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Comparison of sedimentation stability of ampicillin trihydrate suspensions using near infrared extinction profiles

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ABSTRACT

Suspensions are one of the most important and popular dosage forms. A large number of drugs are formulated in the form of suspensions and are available commercially. Stability studies of suspensions are very important to enable the patient to receive the intended amount of the medicine(s) in the dose administered. Physical stability of ampicillin suspensions was studied in terms of sedimentation stability in a rapid way employing infrared extinction profiles by using the instrument Separation analyzer (LUMiReader®) in the present work. The LUMiReader® instantaneously measures the extinction profiles of the transmitted light across the entire length of a suspension sample employing STEP-Technology (Space- and Time-resolved Extinction Profiles Technology). Ampicillin trihydrate suspensions were formulated with different suspending agents like methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose (SCMC) and mucilage of *Plantago ovata* (POM) and their infrared extinction profiles were compared to determine their sedimentation stability. Instability indices and re-dispersibility determined on different suspension formulations indicated that SCMC and POM are preferable suspending agents for the preparation of stable suspensions of ampicillin trihydrate.

1. Introduction

Suspensions are one of the most important and popular dosage forms. A large number of drugs are formulated in the form of suspensions and are available commercially. Stability study of suspensions is a very important aspect to enable the patient to receive the intended amount of the medicine(s) in the dose administered. Chemical as well as physical stability of suspensions are important for maintaining the quality of the product. Ampicillin is the amino-penicillin, has an amino group substitution in the side chain, not resistant to penicillinase or to other beta-lactamase. It is active against all organisms sensitive to Penicillin-G; in addition, many gram-negative bacilli. Ampicillin trihydrate was used as a model drug in the present study to select a suitable suspending agent for

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its suspension formulation. Ampicillin trihydrate is an important antibiotic needed in a basic health system to prevent and treat a number of bacterial infections including respiratory tract infections, urinary tract infections, meningitis, salmonella infections, endocarditis etc. American Academy of Pediatrics also recommends its use in treatment of certain infections in neonates and children.

1.1 Physical stability testing of ampicillin trihydrate suspensions

A number of procedures have been suggested in the past for evaluating the physical stability of suspensions [1-4]. Some of these are empirical in the sense that they have no mathematical base. Some methods currently being used are so drastic that they destroy the structure of the suspension. The evaluation methods used may be classified into:

a) Sedimentation methods
b) Rheological methods
c) Electro-kinetic methods and
d) Micromeritic methods

Under sedimentation methods, measurement of the sedimentation volume and its ease of re-dispersion, form two of the most common basic evaluation procedures. Rheological methods help in predicting the settling pattern and can also provide clues to vehicle particle structure. Data collected on samples stored for various periods can give useful information about the stability of the suspension. Electro-kinetic methods measure the surface electric charges or zeta potential which is instrumental in deciding the stability of disperse systems. Micromeritic methods deal with the particle size changes. The stability of a suspension is inter-related to the size of particles constituting its disperse phase. A growth in the particle size is a pointer towards its instability since such an occurrence can ultimately result in the formation of aggregates or cake destroying the physical structure of a suspension and rendering it useless. Hence, an appreciation of change in particle size with passage of time can provide an insight into the stability aspect of a suspension. Changes in absolute particle size, particle size distribution, crystal habit etc. can be worked out by microscopy, Coulter counter etc. Normally there is a need to carry out a quick assessment of particle size change since no formulator can afford to wait for the normal shelf storage periods to study such changes. Hence, suspensions are subjected to artificial stress conditions in the form of freezing and thawing. Such a treatment is known to promote particle growth and can be used to predict future behaviours. However, an important point to remember is that sometimes hydrocolloids which are usual additives in suspensions can themselves get affected by freezing and thawing leading to caking of suspensions. Hence, observations may not be quite correlated to shelf-life of the products.

