorded a predominance of particles with an average size in range 151-159 µm (60 to 71%). On the other hand, in the size class [50-100], a predominance of particle size was noted for MP with a mean size around 80 µm (68%), while for flocculated suspensions as well as pure IBP, only 15% to 24% of particles were recorded in this class of size with an average size in the range 73-88 µm. Finally, in the interval [0-50], an insignificant percent of particles (1-6%) with an average in the range 40-50 µm were noted for F3 to F7 and IBP versus 15% of particles with an average size equivalent to 42 µm for MP. At the end of the test, compared to MP (Marketed product), whose predominant particle size is around 80 µm, the flocculated suspensions test are in the [100-200] class (60-71%) with an average particle size in the range 151-159 µm, which provides a real challenge for their stabilization.

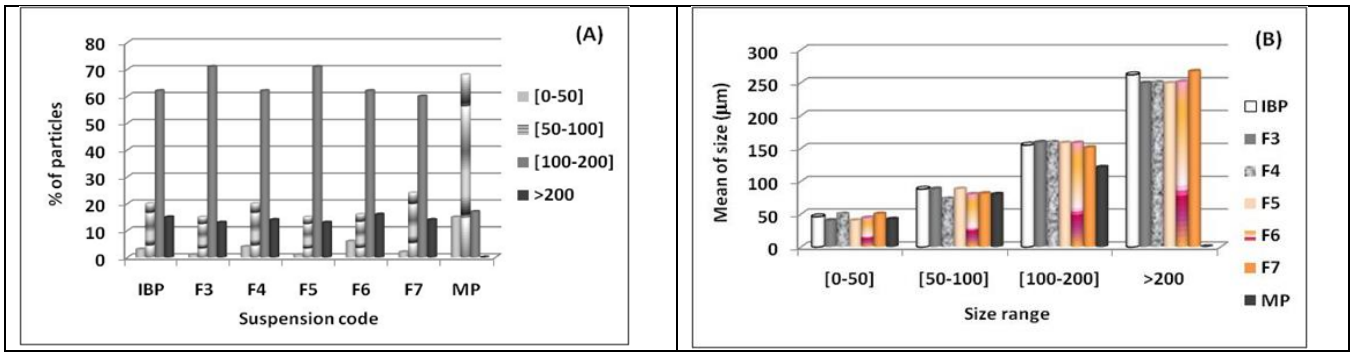

Figure 3 Microscopic analysis of flocculated suspensions "F3 to F7" (A) Percent of particles per size range (B) Mean of size by size range

3.1.5. Drug content and in vitro dissolution

For the flocculated suspensions, F3 to F7, the drug content was between 94.24±3.08% and 104.33±1.95% (Table 2), in accordance with US Pharmacopeia standards (90-110%) [19]. Also, for F3 to F7, the results of *in vitro* dissolution kinetics were in accordance with USP standards (Not less than 80% (Q) of the labeled amount of IBP is dissolved in 60 minutes) [19]. Dissolution was complete at 10 minutes for F3 to F7 as for MP (Figure 4).

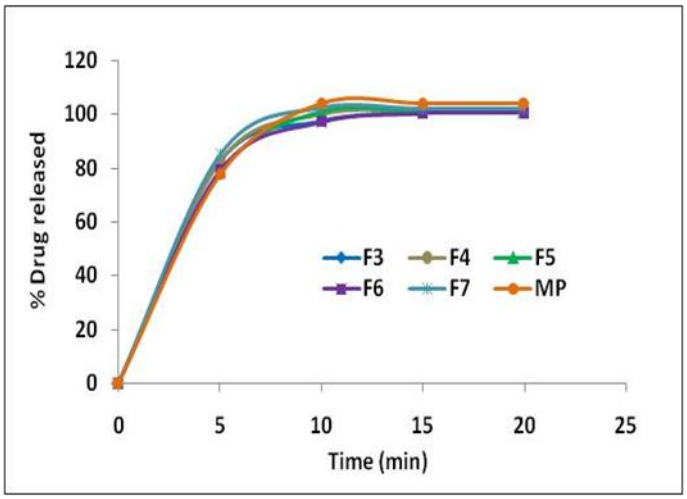

Figure 4 Dissolution profiles of flocculated suspensions "F3 to F7" (One week)

3.1.6. Stability study

The results of stability study were depicted in Tables 3 through 6 and Figures 5 and 6. First, for pH, no major variation was noted, the recorded values were always between 3.6 and 4.6 according to USP standards [19] regardless of storage conditions (Figures 5A and 5B). However, for sedimentation volume and viscosity, some variations were noted. For suspension F5 (0.75%Na CMC-0.25%XG), a sediment (F<0.1) with a caking phenomenon and a decrease in viscosity from 400 to 300 cPs were recorded after one month's storage at room temperature and 40°C (Tables 3 and 4). For suspensions F3 (0.75%XG) and F7 (0.75%Na CMC-0.75%XG), despite physicochemical stability (pH and viscosity), sedimentation with a caking phenomenon was unfortunately observed. F3 and F7 have indeed shown sedimentation (F<0.1) after 3 and 6 months' storage respectively at 40°C (Table 4). It also should be noted that as long as the prepared suspensions were stable, their drug contents complied with USP standards [19]. Finally, only the F6 suspension based on the 1%Na CMC-0.5%XG combination, with satisfactory organoleptic characteristics and a viscosity of 0.8 cPs, was stable (F=1) (Tables 3 and 4). Also, no variation was observed in particle size distribution for this suspension. This suspension also recorded a drug content of between 90% and 110%, in conformity with USP standards [19] (Tables 5 and 6). In addition, the dissolution kinetics of F6 suspension complied with USP standards, regardless of storage conditions (Not less than 80% (Q) of the labeled amount of IBP were dissolved in 60 minutes) [19] (Figure 6). In other hand, similar dissolution profiles were also observed for F6 and MP suspensions (Figure 6). Based on the results of the stability study, it was concluded that F6 is considered the optimized suspension. As a result, the study has demonstrated that F6, despite its coarse particle size (62% for an average particle size of 158 μm), was an oral suspension fully comparable to the commercially available pediatric oral suspension (MP) with instead a particle size predominance of around 80 μm (68%).

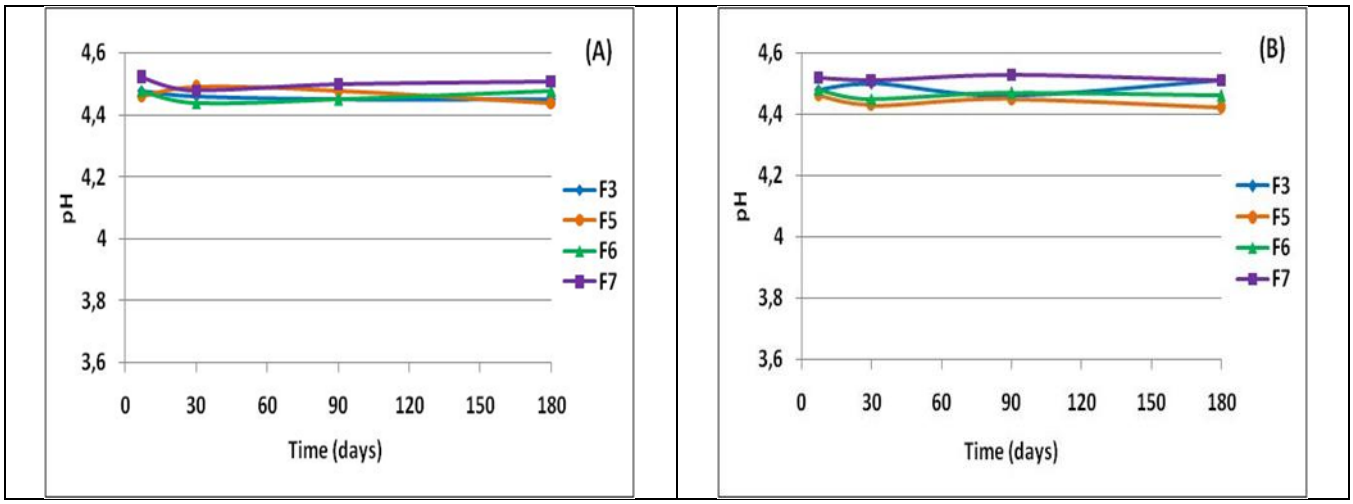

Figure 5 pH stability study of selected suspensions "F3 (0.75% XG) and F5 to F7 (Na CMC-XG)" (**A**) Storage under real-time (room t°) (**B**) Storage at 40°C (accelerated stability)