1.2 STEP-Technology (Space- and Time-resolved Extinction Profiles Technology)

STEP-Technology stands as acronym for Space and Time Resolved Extinction Profiles Technology. It can be used to measure the infrared extinction profiles of the transmitted light across the entire length of a suspension sample from top to bottom instantaneously [5]. By using an instrument called LUMiReader® which operates on STEP-Technology, it is possible to observe and understand different stability/instability phenomena of disperse systems like emulsions and suspensions concurrently; e.g., creaming, sedimentation, coalescence, aggregation and flocculation at original product concentration. Basing on these phenomena the instability index is generated by the software SEPView® installed in the instrument. Depending on the instability index measured for different suspension samples prepared with various suspending agents and other excipients, an ideal suspending agent and its concentration required to get a stable suspension can be selected. Different program components are provided in a LUMiReader® for the qualitative and quantitative analysis of the samples, e.g.,

- The Front Tracking for sedimentation velocity
- The Integral Transmission for the clarification speed
- The Extinction ratio for changes in particle size
- The PSA-Module for the calculation of the particle size distribution.
- The Stability analysis for determination of instability index and for comparison of stability of different samples.

1.2.1. Separation analyser LUMiReader®

The Separation analyser LUMiReader® PSA-453 manufactured by LUM GmbH, Germany was used in the present work to carry out physical stability studies on ampicillin trihydrate suspensions formulated with different suspending agents [5]. The sample cell in a LUMiReader® is illuminated by a multi-colour light source I0, including one near infrared wavelength (870 nm). Behind the sample cell the transmitted light I is detected using a CCD-line detector. The detector contains about 6434 elements, with a detector resolution of 9 µm and detection length of 45 mm. Transmission is converted into extinction by In (I0/I). Frequently optical particle size measurement techniques are used to determine the volume weighted particle size distribution. For this purpose the size and material dependent extinction coefficient is needed which can be calculated with Mie-theory using the complex refractive index of the particles. In this case strong assumptions have to be made like spherical homogeneous particles. However, the determination of the refractive index can be very difficult especially in the submicron range and for heterogeneous particles. No standard measurement methods are available up to now. The way out could be the evaluation of space and time resolved extinction profiles at different wavelengths for sedimenting particles in gravitational or centrifugal field [6,7] Illuminating the dispersion across its entire sample height, and by having many thousand detectors LUMiReader® can measure the light source extinction profile instantaneously, even the smallest changes in concentration can be detected. The instrument measures the extinction profiles over

the whole sample length during physically accelerated separation. Changes in the extinction profile are representative for the changes in particle concentration and allow to determine the velocity of individual particle classes with no assumptions regarding particle properties.

2. Materials and Methods

2.1 Materials

Ampicillin trihydrate IP was a gift sample from Alkem Laboratories Limited, India. Hydroxypropyl methylcellulose (HPMC) - Methocel K4M was procured as a gift sample from Colorcon Asia Pvt. Ltd., Verna, Goa. Carboxymethylcellulose sodium (SCMC) and methylcellulose (MC) were purchased from LOBA Chemi Pvt. Ltd., Mumbai, India. *Plantago ovata* mucilage (POM) was extracted from the seeds of Plantago ovata purchased from local market following the procedure described by Kulkarni *et al*. [8,9]. The seeds were soaked in distilled water for 48 hours and boiled for 10 minutes thereafter. The resulting viscous gel mass was pressed through a muslin cloth. The filtrate so isolated was treated with equal volume of acetone which resulted in precipitation of the mucilage. The isolated precipitate was dried at 40 °C for 2 hours. The dried mass was subjected to size reduction which yielded a powder mass. The powder was finally passed through sieve number 80 and stored in desiccators for further analysis and use. The yield was found to be around 30% w/w. All other chemicals, solvents and reagents used in the study were of analytical grade.

2.2 Methods

2.2.1. Compatibility studies

Compatibility studies were carried out to investigate the incompatibilities between ampicillin trihydrate (AT) and the suspending agents by using differential scanning calorimetry (DSC) and Fourier transform infrared (FT-IR) spectroscopy.

Sample preparation: Drug to excipient ratio of 1:1 provides maximum possibilities of interaction between the drug and various suspending agents thus enabling easy detection of any incompatibility. Therefore, homogeneous 1:1 physical mixtures of AT and suspending agents were prepared by trituration in a clean and dry glass mortar and pestle [10]. These mixtures were stored in glass vials in a stability chamber at 25 ± 2 °C for four weeks after which they were subjected to DSC and FT-IR studies using differential scanning calorimeter, DSC-4000 and FT-IR, model IR Affinity-1, Shimadzu Corporation, Japan.