Table 3 Real-time stability of selected suspensions, F3 (0.75% XG) and F5 to F7 (Na CMC-XG) "Sedimentation volume and viscosity"

6 Months at room t°					
Formulation		**F3**	**F5**	**F6**	**F7**
V_u/V_o	1M	1	<0.1	1	1
	3M	1	-	1	1
	6M	1	-	1	1
Redispersibility	1M	✓	Caking	✓	✓
	3M	✓	-	✓	✓
	6M	✓	-	✓	✓
Viscosity (cPs)	1M	600	300	800	1100
	3M	600	300	800	1100
	6M	600	300	800	1100

✓ No needed redispersibility

Table 4 Accelerated stability of selected suspensions, F3 (0.75% XG) and F5 to F7 (Na CMC-XG) "Sedimentation volume and Viscosity"

6 Months at 40°C					
Formulation		**F3**	**F5**	**F6**	**F7**
V_u/V_o	1M	1	<0.1	1	1
	3M	<0.1	-	1	1
	6M	-	-	1	<0.1
Redispersibility	1M	✓	Caking	✓	✓
	3M	Caking	-	✓	✓
	6M	-	-	✓	Caking
Viscosity (cPs)	1M	600	300	800	1100
	3M	600	300	800	1100
	6M	600	300	800	1100

✓ No needed redispersibility

Table 5 Real-time stability of selected suspensions, F3 and F5 to F7 "Drug content"

6 Months at room t°					
Formulation		**F3**	**F5**	**F6**	**F7**
Drug content (%)	1M	101.67±2.54	-	95.71±1.86	97.40±5.71
	3M	98.17±4.82	-	101.08±3.66	96.57±0.49
	6M	92.38±1.66	-	95.14±3.15	96.60±5.34

Table 6 Accelerated stability of selected suspensions, F3 and F5 to F7 "Drug content"

6 Months at 40°C					
Formulation		**F3**	**F5**	**F6**	**F7**
Drug content (%)	1M	98.53±4.29	-	98.86±4.95	99.78±4.05
	3M	-	-	104.19±1.56	98.18±2.81
	6M	-	-	96.57±3.38	-

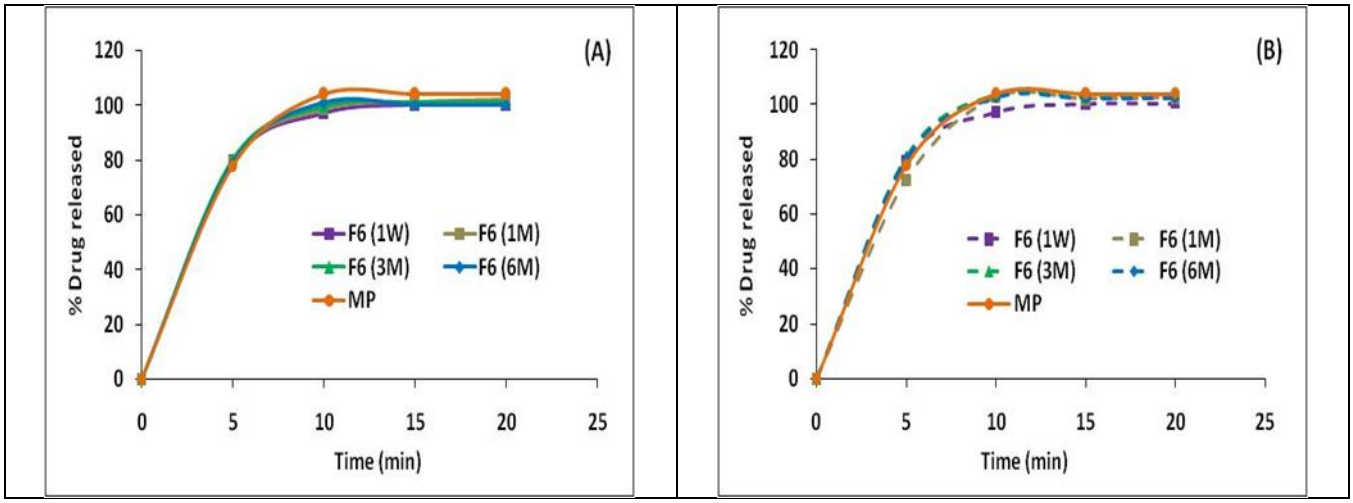

Figure 6 Dissolution profiles of optimized suspension "F6 (1% Na CMC-0.5% XG)" (A) Storage at real-time (room t°); (B) Storage at 40°C (accelerated conditions)

3.1.7. Microbiological quality of optimized suspension

The results of the microbiological analyses of the optimized suspension (F6) stored for three then six months in real-time (room t°) are in conformity with the acceptance criteria for the microbiological quality of non-sterile pharmaceutical forms of the European Pharmacopoeia [25]: Aerobic germs $<10^2$; Fungi & moulds $<10^1$; Test for E. coli negative.