2.2.2. Preparation of ampicillin trihydrate suspensions

Ampicillin trihydrate suspensions were prepared with four different concentrations of each of the four commonly used suspending agents MC, HPMC K4M, SCMC, and POM as described hereunder. Each suspending agent was used in four concentrations at 0.25%, 0.5%, 0.75% and 1.0% as shown in Table 1. Thus, sixteen formulations were prepared with four suspending agents.

Table 1 Formulation of ampicillin trihydrate suspensions.

Formulation code	Amount of ampicillin trihydrate (g)	Sodium benzoate (mg)	Suspending agent used	Amount Of suspending agent (g)	Purified water to (ml)
F1S1	4	100	MC	0.25	100
F2S1	4	100	MC	0.50	100
F3S1	4	100	MC	0.75	100
F4S1	4	100	MC	1.00	100
F1S2	4	100	HPMCK4M	0.25	100
F2S2	4	100	HPMCK4M	0.50	100
F3S2	4	100	HPMCK4M	0.75	100
F4S2	4	100	HPMCK4M	1.00	100
F1S3	4	100	SCMC	0.25	100
F2S3	4	100	SCMC	0.50	100
F3S3	4	100	SCMC	0.75	100
F4S3	4	100	SCMC	1.00	100
F1S4	4	100	PO mucilage	0.25	100
F2S4	4	100	PO mucilage	0.50	100
F3S4	4	100	PO mucilage	0.75	100
F4S4	4	100	PO mucilage	1.00	100

Procedure

The suspending agent kept in contact with about 90 ml of water containing 100 mg of sodium benzoate was thoroughly mixed with a laboratory stirrer (REMI) for about 10 minutes at an average speed of 200 rpm to get a uniform dispersion. Ampicillin trihydrate was then added to the dispersion while

stirring, stirring continued for another 30 minutes and made up to volume. The prepared suspensions were stored at room temperature until further studies.

2.3. Physical stability determination

Separation analyser LUMiReader® PSA 453 manufactured by LUM GmbH, Germany was employed for stability determinations.

Sample cells: LUM 10 mm, PC, synthetic cells were used for separation studies.

2.3.1 Selection of tilt angle and temperature

The instrument has a provision for measurements from 0 to 30˚ tilt allowing the sample to remain in upright or inclined position depending on the angle of tilt selected. Tilting the sample from its normal upright position allows an increase in the separation rate at gravity without any additional external forces. The magnitude of acceleration (upto 10 times) depends on geometric factors, such as tilt angle, sample cell dimensions and sample type. The LUMiReader® has a provision to maintain the temperature between ambient temperature to 60°C. Measurements were carried out at 0˚ and 30˚ tilt at 30°C for the suspension samples. A sample volume of about 2 ml was used in the determinations.

Procedure

The suspension sample of about 2 ml was filled in the sample cell. The instrument was switched on and the SOP was programmed by selecting various parameters like the tilt angle, temperature, number of profiles, interval, number of cycles etc. Once, the instrument was ready with normalization and base line correction applied, a message appeared to insert the sample. The sample tube was gently shaken to disperse the sample and inserted into the sample holder. The instrument started recording the profiles as per the set SOP once the sample holder lid is closed by sliding in the direction shown on the instrument. The extinction profiles were recorded at three wavelengths i.e., 470 nm (blue), 630 nm (red) and 870 nm (NIR) with the help of the software SEPView® installed in the instrument. The profiles were automatically saved in the instrument.[5] The extinction profiles of 870 nm (near infrared) wavelength were taken into account for determination of sedimentation stability in the present work. Different suspension samples were analyzed as per the set parameters discussed above. The stability data obtained by using the instrument is shown in Table 2 and Table 3.

Table 2 LUMiReader® stability data for ampicillin trihydrate suspensions at 0º tilt and 30 °C.

Suspending agent	Instability index at suspending agent concentration of				Front tracking: Sedimentation velocity (µm/s) at suspending agent concentration of			
	0.25%	0.5%	0.75%	1.0%	0.25%	0.5%	0.75%	1.0%
MC	0.3029	0.2812	0.1635	0.1578	7.5542	6.457	5.321	3.3432
HPMC K4M	0.4752	0.3462	0.2256	0.1915	13.636	10.893	10.466	8.843
SCMC	0.0215	0.0011	0.0025	0.0197	-x-	-x-	-x-	-x-
POM	0.0021	0.0015	0.0002	0.0035	-x-	-x-	-x-	-x-

Table 3 LUMiReader® stability data for ampicillin trihydrate suspensions at 30º tilt and 30 °C.
MC- Methylcellulose; HPMC K4M – Hydroxypropyl methyl cellulose K4M; SCMC- Sodium carboxymethylcellulose; POM- Plantango ovata mucilage.

Suspending agent	Instability index at suspending agent concentration of				Front tracking: Sedimentation velocity (µm/s) at suspending agent concentration of			
	0.25%	0.5%	0.75%	1.0%	0.25%	0.5%	0.75%	1.0%
MC	0.3215	0.2873	0.1534	0.1253	8.363	5.387	-x-	-x-
HPMC K4M	0.6568	0.5563	0.4584	0.4532	15.35	13.19	11.232	10.361
SCMC	0.0245	0.0001	0.0043	0.0215	-x-	-x-	-x-	-x-
POM	0.0001	0.0013	0.0002	0.0049	-x-	-x-	-x-	-x-

2.3.2 Determination of resuspendability of suspension samples

Resuspendability is the ability to resuspend the settled particles with a minimum amount of shaking after a suspension has sedimented on standing for some time.

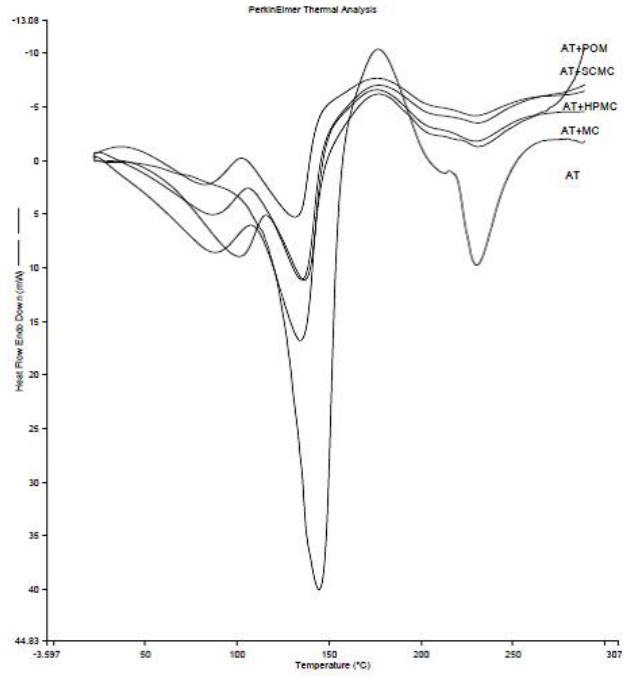
Procedure

The resuspendability of the suspensions was evaluated qualitatively. The suspensions were allowed to sediment in stoppered glass jars for 15 days. The test was performed on samples in triplicate by shaking the sedimented suspensions manually at 180˚movement, after sedimentation was completed [11]. Based on the number of shakings required to disperse the sediment uniformly into a suspension, the formulations were evaluated. Cake formation was also evaluated qualitatively. Formulations requiring more than 10 shakings were considered positive for cake formation.

2.4 Compatibility studies

2.4.1 DSC Studies

Interactions in the samples were studied using DSC by changes in the thermal events, such as elimination of an endothermic or exothermic peak or appearance of a new peak. However, some broadening of peaks leading to changes in the area, onset of peak, and changes in peak temperature occur simply due to mixing of the components without indicating any significant interaction. If all thermal features more or less remain the same, compatibility can be expected. DSC thermograms of ampicillin trihydrate (AT), suspending agents MC, HPMC, SCMC, POM and their physical mixtures were studied on the samples stored at 25 ± 2 °C. The characteristic peak pattern indicated that AT had undergone thermal transition at 144.64 °C (melting endotherm of ampicillin trihydrate), methylcellulose at 88.51 °C, HPMC at 93.57 °C, SCMC at 108.16 °C and PO mucilage at 104.15 °C. The peaks of pure AT and pure suspending agents were retained in the physical mixture during the study period at the storage condition. In a physical mixture of ampicillin trihydrate with each of the suspending agents, the thermal transitions occurring at 144.64 °C were not affected as shown in Figure 1, indicating compatibility. There were no significant changes in the peak shape and peak positions suggesting that there were no significant interactions between the drug and the suspending agents.