3.1.8. Compatibility of active substance and excipients

No interaction between active substance and excipients was observed. The FTIR spectrum (Figure 7) showed that all peaks characteristic of the drug were present in the optimized suspension (F6). This confirms that IBP had no interaction with the suspension excipients.

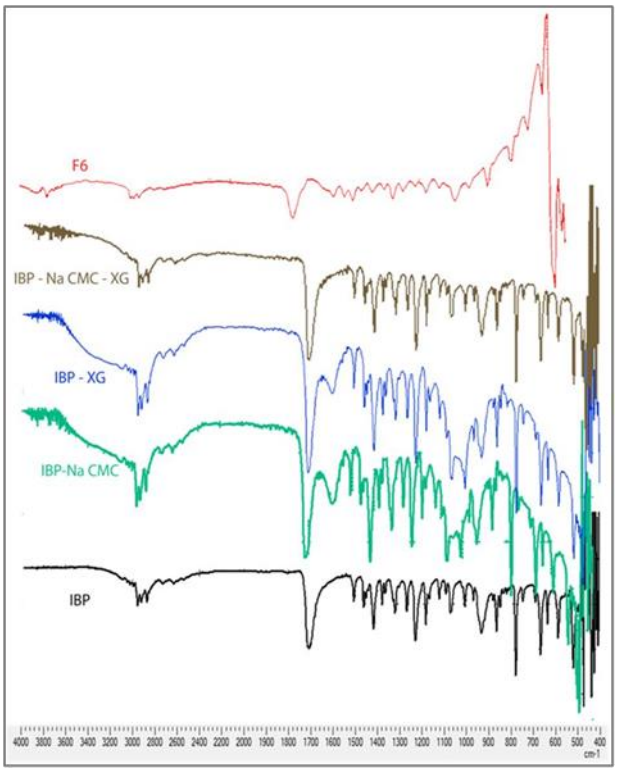

Figure 7 FT-IR spectra: pure drug "IBP", physical mixtures "IBP-Na CMC; IBP-XG; IBP-Na CMC-XG" and optimized suspension (F6)

4. Conclusion

An oral suspension has been developed for pediatric use, based on Ibuprofen with a particular morphology, namely a large particle size (predominance of average particle size at around 150 μm). The study was demonstrated that this is entirely possible. All that's needed is the right choice of suspending agent, or a combination of suspending agents, at optimum concentration. For this purpose, CMC Na and XG were used as suspending agents at different concentrations, separately or in combined form to stabilize the preparation. The stability study was demonstrated that Na CMC combined with XG enabled the optimum viscosity to be achieved. This viscosity of 0.8 cPs, beneficial for the formulation of a stable suspension, was only obtained with the combination, Na CMC-XG, at a total concentration of 1.5% on the one hand, and at a ratio in favor of Na CMC (1%), on the other. Compared with the marketed product, the stability study of F6 suspension (1%Na CMC-0.5%XG) demonstrated correct organoleptic characteristics, homogeneous particle size with no significant variation, stable pH in the range 3.6-4.6, content conforming to standards of between 90% and 110%, satisfactory dissolution (Not less than 80% (Q) of the labeled amount of IBP are dissolved in 60 min) and stable sedimentation volume (F=1). Therefore, the CMC Na-XG combination (1%-0.5%), used as a suspending agent proved beneficial for the formulation of a stable coarse-granulometry IBP suspension, compared with the polymers used separately. In the end, F6 prepared with the 1%Na CMC-0.50%XG combination was found to be a high-performance suspension and, consequently, could be proposed as a base formulation for active substances with particular granulometric morphology. Thanks to its satisfactory characteristics, F6 could be considered as an oral suspension formulation, for pediatric use, guaranteeing drug administration in compliance with the requirements of the pharmaceutical form.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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