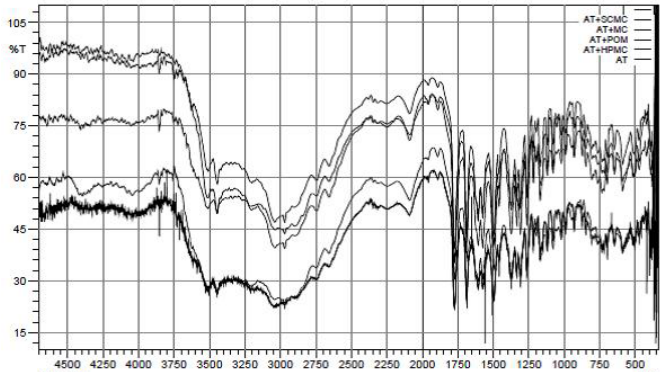


AT – Ampicillin trihydrate; MC- Methylcellulose; HPMC K4M – Hydroxypropyl methyl cellulose K4M; SCMC- Sodium carboxymethylcellulose;POM- Plantango ovata mucilage

Figure 1 DSC thermograms of ampicillin trihydrate (AT) and mixtures of AT and suspending agents.

2.4.2 FT-IR Studies

Compatibility of ampicillin with different suspending agents was studied using FT-IR spectroscopy. Interactions in the sample are derived or deduced by FT-IR studies from changes in the characteristic peaks. However, some broadening of peaks due to hydrogen bonding was expected while using the excipients from natural origin and also due to moisture without indicating any significant interaction. If all the characteristic peaks are retained and there is no significant change in the peak position, compatibility can be expected. The samples were stored at 25 ± 2 °C and were scanned in the region of 4000 cm^{-1} and 400 cm^{-1}. The FT-IR spectrum obtained for ampicillin trihydrate showed two characteristic spikes at 3515 cm^{-1} and 3450 cm^{-1} representing the symmetric and asymmetric stretching for NH_2 group. Peaks in the region of 3042 cm^{-1} indicate the presence of aromatic C-H stretching vibration. The characteristic peaks at 2975 cm^{-1}, 2895 cm^{-1}, 2747 cm^{-1} and 2659 cm^{-1} indicate the presence of C-H stretching vibrations. The strong peak at 1773 cm^{-1} indicate the presence of C=O stretching vibration. The presence of characteristic spikes for NH_2 group, aromatic C-H stretching, aliphatic C-H stretching, C=O stretching and no new bands or shift in characteristic peaks appeared in the physical mixtures of ampicillin trihydrate with different suspending agents as shown in Figure 2 indicated that there was no significant interaction between the drug and the selected suspending agents.



AT–Ampicillin trihydrate; MC- Methylcellulose; HPMC K4M – Hydroxypropyl methyl cellulose K4M; SCMC- Sodium carboxymethylcellulose; POM- Plantango ovata mucilage

Figure 2 FTIR spectra of ampicillin trihydrate(AT) and mixtures of AT and suspending agents.

2.5 Preparation of ampicillin trihydrate suspensions

Sixteen suspension formulations were prepared using four concentrations (0.25%, 0.5%, 0.75% and 1.0%) of each of the four suspending agents i.e., MC, HPMCK4M, SCMC and POM. Sodium benzoate was included as a preservative. The prepared suspensions were studied for sedimentation stability with the help of near infrared

extinction profiles.

2.6 Determination of physical stability of suspensions

2.6.1 Determination of instability index and sedimentation velocity of suspensions

Separation analyser LUMiReader® PSA 453 was employed for stability determinations.5 LUM 10 mm, PC, synthetic sample cells were used for separation studies. Measurements were carried out at 0˚ tilt and 30°C, and 30˚ tilt and 30°C for the suspension samples. Tilting the sample from its normal upright position allows an increase in the separation rate at gravity without any additional external forces. The inclined position of the sample tube due to a tilt of 30˚resulted in accelerated sedimentation velocity compared to the upright position of the tube at 0˚ tilt as evident from the results shown in Table 2 and Table 3. Higher temperatures were avoided due to the anticipated possibility of changes in solubility and viscosity of the suspending agents and dispersion medium at higher temperatures. A sample volume of 2 ml was used in the determinations. Measurements at 30˚ tilt resulted in accelerated measurements. The extinction profiles were recorded at three wavelengths i.e., 470 nm (blue), 630 nm (red) and 870 nm (NIR) with the help of the software SEPView® installed in the instrument. The extinction profiles of 870 nm (near infrared) wavelength were taken into account for determination of sedimentation stability in the present work as the near infrared light region is sensitive for measurement of data of coarse particles. Blue light (470 nm) is sensitive for nano range particles. The results shown in Table 3 indicated that the instability index was lowest (0.0001) with suspension formulations containing 0.5% of SCMC, 0.25% to 0.5% POM as suspending agents. It was highest (0.6568) with formulation containing 0.25% HPMCK4M. Instability index generally ranges between 0 to 1 and the higher this value, more unstable the suspension is. Therefore, Instability index is a very useful tool for comparison of different suspending agents and selection of suitable suspending agents during suspension formulation development. Basing on the results of instability index it is presumed that 0.5% of SCMC or 0.25 to 0.5% of POM are suitable suspending agents for preparation of stable suspensions of ampicillin trihydrate.

2.6.2 Determination of resuspendability of suspension samples

Resuspendability is the ability to resuspend settled particles with a minimum amount of shaking after a suspension has sedimented on standing for some time. The suspension should redisperse with minimum effort on shaking for ease of administration. It is an important prerequisite for a good and stable suspension. Results shown in Table 4 indicate that the formulations F3S2, F4S2, F2S3, F1S4, F2S2, F1S2, F1S3 and F4S3 were easily resuspendable with an average number of 2.00, 2.33, 2.66, 2.66, 3.00, 3.30, 3.30, and 3.30 shakings respectively required for obtaining uniform dispersion.

Table 4 Results of resuspendability evaluation on ampicillin trihydrate suspensions (n = 3)

Sample	Suspending agent	%of suspending agent	Number of shakings required to get a uniform dispersion (n=3)	Remarks
F1S1	MC	0.25	4.33	No caking
F2S1	MC	0.50	5.33	No caking
F3S1	MC	0.75	5.20	No caking
F4S1	MC	1.00	4.66	No caking
F1S2	HPMCK4M	0.25	3.33	No caking
F2S2	HPMCK4M	0.50	3.0	No caking
F3S2	HPMCK4M	0.75	2.0	No caking
F4S2	HPMCK4M	1.00	2.33	No caking
F1S3	SCMC	0.25	3.33	No caking
F2S3	SCMC	0.50	2.66	No caking
F3S3	SCMC	0.75	4.66	No caking
F4S3	SCMC	1.00	3.33	No caking
F1S4	PO mucilage	0.25	2.66	Caking present
F2S4	PO mucilage	0.50	10.50	Caking present
F3S4	PO mucilage	0.75	20.66	Viscous gel
F4S4	PO mucilage	1.00	20.33	Viscous gel

Considering the results of instability index, sedimentation velocity and resuspendability of the suspensions it can be further inferred that 0.5% of SCMC or 0.25% of POM can be considered suitable as suspending

agents for preparation of stable suspensions of ampicillin trihydrate as caking was noticed in the suspensions with 0.5% POM, though the instability index was minimum (0.0001). Hence, higher concentration (0.5%) of POM (mucilage of *Plantago ovata*) should be avoided. Increase in concentration of the mucilage to 0.75% to 1.0% resulted in formation of highly viscous suspensions with poor flow. Hence, 0.25% of mucilage of *Plantago ovata* or 0.5% of sodium carboxymethylcellulose (SCMC) can be considered as ideal suspending agents for the preparation of ampicillin trihydrate suspensions. Further the FT-IR and DSC studies showed that the selected suspending agents were compatible with ampicillin trihydrate. The experimental data indicate the following decreasing order of preference of suspending agents for ampicillin trihydrate suspensions: SCMC≥ POM (0.25%) > MC> HPMCK4M in a concentration range of 0.5 to 1.0%.

3. Conclusion

From the results obtained from separation analysis of suspensions employing LUMiReader®, it can be understood that the suspension formulations can be easily compared by the parameter “Instability index” because this parameter takes into account of all the properties of the suspension like sedimentation velocity, clarifying velocity, particle size distribution changes etc. Instability index ranges between 0 to 1 and the higher this value, more unstable the suspension is. Therefore, Instability index is a very useful tool for comparison of different suspending agents and selection of suitable suspending agents during suspension formulation development. The following suspending agents are recommended in decreasing order of preference for ampicillin suspensions. Order of preference of suspending agents: SCMC ≥ POM (0.25%) > MC >HPMCK4M in a concentration range of 0.5 to 1.0%.

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